THE UNIVERSITY *of* EDINBURGH

SECTION III

IDU RELATED HIV - TREATMENT, NATURAL HISTORY, CLINICAL PRESENTATION AND TRANSMISSION

The recognition of the Edinburgh IDU related HIV epidemic in 1985 allowed medical services to be established at the RIDU, City Hospital in that year specifically to address this problem. These services have been described in the preceding chapters together with an analysis of their effectiveness. In addition to providing appropriate medical care the success of these medical services also facilitated the development of a clinical cohort of HIV patients available for various research activities connected with the Natural History of HIV and the clinical management of its complications. The results of these research activities are detailed in the following chapters

CHAPTER 12

Initial experience of anti-retroviral therapy for IDU related HIV infection

Introduction

Zidovudine has been shown to improve the survival and the morbidity of patients with AIDS or ARC but there are a number of serious side effects notably anaemia and leucopenia[1,2]. The early toxicity studies noted an association between neutropenia and concurrent paracetamol ingestion, utilised a four hourly dosage regime, close monitoring for toxicity and a highly motivated patient group[1,2]. Side effects are in part related to disease state but there is work in children that suggests that the incidence of myelosuppression and neutropenia are related to serum levels above 3 uM/l of zidovudine[3,4]. Sixty to seventy percent of zidovudine is metabolised via glucuronidation and there is therefore the potential for a number of interactions with both prescribed and non-prescribed drugs which also undergo glucuronidation. To date there has been little published work on the pharmacokinetics of zidovudine in injection drug users.

Despite the fact that Injection Drug Use (IDU) is common in both the USA and Europe there has also been little reported with regard to zidovudine treatment in drug users. There was not surprisingly some concern not only over whether the pharmacokinetics of zidovudine were altered in the presence of prescribed and non prescribed drugs, but whether the drug users would be motivated to follow a complicated treatment regime requiring reliability and compliance. This chapter details the differing pharmacokinetics and the initial experience of zidovudine use in drug users.

Patients and Method

Treatment of patients with zidovudine began in March 1987 and for patients with IDU related HIV infection in August 1987. The patients were initially selected on clinical grounds alone when progression to Centers for Disease Control (CDC) stage IV seemed to have occurred but latterly various prognostic factors such as absolute CD4 count, IgA, the presence of anaemia, HIV antigenaemia or loss of core or p24 antibodies were also used. Patients were commenced on doses of 20 mg/kg/day in divided doses four or five times per day administered in the form of oral capsules. A retrospective review of the case notes was conducted to determine details of treatment, complications between March 1987 and 31st December 1988.

The first 13 patients were admitted to hospital to start their treatment because of concern over possible drug interactions but thereafter patients were started on zidovudine as outpatients and reviewed usually at monthly intervals. They were monitored by attendance, weight, clinical examination, haematology, biochemistry, immunoglobulin levels and lymphocyte subset analysis. Later when available, HIV antigen and antibodies were added to the investigations. The initial 13 patients also underwent a pharmacokinetic trial to study the effect of prescribed and non-prescribed drugs on the levels of zidovudine. They gave informed consent for this pharmacokinetic trial (which was approved by the local ethics committee) and all were current or ex injection drug users.

One week prior to the pharmacokinetic study the patients were assessed by clinical examination, as well as by haematological, biochemical and immunological parameters. Urine samples were collected for toxicological analysis. These assessments were repeated weekly thereafter until the completion of the trial. All patients were admitted to hospital for the first week of the trial. On the first day (day 0) the patients took a light breakfast and thereafter fasted. At midday they were commenced on zidovudine 250 mg six hourly. Five ml samples of blood were withdrawn via a 16 gauge butterfly needle at 15 minute intervals for the first hour, 30 minutes intervals for the next two hours and hourly intervals for the last two hours. This procedure was repeated on day 7 and also on day 14 after the patient had been an out patient for a week. The patients were on a variety of opiates, benzodiazepines and cannabis (table 12.1) but during their hospital stay no attempt was made to prevent their use of non prescribed drugs. However they all agreed to keep their drug use constant during the study. No obvious injection drug use occurred during the period of the study.

The serum samples were stored at -20^{o}C until analysis before transportation to Wellcome Foundation Limited, Beckenham, Kent where they were heat inactivated from frozen in a water bath at 56-58 °C for 4 hours. A 1.2 ml aliquot was diluted 1 in 4 with phosphate buffered saline and further heat inactivated for 10 hours in a water bath at 60°C. A sensitive and rapid high pressure liquid chromatography (HPLC) method was used to simultaneously detect in human serum 3'-azido-3'deoxythymidine (zidovudine) and its major metabolite , the 5'-O-glucuronide(ADGT or 3'-azido-3'-deoxy-5'-beta-D-glucopyranuronosylthymidine). Samples and standards (0.5ml) were mixed with an internal marker, the 3'-beta-azido isomer of zidovudine (A22U or 1-[3-azido-2-3-dideoxy-beta-d- threo-pentofu-

ranosyl]thymine) and extracted using disposable cartridges containing 500 mg of C-18 material. The methanolic extracts were dried, re dissolved in 0.2 ml 15% acetonitrile and eluted isocratically from a 4x250 mm, C-18 analytical column using 25 mM phosphate buffer, pH 2.2, containing 15% acetonitrile as mobile phase, a flow rate of 1 ml/min and UV detection at 267 nm. Retention times were 5.2, 7.2 and 8.5 min for ADGT, A22U and zidovudine respectively. Column purge (6 min, acetonitrile:water, 4:1) and restore (12 min) periods were included after each analysis to prevent interference by concurrent medications with subsequent analyses. The total time required per sample was 30 minutes. The assay was linear from 0.03 to 11 ug/ml with good reproducibility. Absolute recoveries from spiked sera were 97, 104 and 103% for ADGT, A22U and zidovudine respectively. The only observed interferences were with ADGT and pyrimethamine and tripolidine.

Model independent pharmacokinetic analysis of the plasma concentrations were performed using a microcomputer package (SIPHAR)[5]. Half-lives of zidovudine were determined by fitting the log terminal concentrations at each of the days 0, 7 and 14 to a straight line. Peak concentrations (Cmax) were those directly measured, and areas under the plasma curve (AUC) were calculated by the linear trapezoidal method from the concentrations pre-dose to six hours on days 7 and 14. The first day AUC was calculated to infinity using the trapezoidal AUC to six hours augmented by the last concentration divided by the half-life rate constant. Clearances/fraction of dose available (CL/f) were calculated by dividing the six-hourly dose administered (250 mg, 935.63 μmoles) by the AUC, and then normalised to patient weight. Statistical analysis was performed using non-parametric Wilcoxon two sample pair tests on the mean (of days 0, 7 and 14) parameter values for each patient.

Results

Pharmacokinetics

A total of 12 patients were studied for zidovudine pharmacokinetics ten of whom (patients 1-10, opiate/benzodiazepine group) were consuming large quantities opiates and benzodiazepines (table 12.1). The majority of these patients had ceased injection drug use but for one or two this was only a matter of weeks before the study. The remaining two patients (patients 11 and 12, non opiate group) were only consuming cannabis, small doses of benzodiazepines and or moderate doses of alcohol (table 12.1). Both of these patients had ceased injecting drugs for at least 2 years. One patient in the opiate group (patient 3) had cirrhosis of the liver secondary to hepatitis

B virus related chronic active hepatitis. The rest had no clinical or biochemical evidence of renal or hepatic impairment.

Table 12.1: Patient demographic details and medication

Patient number	Gender	Age(yrs)	Race	CDC stage	Drugs	Dose
1	F	32	C	IV	Methadone Triludan Chloral hydrate Diazepam Lactulose	40mg/d 120mg/d 1g/d 30mg/d 40ml/d
2	F	23	Asian	IV	Dihydrocodeine Diazopam Triazolam Alcohol Amoxycilllin + Clavulanic acid	240mg/d 80mg/d 0.75mg/d 1 bottle/week 375mg/d
3	M	25	C	IV	Methadone Cyclizene Cimetidine Nefopam HCl Lactulose Spironolactone Bendrofluazide	15mg/d 150mg/d 400mg/d 240mg/d 60ml/d 100mg/d 2.5mg/d
4	F	25	C	IV	Dihydrocodeine Nystatin Amphotericin	300mg/d 5mls/d 5 lozenges/d
5	M	29	C	IV	Dihydrocodeine Temezapam Amoxycilllin + Clavulanic acid Lactulose	450mg/d 100mg/d 375mg/d 20ml/d
6	M	30	C	IV	Dihydrocodeine Lactulose Senna Diazepam Amphotericin Miconazole Clotrimazole Mesalazine	420mg/d 20ml/d 5ml/d 50mg/d 5 lozenges/d topical topical 1200mg/d

Table 12.1 continued: Patient demographic details and medication

Patient number	Gender	Age(yrs)	Race	CDC stage	Drugs	Dose
7	F	26	C	IV	Methadone Diazepam Triazolam Lactulose Fybogel Nystatin Metronidazole	40mg/d 40mg/d 0.25mg/d 40ml/d 1 sachet/d topical 1500mg/d
8	M	29	C	IV	Methadone Temazepam Diazepam	40mg/d 60mg/d 40mg/d
9	M	23	C	IV	Methadone Diazepam	50mg/d 30mg/d
10	F	31	C	IV	Methadone Triazolam Salbutamol Beclomethasone Oestrogen	50mg/d 1.5mg/d inhaler inhaler 1 tab/d
11	M	25	C	IV	Ibuprofen Triazolam	1200mg/d 0.25mg/d
12	M	31	C	IV	Cannabis Alcohol	daily occasional

There were no serious adverse reactions to zidovudine and no biochemical or haematological toxicity during the study period. No alteration in the maintenance opiate or benzodiazepine dosages were required as a consequence of the initiation of zidovudine therapy.

The pharmacokinetic parameters of zidovudine for each patient on each of the sampling days are shown in Table 12.2 together with mean parameter values. A summary of each group's pharmacokinetic parameters is shown in Table 12.4, a plot of the mean zidovudine concentration profile is shown in fig 12.1 and a scatter plot of each parameters distribution shown in Figure 12.3.

Zidovudine half-lives were not different between the two groups (1.06 ± 0.20 hours for the opiate group and 0.72 ± 0.16 hours for the non-opiate group). Mean peak values for the opiate users were higher (7.77 ± 2.82 μmoles) compared with $2.87 \pm$

1.18 μmoles) but there is some overlap in the values. The most striking differences between the two groups occurred with the AUC, which is greater for opiate users (12.33 ± 3.46 μmoles.h compared with 4.69 ± 0.02 μmoles.h) and clearance (CL/f) which is reduced for opiate users (23.41 ± 6.15 ml/min/kg compared with 57.34 ± 15.64 ml/min/kg). The lack of overlap in this small data set is however suggestive of a significant difference.

The pharmacokinetic parameters of the 5'-O-glucuronide of zidovudine for each patient on each of the sampling days are shown in Table 12.3 together with mean parameter values. A summary of each group's pharmacokinetic parameters is shown in Table 12.5, a plot of the mean zidovudine concentration profile is shown in fig 12.2 and a scatter plot of each parameters distribution shown in Figure 12.4.

GAZT half-lives were not different between the two groups (1.17 ± 0.25 hours for the opiate group and 0.94 ± 0.05 hours for the non-opiate group) and close to the zidovudine half-lives. Mean peak GAZT values for the opiate users were similar (10.10 ± 3.51 μmoles compared with 11.78 ± 5.16 μmoles) to the non-users. In contrast to zidovudine differences between the two groups, the GAZT AUC and clearances (strictly zidovudine dose μmoles/l GAZT AUC umoles.h) were similar (20.95 ± 3.98 umoles.h, 20.96 ± 3.11 μmoles.h; and 13.31 ± 2.25 ml/min/kg, 11.99 ± 4.08 ml/min/kg for opiate users and non-users respectively. The high degree of overlap for all parameters is suggestive of little difference between the groups with regard to GAZT.

Table 12.2: Zidovudine pharmacokinetic parameters

Patient number	Weight (kgs)	Day	AUC (uM.h)	Patient Mean	$T_{1/2}$ (h)	Patient Mean	Clearance/F (ml/min/kg)	Patient Mean	C_{max} (uM)	Patient Mean
1	55.2	0	14.83		1.09		19.05		6.0	
		7	19.43	**16.19**	1.09	**0.98**	14.54	**17.78**	11.7	**8.47**
		14	14.31		0.77		19.74		7.7	
2	69.7	0	9.39		0.61		23.82		12.9	
		7	15.80	**13.32**	1.29	**0.90**	14.16	**17.71**	7.0	**11.60**
		14	14.78		0.81		15.14		14.9	
3	63.8	0	16.42		1.19		14.89		9.7	
		7	17.83	**18.59**	1.42	**1.46**	13.71	**13.32**	12.1	**10.27**
		14	21.54		1.78		11.35		9.0	
4	60.6	0	10.66		0.77		24.13		6.9	
		7	10.21	**11.27**	1.22	**0.96**	25.2	**23.07**	3.9	**5.77**
		14	12.94		0.88		19.89		6.5	
5	64	0	11.36		1.33		21.46		5.1	
		7	7.18	**9.23**	1.11	**1.27**	22.96	**27.35**	2.1	**3.5**
		14	9.15		1.37		26.63		3.3	
6	62.8	0	6.29		0.5		39.46		2.8	
		7	8.81	**7.36**	1.22	**0.8**	28.18	**34.41**	3.0	**3.9**
		14	6.98		0.68		35.59		5.9	

Table 12.2 continued: Zidovudine pharmacokinetic parameters

Patient number	Weight (kgs)	Day	AUC (uM.h)	Patient Mean	$T_{1/2}$ (h)	Patient Mean	Clearance/F (ml/min/kg)	Patient Mean	C_{max} (uM)	Patient Mean
7	53.1	0	19.01		1.06		15.45		6.9	
		7	9.16	**15.02**	0.48	**0.98**	32.05	**21.62**	10.9	**11.27**
		14	16.90		1.38		17.38		16.0	
8	60.5	0	10.54		0.96		24.45		12.5	
		7	8.39	**9.56**	1.76	**1.25**	30.73	**27.2**	4.1	**6.93**
		14	9.76		1.01		26.41		4.2	
9	56.9	0	9.51		1.45		28.82		9.9	
		7	13.10	**11.76**	0.87	**1.09**	20.92	**23.79**	8.3	**7.77**
		14	12.68		0.96		21.62		5.1	
10	51.6	0	11.07		0.95		27.29		11.8	
		7	12.24	**10.96**	0.70	**0.92**	24.70	**27.85**	7.2	**8.23**
		14	9.58		1.12		31.56		5.7	
11	74.0	0	3.86		0.37		54.62		2.8	
		7	4.34	**4.70**	0.85	**0.61**	48.53	**46.29**	3.0	**3.70**
		14	5.9		0.61		35.71		5.3	
12	55.9	0	5.45		0.47		51.19		2.2	
		7	5.99	**4.68**	1.02	**0.83**	46.58	**68.40**	2.9	**2.03**
		14	2.60		1.00		107.44		1.0	

Table 12.3: GAZT pharmacokinetic parameters

Patient number	Weight (kgs)	Day	AUC (uM.h)	Patient Mean	$T_{1/2}$ (h)	Patient Mean	Clearance/F (ml/min/kg)	Patient Mean	C_{max} (uM)	Patient Mean
1	55.2	0	19.5		1.02		14.48		8.9	
		7	22.58	**22.46**	0.79	**1.06**	12.35	**12.71**	13.8	**11.23**
		14	25.01		1.37		11.29		11.0	
2	69.7	0	19.27		1.06		11.61		13.7	
		7	30.25	**22.54**	1.90	**1.21**	7.40	**10.46**	8.5	**11.97**
		14	18.10		0.68		12.36		13.7	
3	63.8	0	14.33		1.41		17.05		5.5	
		7	16.34	**16.09**	1.54	**1.43**	14.96	**15.30**	7.0	**5.97**
		14	17.60		1.32		13.89		5.4	
4	60.6	0	21.54		0.87		11.95		10.5	
		7	22.21	**24.18**	1.13	**1.06**	11.58	**10.82**	6.5	**9.77**
		14	28.80		1.19		8.93		12.3	
5	64	0	12.96		1.48		18.79		5.1	
		7	19.90	**18.99**	1.66	**1.48**	12.24	**13.72**	7.0	**6.30**
		14	24.10		1.29		10.11		6.8	
6	62.8	0	12.77		0.89		19.45		5.2	
		7	20.65	**15.79**	1.73	**1.58**	12.02	**16.42**	5.6	**6.13**
		14	13.96		2.10		17.78		7.6	

Table 12.3 continued: GAZT pharmacokinetic parameters

Patient number	Weight (kgs)	Day	AUC (uM.h)	Patient Mean	$T_{1/2}$ (h)	Patient Mean	Clearance/F (ml/min/kg)	Patient Mean	C_{max} (uM)	Patient Mean
7	53.1	0	20.02		1.18		14.67		6.0	
		7	18.63	**23.86**	0.67	**1.03**	15.76	**13.12**	12.6	**11.77**
		14	32.94		1.24		8.92		16.7	
8	60.5	0	14.16		1.11		18.21		9.7	
		7	16.89	**15.53**	0.93	**0.90**	15.26	**16.68**	7.9	**7.97**
		14	15.54		0.68		16.59		6.3	
9	56.9	0	20.47		0.86		13.39		15.8	
		7	24.65	**25.95**	1.34	**1.03**	11.12	**10.96**	14.9	**13.37**
		14	32.73		0.89		8.37		9.4	
10	51.6	0	29.02		1.23		10.41		27.3	
		7	24.32	**24.14**	0.60	**0.88**	12.43	**12.90**	13.7	**16.50**
		14	19.06		0.81		15.85		8.5	
11	74.0	0	22.26		1.45		9.47		12.2	
		7	22.95	**23.16**	0.88	**0.97**	9.18	**9.11**	15.2	**15.43**
		14	24.26		0.59		8.69		18.9	
12	55.9	0	19.18		0.46		14.54		8.3	
		7	18.53	**18.76**	0.78	**0.90**	15.06	**14.88**	9.4	**8.13**
		14	18.57		1.46		15.02		6.7	

Table 12.4: Summary of pharmacokinetic parameters for zidovudine

	AUC	$T_{1/2}$	Clearance/F	C_{max}
Mean value for opiate group (pts 1-10)	12.33	1.1	23.4	7.8
± SD	3.5	0.2	6.2	2.8
Mean value for non opiate group (pts 11-12)	4.7	0.72	57.3	2.9
± SD	0.02	0.16	15.6	1.2

Table 12.5: Summary of pharmacokinetic parameters for glucuronide of zidovudine (GAZT)

	AUC	$T_{1/2}$	Clearance/F	C_{max}
Mean value for opiate group (pts 1-10)	21.0	1.2	13.3	10.1
± SD	4.0	0.3	2.3	3.5
Mean value for non opiate group (pts 11-12)	21.0	0.9	12.0	11.8
± SD	3.1	0.05	4.1	5.2

Results of formal statistical analysis using non-parametric Wilcoxon two sample pair tests on the mean parameter values for each patient are shown in Tables 12.6 and 12.7 for zidovudine and GAZT respectively. Although sample sizes of 10 and 2 for the two groups are small, significant differences at the $p < 0.05$ level are noted for the AUC and CL/f for zidovudine. The difference between the Cmax of zidovudine for opiate and non opiate users just fails to reach statistical significance ($p = 0.07$), whereas zidovudine half-life differences were not significant. There were no differences approaching significance for any of the GAZT pharmacokinetic parameters (Table 12.7). Unfortunately there was only one set of results available on patient 2 because of a technical failure.

Table 12.6: Wilcoxon comparison of samples by pairs for zidovudine pharmacokinetic parameters

	AUC	$T_{1/2}$	Clearance/F	C_{max}
Average Rank of opiate group (pts 1-10)	7.5	7.4	5.5	7.4
Average Rank of Non opiate group (pts 11-12)	1.5	2.0	11.5	2.0
Large sample test statistic Z	-2.04	-1.83	2.04	-1.83
Two tailed probability of being = or > Z	0.041	0.067	0.041	0.068

Table 12.7: Wilcoxon comparison of samples by pairs for GAZT pharmacokinetic parameters

	AUC	$T_{1/2}$	Clearance/F	C_{max}
Average Rank of opiate group (pts 1-10)	6.6	7.15	6.8	6.2
Average Rank of Non opiate group (pts 11-12)	6.0	3.25	5.0	8.0
Large sample test statistic Z	0.11	-1.30	-0.54	0.54
Two tailed probability of being = or > Z	0.91	0.2	0.59	0.59

Figure 12.1: **Mean zidovudine plasma concentration profile**

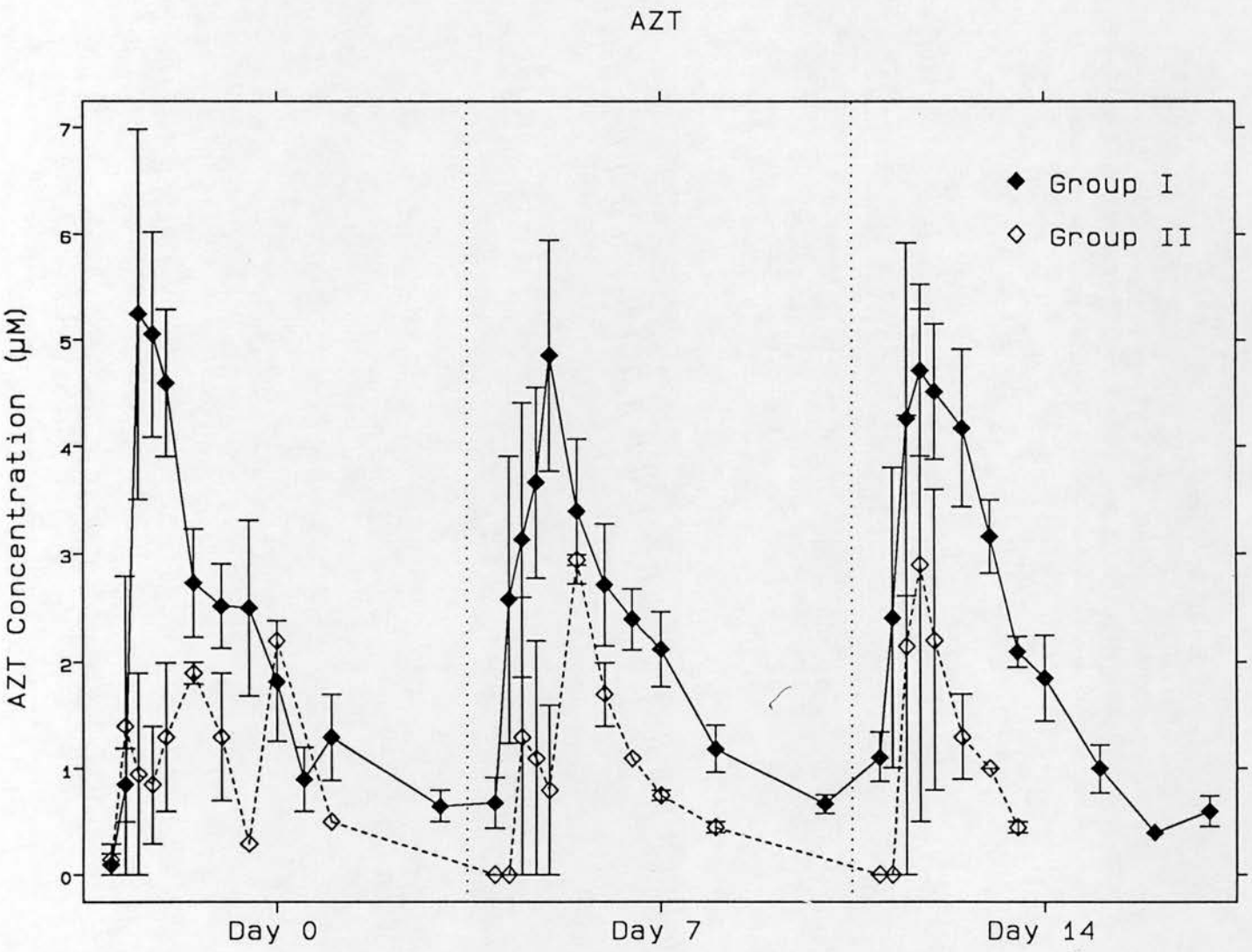

AZT
AZT Concentration (μM)
0
1
2
3
4
5
6
7
Day 0
Day 7
Day 14
Group I
Group II

Figure 12.2: Mean GAZT plasma concentration profile

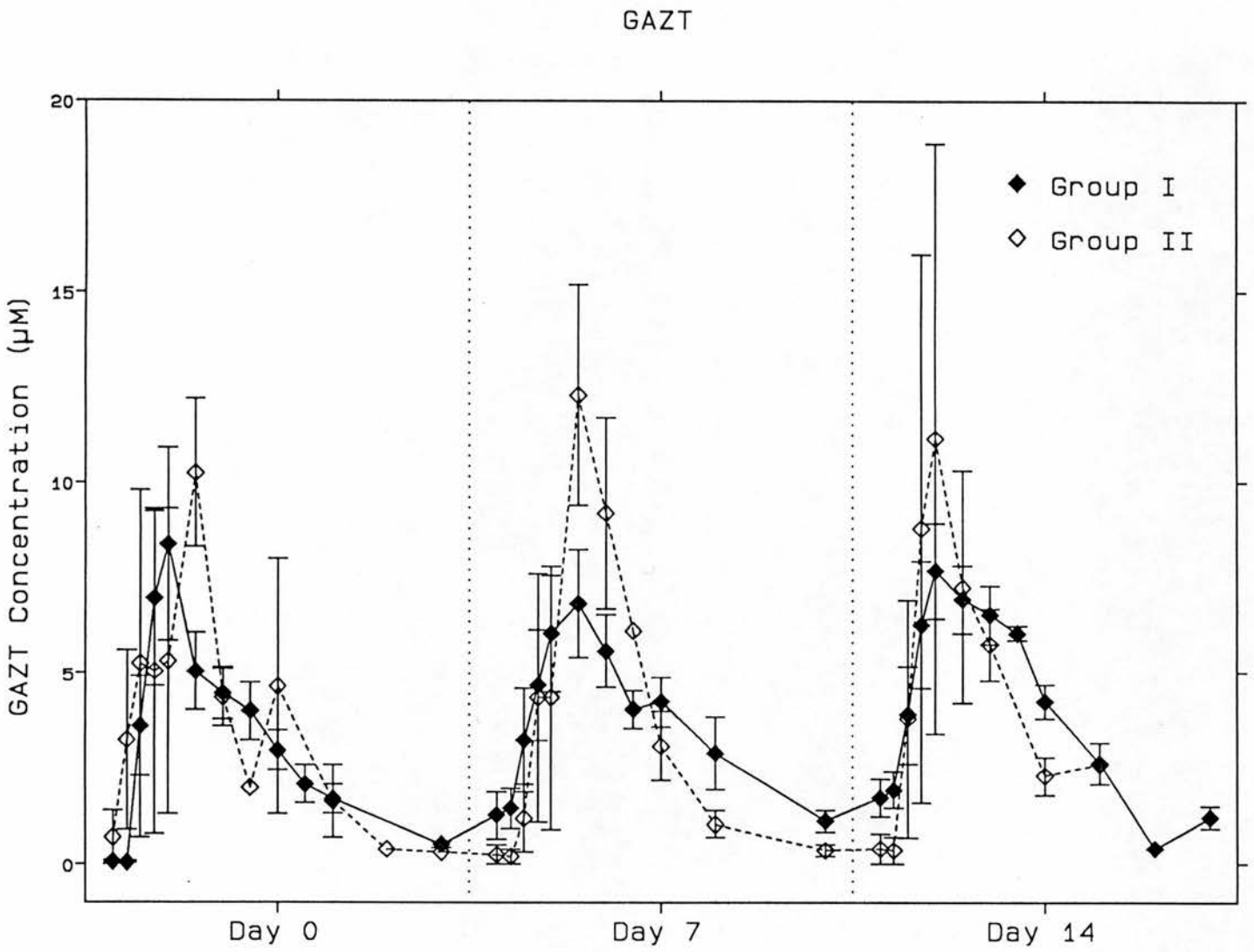

GAZT
GAZT Concentration (μM)
20
15
10
5
0
Day 0
Day 7
Day 14
Group I
Group II

Figure 12.3: **Scatter Plot of Zidovudine Pharmacokinetic Parameters**

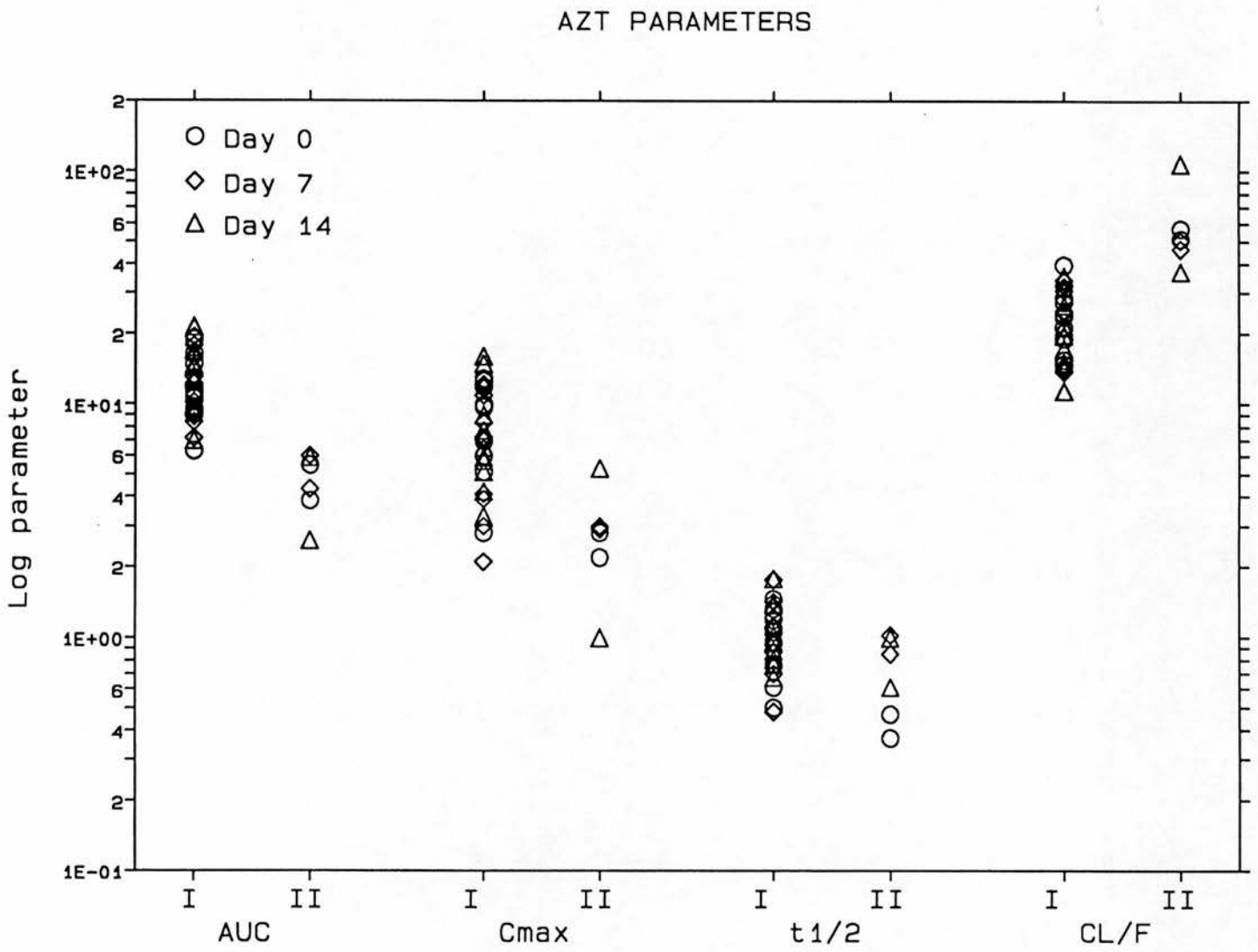
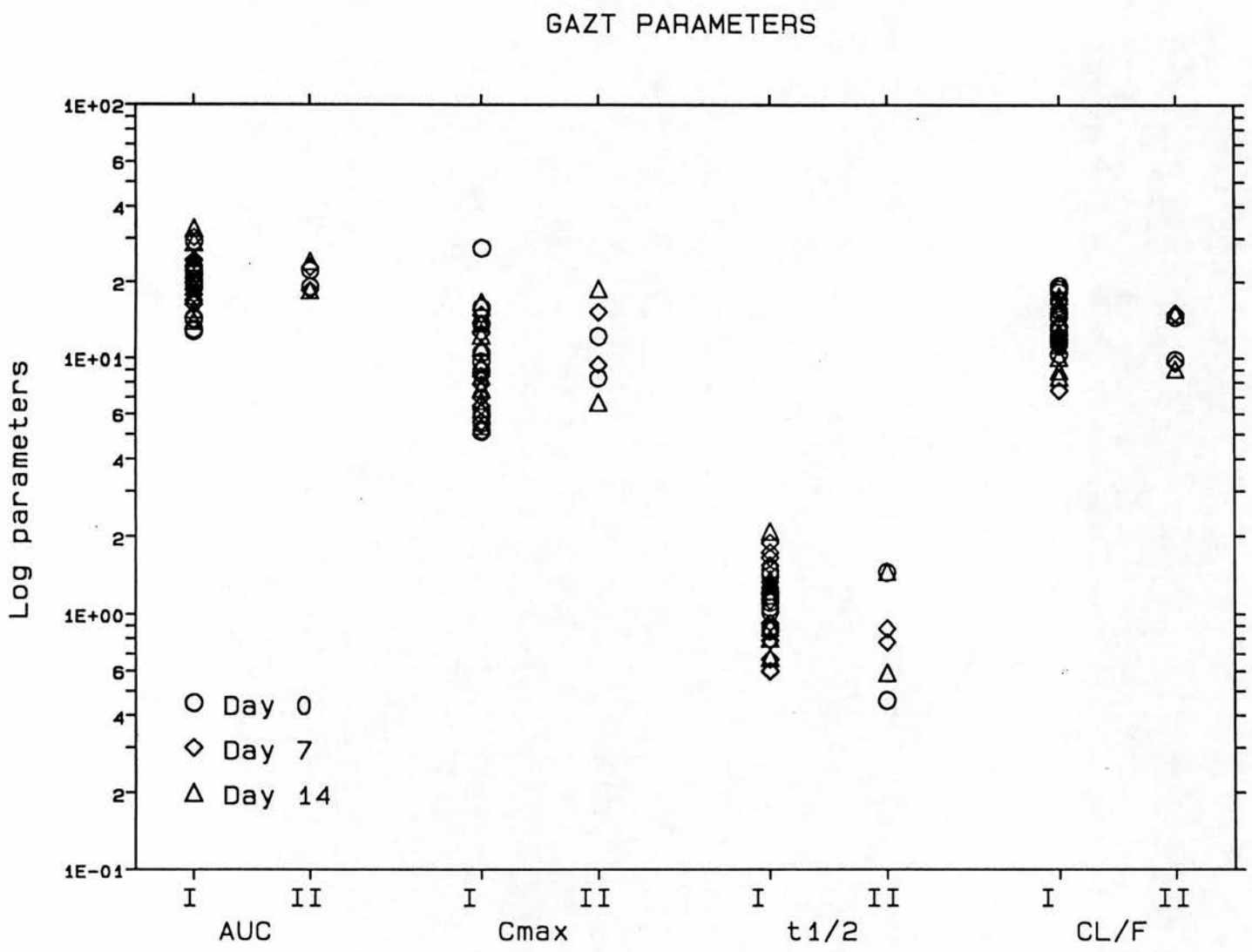

AZT PARAMETERS
Day 0
Day 7
Day 14
Log parameter
2
1E+02
6
4
2
1E+01
6
4
2
1E+00
6
4
2
1E-01
I
II
AUC
Cmax
t1/2
CL/F

Figure 12.4: Scatter plot of GAZT pharmacokinetic parameters


GAZT PARAMETERS
Log parameters
1E+02
6
4
2
1E+01
6
4
2
1E+00
6
4
2
1E-01
Day 0
Day 7
Day 14
I
II
AUC
Cmax
t1/2
CL/F

Retrospective Review of initial Zidovudine therapy

Zidovudine therapy was first used in March 1987 and by December 1988 40 (14%) patients had been treated with zidovudine, 30 males and 10 females. Thirteen patients acquired the virus homo/bisexually, while 26 patients became infected secondary to IDU related HIV and 1 patient from a blood transfusion. The average age of the homo/bisexual patients was 38 years (range 29-58 years), while those with IDU related HIV infection had an average age of 29 years (range 22-39 years). The patient who became infected following a blood transfusion was 47 years old.

Patients were started on zidovudine when they developed AIDS or other CDC stage IV problems and the numbers in each risk group and CDC group are shown in Table 12.8. The mean absolute CD4 lymphocyte counts of patients commencing on treatment with zidovudine were as follows: IDU related HIV with AIDS (4 patients) 150 cells/cumm (range 60-260), Others with AIDS (11 patients) 110 cells/cumm (range 50-200), IDU related HIV without AIDS (22 patients) 280 cells/cumm (range 100-460), Others without AIDS (3 patients) 120 cells/cumm (range 90-160). Thirty four of the 40 patients have had HIV antigen tests performed to date and 24 (70.5%) were found to be positive. There was no significant difference between the risk groups or CDC status as far as HIV antigenaemia was concerned.

Table 12.8: CDC status of patients commenced on zidovudine

CDC stage	Risk activity of patients		
	IDU	Ho/bisexual	Transfusion
4A	7	1	0
4B	2	0	0
4C1	4	7	0
4C2	12	1	0
4D	0	2	0
4E*	1	0	1
Dual+	0	2	0
Total	26	13	1

* thrombocytopaenia, + 4C1 and 4D occurring in the same patient

Three (7.5%) patients who received zidovudine had died by the end of the study. One homosexual patient was unable tolerate zidovudine because of marrow toxicity and died AIDS 16 months after commencement of zidovudine therapy of; one bisexual died 7 months after commencement of zidovudine of recurrent cerebral toxoplasmosis and 1 IDU related HIV with concomitant cirrhosis secondary to hepatitis B virus related chronic active hepatitis died after six months of zidovudine

therapy of a massive variceal haemorrhage. His HIV related problems did not progress whilst he was taking zidovudine.

The drugs most commonly used in Edinburgh include heroin, methadone, dihydrocodeine (DF118), buprenorphine (temgesic), dipipanone (diconal), temazepam, triazolam, diazepam, cannabis and alcohol. Of the 26 IDU related HIV patients, 7 (28%) no longer used oral or injection drugs, (although 4 continued to smoke cannabis), 18 (72%) patients were on oral substitution therapy (12 prescribed oral methadone by the City Hospital HIV Clinic and 6 oral replacement therapy from their General Practitioners). In total 6 (24%) patients admitted to having injected drugs whilst taking zidovudine (this includes 5 patients who received oral methadone from the City Hospital). The average length of follow up for the 26 IDU related HIV patients was 8.2 months (range 2-14 months) compared with 8.76 months (range 3-18 months) for the 13 homo/bisexual patients.

Of the 40 patients started on zidovudine, 14 (35%) developed side effects severe enough to necessitate a reduction in the dose of zidovudine. Table 12.9 demonstrates the CDC category and risk factors of these patients.

Table 12.9: **CDC stage and risk factor of patients with side effects on zidovudine**

CDC	IDU(*)	Ho/bisexual(*)	Transfusion
4A	0	0	0
4B	2(1,0,1)	0	0
4C1	3(3,1,0)	2(2,0,1)	0
4C2	4(2,1,1)	0	0
4D	0	1(1,0,0)	0
4E	0	0	0
Dual+	0	2(2,1,0)	0
Total	9	5	0

*side effects denoted by numbers (anaemia, neutropenia, gastro-intestinal,) in table,
+ 4C1 and 4D occurring in the same patient

Two patients suffered more than one side effect; 3 patients had gastrointestinal symptoms on starting therapy which resolved when treatment was withdrawn and then slowly reintroduced; 11 (27.5%) patients became anaemic, 10 (25%) severely enough to require transfusion and 1 who was stabilised on a reduced dose of zidovudine. Transfusion requirements for those patients who became anaemic on zidovudine are shown in Table 12.10. As has been shown previously, the patients with full blown AIDS were more likely to become transfusion dependent than those with the AIDS Related Complex (ARC) (χ^2= 10.98 with Yate's correction, p <

0.001). The presence or absence of HIV antigen or the level of the absolute CD4 lymphocyte count at the start of treatment did not predict the likelihood of becoming anaemic or requiring a transfusion. Continuing to use drugs orally or via injection did not have an adverse effect on the CD4 lymphocyte count or make transfusion more likely

Table 12.10: Transfusion requirements of patients becoming anaemic on zidovudine according to CDC category and risk factor

Units required	4C1 or 4D		Others	
	Ho/bisexual	IDU	Ho/bisexual	IDU
*>4	1	0	0	0
>3,<4	0	0	0	2
>2,<3	2	1	0	0
>1,<2	0	2	0	0
<1	2	0	0	0

*= Number of units of blood transfused per month since becoming transfusion dependent.

Three (7.5%) patients became neutropenic on zidovudine (2 with AIDS). In one this was recurrent despite decreasing dosages. In this patient the zidovudine was eventually discontinued. The other 2 patients (both IDU related HIV and one with AIDS) were stabilised on a lower dose of zidovudine. The non AIDS IDU related HIV patient had previously been stable on treatment for one year.

Injection drug users are notorious for defaulting from out-patient appointments and for non-compliance with treatment due to their chaotic lifestyle. The defaults from the HIV medical clinic were analysed and are shown in Table 12.11.

Table 12.11: Defaults from HIV medical clinic according to drug use

Defaults	Ex/Non IDU	Oral DU	Oral + IDU	Total (%)
0	2	6	3	11 (42)
1-3	5	4	3	12 (46)
4-5	1	2	0	3 (12)
Total (%)	8 (31)	12 (40)	6 (23)	26 (100)

None of the homo/bisexual group missed any clinic appointments. Of the 26 IDU related HIV patients on zidovudine 11 (42%) patients had no defaults, 12 (46%) missed 1 to 3 clinic visits and 3 (12%) missed 4 to 5 clinic visits. When the

attendance of drug users was further assessed it was apparent that missed appointments were not related to continued IDU, current versus ex IDU, AIDS versus non AIDS or gender. The most reliable attendees were those receiving oral methadone from the clinic (χ^2= 3.72 with Yate's correction, p=0.05).

If a rise in red blood cell mean corpuscular volume (MCV) is taken as an indication of zidovudine compliance, this data suggests that compliance in the IDU related patients is comparable with those in the other groups (mean rise in MCV in IDU related HIV patients on zidovudine is + 21.2 fl, in the other groups it is + 18.0. fl (the data from those patients who have received transfusions has not been included in this analysis).

In 12 (30%) patients the course of zidovudine was interrupted and in 5 (12.5%) patients this was for medical reasons, (anaemia, neutropenia, or gastro-intestinal upset). One of these patients already mentioned had to discontinue zidovudine permanently. Six patients, all IDU related HIV, discontinued the drug without consulting the clinic. In 1 patient whose lifestyle was particularly chaotic it was felt unsafe to continue with zidovudine as its effects were being inadequately monitored. None of these patients suffered ill effects as a result of these stoppages. Two patients, one who had not used drugs for 4 years and one on oral methadone defaulted for long periods (mean 5.5 months) and then returned to the clinic. None of the homo/bisexual patients had given up zidovudine without medical indication.

Eight out of the forty (20%) patients developed infections and or malignancy after having been on zidovudine for 6 weeks or longer. 1 homosexual man in category 4C1 developed lymphoma, 1 homosexual man who had candidal oesophagitis prior to starting zidovudine developed a co-trimoxazole sensitive pneumonia which was assumed to be due to PCP, 1 homosexual man had a probable recurrence of his PCP and 1 bisexual man had a recurrence of his cerebral toxoplasmosis. One IDU related HIV patient moved from category 4A to 4C2, another had a proven recurrence of her PCP and 2 IDU related HIV patients had attacks of herpes zoster.

Clinical trials

Recruitment for the first MRC/Inserm Clinical trial (Concorde) started in June 1989. This was a randomised double blind placebo controlled trial to determine the efficacy of zidovudine in reducing progression to AIDS or symptomatic disease amongst patients in CDC stage II or III of HIV disease. Recruitment for the second

MRC/Inserm Clinical trial (Alpha) started in June 1990. This was a randomised double blind trial of the efficacy and safety of DDI (2,3 dideoxyinosine) in patients with symptomatic HIV infection (CDC stage IV) who were intolerant of zidovudine. Recruitment for the third MRC/Inserm Clinical trial (Delta) started in March 1992. This was a randomised double blind trial to assess the efficacy and safety of combinations of zidovudine, DDI and DDC (2,3 dideoxycytidine) in patients with HIV infection (CD4 count of between 350 and 50 cells/cumm without AIDS).

Between June 1989 and October 1992 a total of 542 patients with HIV had attended the RIDU at the City Hospital. The proportion of patients from each of the risk activities recruited in to Concorde and Alpha were similar to that of the total clinic population (Table 12.12).

Table 12.12: Recruitment into clinical trials June 1989-October 1992

Patient Group	RIDU clinic(%)	Concorde(%)	Alpha(%)	Delta(%)
No. of patients	542(100)	48(100)	40(100)	13(100)
IDUs	392(71)	38(79)	27(68)	6(46)
Males	274(50)	22(45)	20(50)	6(46)
Females	118(21)	16(33)	7(18)	0
Methadone	233(43)	23(48)	15(37)	2(15)
Non-methadone	159(29)	15(31)	12(30)	4(31)
Sexually acquired HIV	150(28)	10(21)	13(32)	7(54)
Ho/bi	74(13)	5(10)	13(32)	3(23)
Male Het	26(5)	1(2)	0	1(8)
Female Het	50(9)	4(8)	0	3(23)

As far as the overall clinic population was concerned, 7% of the IDUs were recruited into the Concorde trial, 5% into the Alpha trial and 1% into the Delta trial. The figures for sexually transmitted HIV patients was that 2% were recruited into both the Concorde and Alpha trials whilst 1% were recruited into the Delta trial.

The length of time that patients from various risk groups participated in the trials were similar. The number of missed appointments was higher in the Concorde trial for drug users compared to those acquiring the illness via sexual transmission (4.9 vs. 1.8, $p<0.02$). However the number of missed appointments/month of the Concorde trial was not signficantly different between the two groups.

Table 12.13: Length of trial treatment and number of missed appointments

	Mean no. months in trial (range)	Mean no. of missed appointments (range)
Concorde		
IDUs	11.8(1-38)	4.9(1-16)
Methadone	13.0(1-38)	4.4(1-16)
Non methadone	10.1(1-37)	5.8(1-11)
Sexually acquired	10.4(3-31)	1.8(1-4)
Alpha		
IDUs	8.7(1-23)	1.4(0-5)
Methadone	9.4(1-21)	1.7(0-5)
Non methadone	7.9(2-23)	1.1(0-3)
Sexually acquired	7.9(1-25)	0.7(0-3)

There was no significant difference in the frequency of zidovudine related side effects, non compliance or missed appointment rate between the two main risk activities.

Discussion

Pharmacokinetics of zidovudine

The pharmacokinetics of zidovudine in patients taking opiates and benzodiazepines were different from those of ex users not on opiates (but taking small doses of benzodiazepines and or cannabis) although they were of the same order as those published for other non drug using patients. In a study on patients with AIDS or ARC the mean AUC following 250 mg of oral zidovudine was 6.74 $\pm$ 2.43 umol/l.h and the mean peak level was 4.42$\pm$ 2.21umol/l[6]. In a study of uninfected subjects receiving 200 mg oral zidovudine, conversion of the results presented (mg/l) and scaling to 250 mg dose yields pharmacokinetic parameters of mean AUC of 6.51 $\pm$ 1.71 umol/l.h, a clearance of 36.5 $\pm$ 4.7 ml/min/kg and a peak of 5.01 $\pm$ 1.25 umol[7].

The most striking differences in this study were that users of large doses of opiates and benzodiazepines had approximately twice the AUC, twice the peak values and half the clearance of zidovudine but without alteration in the zidovudine half-life. In consequence this group of patients would therefore have an increased exposure to zidovudine (but an unchanged GAZT exposure) compared to ex or non-drug users. Since these results were first presented at the Fifth International Conference on AIDS[8], the findings were confirmed by a second group at the Sixth International Conference on AIDS[9]. This latter report not only confirmed the doubling of the

zidovudine AUC for methadone users but also noted, in an in vitro model, that there was no apparent inhibition of zidovudine glucuronidation by methadone itself[10]

Possible mechanisms to explain these altered pharmacokinetics might include all or one of the following; reduced intestinal mobility as a consequence of opiate use resulting in increased absorption of zidovudine, inhibition of glucuronidation by opiates and benzodiazepines, increase bioavailability and/or an effect on renal clearance. The data on the GAZT pharmacokinetics and a lack of effect on the zidovudine half-life suggests a combination of the above possibilities. A recent report from the United States, suggested that the mechanism was at the level of the kidney since they observed reduced zidovudine/GAZT levels in urine[10].

Despite these results there have been no reports of any undue toxic side effects in injection drug users treated with zidovudine[11-18]. However caution is required because the observation period is relatively short. These observations will be particularly important in the context of trials for asymptomatic patients where the length of treatment with zidovudine may be prolonged.

Caution is required in the extrapolation from these results, although the similar pharmacokinetic data in a second group of methadone users does suggest that this is an important and real observation. These observations are relevant not only for drug users but also for other patients who might receive large doses of opiates or benzodiazepines in the course of managing their illness. Such results are particularly important when considered in the context of zidovudine prescribing for asymptomatic patients when the length of treatment will be prolonged. In addition, the current dosage guidelines are based on trials which have enrolled just 0-13% of patients with a history of drug use.[1,19-22] The suggestion that opiate users may be receiving increased doses of zidovudine has important implications for all trials conducted with zidovudine to date. If these increased doses of zidovudine are important then they might account for a significant amount of toxicity and a meta analysis of those trials involving drug users could answer this question.

Initial experience of the use of zidovudine in drug users

The medical care of individuals engaged in drug use is difficult and is complicated by a lack of support in the community and often differing goals for doctors and users. Periods of drug use are interspersed with variable periods of abstinence such that therapy which demands abstinence would be fraught with dangers. It was

consequently necessary to establish the safety of zidovudine in drug users under a variety of conditions. Abstinence or a particular form of drug use (e.g. oral vs. inhalation vs. injection) is not a safe criteria on which to base therapy since drug use may alter during the long treatment periods required for HIV.

It is not surprising perhaps that IDU related HIV as a group had a worse attendance record than homo/bisexual patients and this was probably more related to differing life styles and background. A study of general practice in Muirhouse, Edinburgh revealed a uniform default rate of 2 visits per patient per year irrespective of drug use[23].

Overall 58% of the IDU related HIV patients missed one appointment but 75% of the ex or non IDU also missed at least one appointment. By comparison only 50% of those judged to be still injecting whilst on oral substitute therapy missed at least one appointment. A study from New York of IDU related HIV and zidovudine use, reported surprisingly similar results to the present one in that 81% of patients from New York missed from 0 to 3 appointments compared to 86% in Edinburgh[12]. This despite the fact that the population studied was not the same as in Edinburgh; 14/60 or 23% of the IDU related HIV patients from New York were heterosexual contacts compared to only 4% (one patient) in Edinburgh, only 30% admitted to concurrent medication whereas at least 88% of the Edinburgh patients were using concurrent drugs and 24% admitted to current IDU. However only 1% of the patients in New York had no defaults compared to 42% in Edinburgh and New York had 12/60 or 20% lost to follow up compared to 8% (2) in Edinburgh. Even these latter two patients are still in contact with their general practitioner's or the counselling clinic.

A further study concluded that: "***addicts stabilised on methadone or in drug free treatment regimes were as reliable as homosexual patients and seemed to become less sociopathic"*** with zidovudine treatment[24]. Lastly, an inner city population, predominantly black and drug using, showed acceptable although not ideal compliance with zidovudine[25].

To date the RIDU has not been able to study the safety and efficacy of zidovudine with continued heroin injection drug use since at present the majority of injection users are injecting black-market pharmaceutical preparations. The use of illicit pharmaceutical opiates by injection did not appear to interact with zidovudine.

Since patients are issued with a one month's supply of zidovudine at each visit intermittent treatment has occurred because of missed appointments but this has not resulted in any harm to the patients. In addition several treatment courses were interrupted on medical grounds and no deterioration was observed unlike other reports[26].

A commonly expressed fear is that IDU related HIV patients will sell their zidovudine on a black-market. Whilst this may have happened the rise in MCV suggests it is not common. It would also appear to be uncommon when a reasonable supply of an oral opiate substitute is given even if injecting does continue. Thus the MCV change is a convenient and cheap method of assessing compliance. Thus only those patients who did not experience an MCV rise need be further investigated for malabsorption or lack of compliance. Interestingly the MCV change also occurred with a far less rigorous regimen, usually four or five times per day organised around meal times. The more widely spaced regimens do not so far appear to be detrimental but continued monitoring is required.

There are a number of practical issues which are more specific to this group. Because of the unknown effect of zidovudine upon the foetus, termination was considered in the case of pregnancy although treatment was continued if requested by the patient. One of the patients became pregnant on treatment.

Venous access was a considerable problem in a few patients and because of the need for repeated venepuncture over many months or years sampling from the external jugular in the head down tilt continues to be favoured over the femoral vein or artery.

As a consequence of limited resources, large numbers of patients, the problem of compliance with clinic appointments and a relatively well population, monthly monitoring for those on zidovudine was adopted. Provided that haematological values were normal before treatment monthly monitoring was found to be safe and did not result in unexpected leucopenia or anaemia.

The improvement in health induced by zidovudine, unfortunately on a number of occasions resulted in individuals feeling well enough to return to injection drug use. Continued IDU does and will occur in patients on zidovudine treatment. Thus it is important to keep up the harm reduction message.

A number of patients commenced on zidovudine whilst being in prison and others have spent time there after commencing treatment. It might be expected that this

would result in difficulties with therapy but this has not occurred and prison authorities and their medical staff have provided the service for such patients to continue with their treatment and attend follow up appointments.

Thus it is possible to treat IDU related HIV with zidovudine. The results of clinical monitoring of zidovudine treated IDU related HIV suggest that it is safe in a variety of drug use situations including recent injection drug use. Attendance was no different between those judged to be still using drugs and those thought to have discontinued IDU. In the absence of initial haematological abnormalities monthly monitoring appeared safe and the patients came to no harm as a consequence of their intermittent treatment.

Clinical trials

The majority of clinical trials of anti-retroviral therapy to date have recruited predominantly homosexual men despite the fact that in Europe and the USA ,drug use is the second largest patient group. The current dosage guidelines are based on trials which recruited only 5-8% of women and just 0-13% of patients with a history of drug use[1,19-22]. The experience of the RIDU in Edinburgh however has been that both drug users and women could be successfully recruited into and retained in clinical trials. The frequency of missed appointments was similar to the rest of the clinic (Chapter 7) and provided this is taken into account recruitment and retention of difficult patients into clinical trials is possible.

Conclusion

The pharmacokinetics of zidovudine in patients taking opiates and benzodiazepines are different from ex users not on opiates. The most striking differences were that users of large doses of opiates had approximately twice the AUC, twice the peak values and half the clearance of zidovudine but without alteration in the zidovudine half-life. In consequence opiate users in general would have an increased exposure to zidovudine compared to ex or non-drug users suggesting that for such patients smaller doses of zidovudine, possibly only half the regular dose, are required.

Despite the practical problems it is perfectly possible to treat IDU related HIV with zidovudine. The experience of clinical monitoring of zidovudine treated IDU related HIV suggest that it is safe in a variety of drug use situations including recent injection drug use. The MCV change induced by zidovudine therapy is a convenient and cheap method of assessing compliance. Attendance is no different between those

judged to be still using drugs and those thought to have discontinued IDU. After the initial experience, clinical trials undertaken at the RIDU in Edinburgh were successful in recruiting both drug users and women into MRC clinical trials.

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CHAPTER 13

Clinical and epidemiological implications of CDC/WHO reclassification of AIDS cases

Introduction

An entirely satisfactory staging system for HIV disease and AIDS has not yet been developed, although a number have been described. Some, such as the Centers for Disease Control[1], are purely clinical except for requiring confirmation of HIV status. Others, such as the Walter Reed Staging and Classification system[2], are based on a combination of both clinical and laboratory assessments. Skin reactivity to a panel of antigens and a CD4 count above or below 400 cells/cumm are used as laboratory assessments in the Walter Reed classification. However a failure to utilise CD4 counts as a continuous variable reduces their informativeness. In addition, the system was not very convenient from a clinician's or patients' point of view since it requires repeated clinic visits to read the skin tests.

In 1990, the World Health Organisation (WHO) proposed a simplified HIV classification system based on four clinical criteria (acute infection or persistent generalised lymphadenopathy or asymptomatic; minor symptoms; major symptoms; and AIDS) combined with three laboratory groups to provide 12 distinct stages[3]. The laboratory groups were based on **either** the level of the lymphocyte count **or** the CD4 count (see Table 13.1). This proposal had the merits of a simplified clinical staging, a powerful predictor in the CD4 count, and a cheap alternative in the lymphocyte count.

Table 13.1: WHO interim proposal for staging of HIV infection

Laboratory Classification				Clinical Group *			
	Absolute CD4 count	or	**Total lymphocyte count (TLC)**	**1**	**2**	**3**	**4**
A	≥500/cumm		≥2000/cumm	A1	A2	A3	A4
B	200-499/cumm		1000-1999/cumm	B1	B2	B3	B4
C	≤200/cumm		≤1000/cumm	C1	C2	C3	C4

**Definitions of Clinical Groups for Table 13.1*

***Clinical group 1**: acute HIV infection, persistent generalised lymphadenopathy, asymptomatic/normal activity.*

***Clinical group 2**: (early stage disease): weight loss <10% of body weight, minor muco-cutaneous problem, herpes zoster within 5 years, recurrent upper respiratory tract infection with normal activity.*

***Clinical group 3**: (intermediate stage disease): weight loss > 10% of body weight, unexplained chronic diarrhoea and/or prolonged fever for > 1 month, oral candidiasis, oral hairy leukoplakia, pulmonary tuberculosis within 1 year, severe bacterial infections and/or bed ridden < 50% of day during previous month.*

***Clinical group 4**: (late stage disease): definitive or presumptive diagnosis of any AIDS defining illness as per 1987 CDC surveillance definition and/or bed ridden > 50% of day during previous month.*

The Centers for Disease Control (CDC) also began to develop a modified classification system for HIV and in order to avoid two different schemes the CDC and WHO worked closely to combine the two proposals into a joint CDC/WHO classification system for HIV disease in adolescents and adults[4]. The joint CDC/WHO classification system (Table 13.2) was based on three clinical groups (A = acute infection or persistent generalised lymphadenopathy, or asymptomatic; B = all symptomatic conditions other than AIDS; C = the 1987 definition of AIDS) and three laboratory groups (1 = 500 or more CD4 cells/cumm **or** 2000 or more lymphocytes/cumm; 2 = 200-499 CD4 cells/cumm **or** 1000-1999

lymphocytes/cumm; and 3 = less than 200 CD4 cells/cumm **or** less than 1000 lymphocytes/cumm).

Table 13.2: CDC/WHO classification of HIV infection

Laboratory Classification				**Clinical Category***		
	Absolute CD4 count	or	**Total lymphocyte count (TLC)**	**A**	**B**	**C**
1	≥500/cumm		≥2000/cumm	A1	B1	C1
2	200-499/cumm		1000-1999/cumm	A2	B2	C2
3	≤200/cumm		≤ 1000/cumm	A3	B3	C3

**Definitions of Clinical Groups for Table 13.2*

***Clinical category A**: (Asymptomatic) Acute infection with HIV; persistent generalised lymphadenopathy; asymptomatic. Conditions in Groups B and C must be absent.*

***Clinical category B**: (Symptomatic) Any symptomatic conditions not included in Category C. Examples are bacterial infections, candidiasis (oral or vulvovaginal) for >1 month, cervical dysplasia or carcinoma, constitutional symptoms, oral hairy leukoplakia. Two distinct episodes of herpes zoster or involving more than one dermatome, idiopathic thrombocytopenic purpura, mycobacterium tuberculosis, peripheral neuropathy.*

***Clinical category C**: Any condition which meets the 1987 CDC/WHO case definition for AIDS.*

Perhaps more importantly, the Centers for Disease Control also proposed that in addition to the clinical diagnosis of AIDS based on the 1987 revision (i.e. C1-3 of the modified CDC/WHO classification system, Table 13.2), there should also be a definition of AIDS based on all patients with a single CD4 count of below 200 cells/cumm irrespective of symptoms (i.e. A3 and B3 of the modified CDC/WHO classification system, Table 13.2). This latter suggestion has produced considerable debate, and dissent,[5] but little data has been published on whether or not these new definitions have validity either clinically or epidemiologically.

Several arguments have been put forward for changing the AIDS case definition. One of the most compelling is to facilitate assessment of the number of HIV infected individuals who need intensive medical care, and are at highest risk of serious opportunistic illness. Secondly, with the increasing number of patients from diverse risk activities and regions, such as Asia, being affected by HIV disease, expansion of the clinical definition of AIDS will produce an endless list of opportunistic events[6]. In Thailand, for instance, it has been suggested that a fungal infection, *penicillium marneffei*, should be considered an AIDS diagnosis[7]. Whilst this may be reasonable such local definitions would reduce the strength of the current world wide surveillance system for following the epidemic.

Claims that the 1987 definition of AIDS excludes the clinical features of immunodeficiency that manifest in women and drug users have not been supported in reviews of AIDS diagnoses, which have revealed that women present with the same opportunistic infections as men and, except for Kaposi's sarcoma[8], as do drug users. However, this reassurance is perhaps illusory. Since the 1987 definition of AIDS was based mostly on homosexual men in the USA, it only counts those patients who develop a similar illness. It is not surprising therefore that no difference to date in presentation of AIDS has been noted, since other presentations are not considered.

Whilst the natural history of AIDS does not appear markedly different for drug users[8], a more important question is whether HIV infected patients die of non-AIDS conditions before they achieve an AIDS diagnosis. This certainly appears to be the case for drug users. In New York, Stoneburner et al[9] have reported that there has been a rapid increase in both AIDS and non-AIDS narcotic related deaths. By 1986, for every AIDS related death in a drug user, there was one other as a consequence of conditions such as tuberculosis, endocarditis and bacterial pneumonia. Similar data have also been reported from Europe[10,11], and therefore support the argument that the current AIDS definition does not adequately describe the clinical problems of HIV immunodeficiency in drug users.

As far as women are concerned, the Edinburgh experience[12] is that only admissions for urinary tract infections are increased among females, whilst admissions for other infections show no gender difference. One major problem which particularly affects women is neoplasia of the genital tract, and there are some studies that suggest that women with HIV disease do have an increased risk of progression[13]. Other than genital tract infections and neoplasms however, there have not been many reports so far to suggest that HIV infected women have a particular disease spectrum that

differs from men. Unfortunately many studies have not addressed the issue of gynaecological problems. Reports have also been mixed[11] when it comes to comparing the survival of HIV infected men and women. To date, the Edinburgh data has not suggested any difference in survival according to gender for patients with known seroconversion dates[14]; but larger studies are needed which investigate the causes of death of HIV infected women.

In the USA, the change of AIDS definition has been linked to the debate over access of HIV infected individuals to medical care. Patients with AIDS, but not HIV infected individuals, qualify for financial help with medical care, and so altering the clinical AIDS definition could widen the number of patients qualifying for financial assistance. There was strong criticism of the Centers for Disease Control by the advocacy groups at the 1992 International Conference on AIDS, and this pressure is probably not going to abate since the Social Security Administration has decided not to accept the proposed new CDC definition of AIDS as a criterion for assistance[6].

Other problems with the proposed 1992 definition of AIDS centre on the fact that CD4 counts are costly and not widely available, even in the USA. Whilst the clinical definition of AIDS relied on patients presenting with ill health, the 1992 definition will depend on individuals presenting to the health care system and that health care system being willing to pay for an investigation - especially in an asymptomatic patient - in order to clinch the diagnosis. Inequalities may exacerbate, not reduce, as has been recognised in the reasons[5] given for the European rejection of CDC's proposal. These include that: immunological monitoring of HIV disease requires patients to have enlisted in clinical care, the propensity to do this differs between risk groups and over time, and CD4 cell counting is not well standardised throughout Europe.

Standardised and quality controlled methodologies for lymphocyte subtyping have been in place throughout Scotland since 1988 and earlier still in Glasgow and Edinburgh[15]. Scotland has capitalised on CD4 monitoring of HIV disease for short-term predictions of the AIDS epidemic[15,16], using the date of the **earlier** of two consecutive CD4 counts of 200 or less to define when a patient passes the CD200 (x2) threshold. A patient whose immunological depletion has reached this point is referred to as a CD200(x2) case.

In order to consider the effect if any of possible re-classification on the patients in Edinburgh this chapter considers the data on annual numbers of "AIDS cases" and

their survival based on clinical and immunological follow-up (to the end of July 1991) of the Edinburgh City Hospital Cohort of 532 HIV-1 antibody positive patients, of whom 397 (75%) were injecting drug users (IDUs).

Methods

The annual numbers of potentially reportable cases from the Edinburgh City Hospital Cohort are documented according to a series of proposed AIDS case definitions as follows:

- according to the date of the first total lymphocyte count (TLC) of 1000 or less cells/cumm
- according to the date of the first CD4 count of 200 or less cells/cumm [CD200(x1) diagnosis]
- according to the date of the earlier of two consecutive CD4 counts of 200 or less cells/cumm [CD200 (x2) diagnosis]
- according to the date of AIDS diagnosis [AIDS 1987 definition[1]].

Laboratory Methods

Lymphocyte surface markers including the CD4 count were performed throughout by flow cytometry on whole blood analysis. Blood samples were stained by directly conjugated monoclonal antibody pairs using CD16/CD45 to confirm a lymphocyte gate (Becton Dickenson Leukogate) and CD4/CD8 to identify T cell sub populations (Becton Dickenson). Data analysis was performed using Simulset software following flow cytometry on a Facscan analyser (Becton Dickenson). Absolute CD4 counts were derived from the total white cell count performed by the Department of Haematology, Royal Infirmary, Edinburgh (Sysmex) and lymphocyte and CD4 percentages obtained by flow cytometry. Since 1989 the HIV Immunology Laboratory has regularly participated in the MRC/NEQAS National Quality Assurance Scheme for T lymphocyte numbers and has consistently demonstrated acceptable performance.

The interchangeability of the definitions based on the TLC and the CD200 (x1) as proposed by the World Health Organisation is assessed for patients enrolled in the Edinburgh City Hospital Cohort. Lifetables to death (irrespective of cause) from month of satisfying case definition CD200 (x1), CD200 (x2) or AIDS (1987) are presented as a basis to judge which of the modified AIDS case definitions has

validity as a measure of severe HIV immunodeficiency[17]. The proportion of patients who satisfy each definition in their calendar year of enrolment to the cohort is also documented.

Since three quarters of patients in the Edinburgh City Hospital Cohort to end July 1991 were injecting drug users, amongst whom deaths from overdose have been as frequent as AIDS-related deaths, lifetables to death are presented separately for injecting drug users and other patients satisfying case definitions CD200 (x2) and AIDS (1987). The deaths of patients who have been lost to clinical follow-up for at least one year are ascertained confidentially from the Registrar General. Lifetables have therefore been calculated on the basis that enrolled patients were alive at the end of July 1991 unless known to have died. This convention reflects the best quality of information that is available to reporting clinicians, and so the best that surveillance centres might routinely have access to.

Results

Edinburgh City Hospital Cohort

The Edinburgh City Hospital Cohort was initiated by the referral of three patients in April, August and October of 1984. The October patient was diagnosed with AIDS in the same month; the August patient developed AIDS related complex in September 1990; and the April patient developed it in November 1987, followed by AIDS in June 1989. Annual referrals thereafter were: 26 in 1985, 105 in 1986, 110 in 1987, 102 in 1988, 109 in 1989, followed by 56 in 1990 and 21 patients in the first seven months of 1991.

Of the 532 patients in the cohort to end of July 1991, 397 (75%) were injecting drug users. The oldest patient was born in 1930, the youngest in 1973. Median year of birth for the cohort was 1961 with a quarter of patients born in 1956 or before, and a quarter in 1964 or later. Mean age at referral was 28 years (SD = 7.0 years), ranging from 16 to 60 years of age. One hundred and seven AIDS diagnoses had been recorded as follows: one each in 1984 and 1985, two in 1986, 12 in 1987, 16 in 1988, 30 each in 1989 and 1990, and 15 in the first seven months of 1991. There were 96 deaths: 58 (60%) were AIDS related, 11 were medical non-AIDS , 23 (24%) were overdoses and four causes were unclassified. Deaths were recorded as follows: one in 1984, none in 1985, four in 1986, seven in 1987, nine in 1988, 13 in 1989, 28 in 1990, and 34 in the first seven months of 1991.

Median year of birth for the 397 injecting drug users was 1961, ranging from 1942 to 1972. Their mean age at enrolment in the cohort was 27 years (SD = 5.3 years) and 205 (52%) had enrolled prior to 1988. Fifty-six injecting drug users developed AIDS before end of July 1991; and there had been 60 deaths, including 23 which were AIDS-related and 23 overdoses. Until now, no change has been made to certified cause of death to reflect post mortem findings of AIDS - related causes in sudden deaths certified as overdose.

Median year of birth was 1959, ranging from 1930 to 1973, for the 135 non-injectors (of whom 71 were homosexual men and 55 were heterosexual contacts). Their mean age at enrolment in the cohort was older at 31.9 years (SD = 9.7 years) and only 39 (29%) non-injectors had enrolled prior to 1988. Fifty-one non-injectors developed AIDS before end of July 1991; and there have been 36 deaths, 35 of them AIDS-related.

Cases according to modified AIDS case definitions

Table 13.3 shows the frequency distributions for annual numbers of cases in the Edinburgh City Hospital Cohort according to the proposed modified AIDS case definitions. Whereas 107 patients had developed AIDS (1987), half of them in their calendar year of enrolment to the cohort (that is 54 patients, of whom 40 were non-injectors), 341 patients have had a first total lymphocyte (TLC) count of 1000 or less and 308 patients a first CD4 count of 200 or less (CD200 x1). Modified AIDS case definitions based on a TLC and CD200 (x1) were met in the calendar year of enrolment by 158 (46%) and 145 (47%) of the respective cases. These proportions are, however, very significantly different by risk group (Table 13.4): modified AIDS case definition CD200 (x1) was met in the calendar year of enrolment by 88 (39%) of 225 drug user cases but by 57 (69%) of 83 non-injector cases ($\chi^2_1 = 21.3$, $p < 0.001$); alternatively, by 88 (22%) out of 397 enrolled injecting drug users but by two fifths of non-injector patients in the cohort, that is by 57 (42%) out of 135 non-injectors.

The end point CD200 (x2) as implemented by HIV immunology laboratories in Scotland[15], was met by 205 patients in the Edinburgh City Hospital Cohort by end July 1991, of whom 81 (40%) met it in their calendar year of enrolment, these 81 patients being 12% of injecting drug user patients (46 out of 397) but 26% of non-injectors (35 out of 135). Throughout the period of enrolment from 1986 (when CD4 count monitoring became established) there was evidence of earlier disease presentation by injectors: only 7% of injectors in 1986-87 presented as CD200 (x2)

cases in their calendar year of enrolment (12 out of 184 patients) compared to 13% of non-injectors (4 out of 31 patients) and in 1988-90, compared to 17% of injectors presenting as CD200 (x2), that is 31 out of 179 patients, 32% of non-injectors were CD200 (x2) in their calendar year of enrolment, that is 28 out of 88 patients. A period effect was also evident, with relatively more CD200 (x2) presentations in calendar year of enrolment during 1988-90 for both transmission categories than in 1986-87, and a marked increase in the enrolment of non-injectors in 1988-90 compared to 1986-87.

Table 13.3: Modified AIDS case definitions: reportable cases from the Edinburgh City Hospital Cohort

	Modified AIDS case definitions (no. meeting criterion in calendar year of enrolment)											
Year ENTIRE COHORT	No. enrolled (No. with AIDS by July 1991)		No. with first TLC ≤1000		No. with first CD200 (x1)		No. with first CD200 (x2)		No. with AIDS diagnosis (1987)		Deaths ALL CAUSES	Deaths AIDS-RELATED
1984	3	(2)	1	(1)					1	(1)	1	1
1985	26	(9)	6	(6)					1	(1)	0	0
1986	105	(16)	31)	(29	21	(18)	6	(5)	2	(0)	4	2
1987	110	(20)	21	(17)	38	(23)	21	(11)	12	(8)	7	3
1988	102	(20)	47	(29)	65	(31)	39	(17)	16	(12)	9	6
1989	109	(20)	96	(37)	78	(39)	62	(26)	30	(15)	13	7
1990	56	(17)	90	(29)	74	(26)	50	(16)	30	(14)	28	15
part 1991	21	(3)	49	(10)	32	(8)	27	(6)	15	(3)	34	24
Total	532	(107)	341	(158)	308	(145)	205	(81)	107	(54)	96	58

Table 13.4: Modified AIDS case definitions: reportable cases in drug users from the Edinburgh City Hospital Cohort

	Modified AIDS case definitions (no. meeting criterion in calendar year of enrolment)											
Year DRUG USERS	No. enrolled (No. with AIDS by July 1991)		No. with first TLC ≤1000		No. with first CD200 (x1)		No. with first CD200 (x2)		No. with AIDS diagnosis (1987)		Deaths ALL CAUSES	Deaths AIDS-RELATED
1984	2	(1)										
1985	19	(3)	3	(3)								
1986	94	(12)	28	(26)	15	(14)	4	(4)			2	
1987	90	(12)	15	(13)	30	(17)	14	(8)	2	(1)	4	
1988	75	(10)	30	(17)	46	(18)	23	(8)	4	(2)	4	1
1989	77	(9)	72	(21)	59	(23)	47	(15)	18	(5)	9	3
1990	27	(8)	63	(12)	54	(11)	34	(8)	19	(5)	18	6
part 1991	13	(1)	36	(5)	21	(5)	18	(3)	13	(1)	23	13
Total	397	(57)	247	(97)	225	(88)	140	(46)	56	(14)	60	23

Interchangeability of criteria (i) and (ii)

Table 13.5 presents data on the ability to interchange criteria based on either a single TLC $\leq$ 1000/cumm or a single CD4 count $\leq$ 200/cumm for patients enrolled since 1988 in the Edinburgh City Hospital Cohort. (By 1988, CD4 count monitoring was available in most UK centres). Ninety-eight (34%) out of 288 patients met neither criterion, 57 (20%) met one but not both criteria (37 met the TLC criterion only, 20 the CD4 criterion); and of the 133 (46%) who met both criteria, 103 satisfied them in the same calendar year, 13 satisfied the TLC criterion earlier and 17 the CD4 criterion first.

Table 13.5: Cross-tabulation of when the proposed new AIDS definitions based on a single TLC and CD4 count were met by 288 patients enrolled in 1988 or later

	First lymphocyte count (TLC) of 1000 or less					
First CD4 count of 200 or less	1988	1989	1990	1991	not met	Total
1988	21	4	1	2	3	31
1989	4	40	4	0	8	56
1990	3	1	31	6	6	47
1991	0	2	3	11	3	19
not met	1	6	20	10	98	135
Total	29	53	59	29	118	288

Lifetables

Of the 96 known deaths in the Edinburgh City Hospital Cohort to July 1991, 58 were AIDS-related. Amongst the 397 injecting drug users, as many deaths were from overdose as were AIDS-related (23 deaths each), as previously reported for both European and American drug users.[9,10,11] Table 13.6 shows the six monthly the probabilities of survival after CD200 (x1), after CD200 (x2), and after AIDS (1987) diagnosis. Median survival was 50 months, 40 months and 20 months respectively with 80% and 71% of patients surviving at least two years after the proposed new AIDS diagnoses based on CD200 (x1) and CD200 (x2) compared to 42% of patients still alive at two years after the current AIDS (1987) diagnosis.

Table 13.6: Lifetables from CD200 (x1) to death, CD200 (x2) to death and AIDS (1987) diagnosis to death

	CD200 (x1)		CD200 (x2) diagnosis		AIDS diagnosis	
Months	At risk	Pr (surviving)	At risk	Pr (surviving)	At risk	Pr (surviving)
0	308		205		107	.99
3	286	.98	187	.98	95	.88
6	270	.96	177	.95	79	.78
9	251	.94	162	.91	71	.74
12	232	.94	137	.87	57	.68
18	189	.88	109	.78	43	.54
24	148	.80	86	.71	28	.42
30	101	.72	49	.59	9	.22
36	72	.69	28	.54		
42	44	.58	17	.47		
48	24	.53				
Median survival		50 months		40 months		20 months
AIDS related deaths		58		50		58
Medical non AIDS		10		8		4
Overdose deaths		9		9		3
Unknown cause of death		0		1		0
Total No. deaths		77		68		65

Table 13.7 presents selected lifetables separately for injecting drug users and for non-injectors. Non-injectors were on average five years older at enrolment and were also more likely to have satisfied both the modified AIDS case definition based on CD200 (x2) and current the AIDS (1987) definition in their calendar year of enrolment.

HIV-1 antibody positive injecting drug users in the Edinburgh City Hospital Cohort experienced non-AIDS mortality of the order of 2.5% per annum, three fifths of which was attributed to overdose (23 out of 37 non-AIDS deaths). Nine overdoses were recorded in patients who had passed the CD200 (x2) threshold, and three after AIDS diagnosis. Amongst injectors who met a modified AIDS case definition based on CD200 (x2) diagnosis, only half the reported deaths were AIDS-related (19 out of 36 deaths) compared to 34 AIDS-related out of 35 deaths in other patients who were CD200(x2) cases. For injectors, the time from CD200 (x2) diagnosis to death from any cause was significantly longer than for non-injectors in the Edinburgh City Hospital Cohort; but a common lifetable applied from AIDS diagnosis. If non-AIDS related deaths amongst injectors are censored, the resulting lifetable from CD200 (x2) diagnosis to AIDS-related death (data not shown) is approximated by the square root of the all causes survival probabilities shown in Table 13.7. For example the probability that an injecting drug user did not die from AIDS within 1 or 2 years of CD200 (x2) diagnosis was 0.97 or 0.87 (SE 0.04) respectively.

Table 13.7: Selected lifetables for injecting drug users and other patients

	Injecting drug users						Other patients			
	Enrolment to non-AIDS deaths		CD200 (x2) to death		AIDS to death		CD200 (x2) to death		AIDS to death	
Months	At risk	Pr (surviving)	At risk	Pr (surviving)	At risk	Pr (surviving)	At risk	Pr (surviving)	At risk	Pr (surviving)
0	397		140		56	.92	65		51	
3	389	.99	137	.99	50	.86	63	.95	45	.90
6	378	.99	123	.98	39	.77	54	.89	40	.80
9	370	.98	113	.96	34	.72	49	.82	39	.76
12	363	.96	103	.94	23	.62	37	.72	36	.74
18	342	.95	80	.84	15	.44	31	.66	28	.62
24	311	.94	63	.78	12	.40	23	.56	17	.44
30	273	.94	44	.68			11	.40		
36	262	.93	25	.64						
42	198	.91	17	.57						
48	156	.90	12	.48						
54	120	.89								
60	89	.87								
AIDS related		Censored		19		23		31		35
Medical non-AIDS		10		7		4		1		0
Overdose deaths		23		9		3		0		0
Unknown deaths		4		1		0		0		0
Total deaths		37		36		30		32		35

Discussion

By July 1991, 107 patients (20%) in the Edinburgh City Hospital Cohort were diagnosed with AIDS (1987 definition) but 205 (39%) would have been notifiable as CD200 (x2) cases and 308 (59%) by the criterion of CD200 (x1). Fifty-four patients (10%) were diagnosed with AIDS in their calendar year of enrolment; 81 (15%) as CD200 (x2) cases and 145 patients (27%) had a CD4 count of 200 or less cells/cumm in their calendar year of enrolment.

CD200 (x2) case definition doubles, and the CD200 (x1) trebles the numbers of AIDS cases reportable from the Edinburgh City Hospital Cohort according to proposed new definitions of AIDS. This is a substantial change, and is unlike the findings of Velaquez et al[18] who surveyed 305 HIV-infected Spanish patients, 21% of whom fulfilled the 1987 AIDS definition and 30% the criterion of any CD4 count of 200 or less, which Centers for Disease Control propose as the 1992 AIDS definition. At the 1992 International AIDS Conference, Cohn[19] reported on a case series from Denver, Colorado which suggested a 49% increase in CD200 (x1) reports over the 1987 AIDS definition. Clearly, the impact of the proposed new definitions on reportable cases will be greater in cohorts of patients who seroconverted in the mid-1980s rather than in the late 1970s, many of whom have already met the 1987 AIDS definition.

Lifetable analysis for the Edinburgh City Hospital Cohort, again unlike the Spanish report, clearly shows that the 1987 AIDS definition and the 1992 modified definitions are not identical in terms of patient survival. The probability of being alive one year after having met the 1987 AIDS definition was 0.68, compared to 0.87 after CD200 (x2) diagnosis, and 0.94 after CD200 (x1) diagnosis. Corresponding median survival times were 20 months from AIDS, 40 months from a CD200 (x2) diagnosis, and 50 months for patients from a CD200 (x1) diagnosis. This variation in survival for the possible definitions of AIDS emphasises the fact that any proposals for new AIDS conditions or diagnoses should have comparable survival times to the original definition. A condition which has a median survival time substantially different from AIDS, which after all is a functional assessment of the state of the immune system , would appear to be providing a different assessment of the immune system. It does not therefore seem sensible to lump them all together under the same terminology.

This study has drawn attention to the possible confounding of risk group and differential entry into health care on estimation of lifetables from redefined AIDS to death. When the Edinburgh City Hospital Cohort was subdivided according to injecting drug user or not, differences in both enrolment pattern and immunological progression at enrolment were evident. Injecting drug users were 184 (86%) of the 1986-87 cohort of 215 patients and two thirds of the 1988-90 cohort of 267 patients. In both periods, injecting drug users were only half as likely to be CD200 (x2) cases in their calendar year of enrolment as were other patients; and were only half as likely to be dead within two years of CD200 (x2) diagnosis as were other patients (44%). Younger age at enrolment, clinical care from an earlier stage of HIV disease[20] (as measured by immune depletion) and, because of prior immunological monitoring, earlier recognition of when the CD200 (x2) threshold was passed may each have contributed to drug users' longer survival after reportable CD200 (x2) diagnosis. Patients who truly have passed the CD200 (x2) threshold **before** being enlisted in clinical care necessarily have their CD200 diagnosis delayed until after the start of immunological monitoring. Date of first CD4 count, as well as date of meeting modified AIDS criterion CD200 (x1) or CD200 (x2), is thus required for surveillance centres to recognise differential patterns of entry into health care by risk group. In the Edinburgh City Hospital Cohort, lifetables from AIDS diagnosis, as distinct from CD200 (x2) case definition, were similar for injectors and other patients, but the clinical symptoms which qualified the patients as AIDS cases also differed by risk group, Kaposi's sarcoma being unusual in drug users. Complex survival patterns will not be resolved satisfactorily by surveillance data; this requires regression modelling[21] of survival and progression from the time of seroconversion for well characterised clinical cohorts .

For epidemiological purposes, it appears that the proposed WHO reclassifications of HIV disease, based respectively on single lymphocyte count (TLC) of 1000 cells/cumm or less and single CD4 count of 200 cells/cumm or less, appear interchangeable. This suggests that lymphocyte counts, which are a relatively simple immunological assessment, can be used in centres without CD4 monitoring. But lymphocyte and CD4 counts are not equally effective for monitoring the progression of HIV disease in individual patients and equally they also may not be interchangeable for epidemiological work. If immunological staging is to be used, it should have biological plausibility. Lymphocyte counts do not equate with CD4 counts because the other lymphocytes such as CD8 count may fluctuate widely and unpredictably in HIV infection. The relationship between CD4 count and absolute

lymphocyte count in other, ethnically different, HIV-infected populations should not be extrapolated from the Edinburgh data; different lymphocyte count thresholds may be required. In addition and most importantly, the inherent variability of individual CD4 and lymphocyte counts, associated with biological changes and contributed to by measurement error, determines that in some individuals a single low count is obtained considerably earlier than genuine passage below a particular threshold. For this reason, consecutive counts provide a more reliable marker of disease progression in individual patients. For example, in 1986 when CD4 monitoring was just beginning in the Edinburgh City Hospital Cohort, 21 patients had a single CD4 count below 200, but only six were CD200 (x2) cases (see Table 13.1).

The WHO proposal to use lymphocyte counts is a cheap alternative to CD4 counts but, as yet, its validity in different risk groups and areas of the world has not been widely examined. In a cohort of homosexual men from Canada, Montaner et al showed a modified WHO staging system to be prognostically meaningful, and that the lymphocyte count was a valid alternative laboratory marker to CD4 count in describing survival[22] . Based on their data, lymphocyte ranges of <1000, 1000-1500 and >1500 cells/cumm were suggested. Still cheaper and easier markers, which can be evaluated in stored sera such as IgA and β-2-microglobulin or neopterin, also need to be investigated.

It is important that any staging system is broadly comparable between population. Whereas CD4 percentage has been successfully evaluated with standardised procedures and quality control between laboratories, the absolute lymphocyte cohort - upon which the CDC/WHO staging system would be based - has not yet been subject to similar scrutiny. Indeed, recent studies suggest that the choice of an individual haematology analyser can result in wide variations in individual total lymphocyte counts[24]. Adoption of the revised CDC and WHO classifications would require the introduction of national and international quality assurance of total lymphocyte determinations.

Conclusions

In summary an AIDS definition based on our CD200 (x2) case definition has greater biological plausibility than immunological staging based on a single CD4 count of 200 or less, as proposed by the CDC/WHO classification. Survival analysis of the Edinburgh City Hospital Cohort indicates that the 1987 and 1992 definitions of AIDS are not identical, describing as they do patients at different stages of HIV infection.

The CDC/WHO proposal and the CD200 (x2) case definition have merit as descriptions of imminent immunodeficiency and therefore an increased risk of ill health; all these are useful in clinical practice. The current AIDS definition is essentially a functional assessment of the immune system, as described by a constellation of clinical symptoms. CD4 counts, by comparison, yield a numerical assessment of the immune system, which is of value in identifying those at risk of developing clinical illnesses, against which prophylaxis and anti-viral therapy have some success.

There is a strong argument for a better classification of HIV disease which does not rely purely on either clinical symptoms or laboratory measurements alone. The controversy over the proposed CDC reclassification of AIDS is associated with the term AIDS rather than the condition of immunodeficiency itself[23] . That this reclassification needs to involve the term AIDS is in doubt. A reclassification system such as the CDC/WHO proposal which defines severe HIV immunodeficiency (A3 and B3 utilising lymphocyte counts or CD4 counts) is certainly required. The major criticism of the CDC/WHO system is that the use of consecutive CD4 or lymphocyte counts provides a better definition of staging. HIV immunodeficiency described by **consecutive** CD4 counts of less than 200 cells/cumm could be called simply A3/B3, or perhaps severe HIV related immunodeficiency (SHRID).

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CHAPTER 14

Analysis of Enrolment, Progression, Survival, Mortality and Baseline Covariates in the Edinburgh City Hospital Cohort

Introduction

As has been detailed in Chapter 2, the IDU related HIV epidemic is known to have started in Edinburgh in early 1983 and to have spread rapidly through a young group of needle-sharing drug users in the city housing estates[1-4]. The HIV epidemic was recognised in 1985 and medical services were established in that year to specifically address this risk activity[1,5] (and Chapters 4 and 6). Injection drug users (IDUs), not surprisingly therefore, form the core of the Edinburgh City Hospital cohort and their homogeneity with respect to time of infection, age and risk activity make them a valuable cohort for the study of HIV disease progression. They also have the advantage of having reasonably easy access to a health care system. This chapter describes the cohort, its pattern of enrolment and diagnosis, its overall progression to defined clinical and immunological endpoints and its survival from these endpoints. The effect of fixed descriptive covariates, that is cofactors describing gender, risk activity, age and enrolment year, on progression and survival is also investigated.

Methods

Patients

The voluntary self referral HIV clinic (Chapter 5) and the subsequent HIV medical clinics (Chapter 7) have been previously described[3,5].

All HIV positive patients visiting the self-referral clinic at the RIDU of the City Hospital, Edinburgh between its inauguration in October 1985 and December 1992 (plus a small number of HIV positives seen in 1984 and 1985 before the opening of the clinic) were included in this analysis. Those patients who did not attend for more than one year were flagged with the Registrar General to provide information about date and cause of death.

Laboratory Methods

The methods employed in the measurement of lymphocyte surface markers including the CD4 count were as described in Chapter 13.

Prior to June 1990 serum IgA quantification was performed by a nephelometric method using polyclonal specific antisera (Scottish Antibody Production Unit, Carluke). After that time a commercial radial immunodiffusion method was used (Binding Site: Birmingham). The two methods were cross validated at the time of technique transfer.

Statistical Methods

Enrolment patterns were investigated by a regression analysis of root CD4 count at enrolment against descriptive cofactors. Enrolment CD4 count was regarded as a surrogate for duration of infection at enrolment and was taken to be the first CD4 count in the initial 365 days of follow-up regardless of the clinical stage of the patient; the root transformation was used to symmetrize and normalise errors in the regression model.

Progression rates to Centers for Disease Control (CDC) stage IV, AIDS and CD200 were calculated using the Kaplan Meier method. A CD200 diagnosis was defined as the first of two consecutive CD4 counts below 200 or an AIDS diagnosis, whichever was earlier. Patients not reaching these endpoints were censored in two ways according to whether they were deemed "active" or "inactive" participants in the study at 31st December 1992. Because of a high number of missed appointments, and a significant phenomenon of temporary dropout from the study, an active participant was defined as a patient who had been seen within the last year of the study and was censored at the close of the study; an inactive patients was one who had not been seen for a year or longer and was censored at the last clinic visit. This strategy was designed to induce independent censoring by (1) making some adjustment for "walking-well" patients whose drop-out was linked to continuing good health whilst (2) allowing for the presence of genuine lost-to-follow-ups in whom status post-dropout could not be ascertained. It is likely to be the correct approach for progression to clinical endpoints.

On the other hand because flagging with the Registrar General should provide good ascertainment of deaths post-dropout a different policy was adopted for analyses of survival. Active participants were again censored at 31st December 1992; inactive participants were censored at 30th June 1992, because of a possible six-month lag in death reports from the Registrar General reaching the City Hospital. Mortality rates were calculated from enrolment and also from AIDS, CDC stage IV and CD200

diagnoses, again by the Kaplan Meier method. Mortality from all causes, including drugs overdose, was included in the endpoint definition.

The effect of descriptive cofactors (age, gender, risk activity, year of enrolment) on progression was analysed using the Cox proportional hazards model; endpoints of AIDS, CDC stage IV and mortality from all causes were considered. Eligible patients in these analyses were patients who enrolled free of the endpoint defining conditions in question and who had marker values within 365 of enrolment and before experiencing the endpoint. To control for differential enrolment patterns across cofactor groups, and thus to minimise the bias of onset confounding[6], baseline CD4 counts and IgA measurements were included as surrogates for duration of infection in cofactor models. Cofactors were analysed multifactorially to reveal their separate contributions. (Cofactor effects on progression to CD200 were not analysed in this way because of circularity problems in using CD4 count to control for duration of infection and to define the endpoint.)

Cofactor effects on post-diagnosis survival from AIDS, CDC stage IV and CD200 were also investigated. In this analysis the advantages of pre- and post-diagnosis zidovudine treatment were considered using time-dependent switch cofactors in proportional hazards models.

Changing administration of zidovudine over the years of its availability to the cohort was investigated by an analysis of disease stage at the uptake of treatment. Four stages were defined: patients with AIDS; patients AIDS-free but with CD4 counts below 200; patients AIDS free with counts between 200 and 500; patients AIDS free with counts above 500. In each calendar year of follow-up a patient living in that year was assigned to a stage according to his lowest CD4 count in that year and his AIDS status. Patients in each category were then further divided into three groups according to whether they had commenced zidovudine in a previous year, commenced the drug in that year, or not yet taken zidovudine. Thus a three-way cross-tabulation of the patients by year, disease stage and zidovudine treatment was obtained.

Patients with ten or more serial CD4 determinations were assigned a rate of root CD4 loss from linear regressions of CD4 count against time on the root scale. The dependence of rate of loss of root of CD4 count on Cofactors was then explored.

Results

Cohort Summary

Between October 1985 and 31st December 1992, 624 patients were enrolled in the cohort. Of these, 436 (70%) were IDUs, 93 (15%) were homosexual or bisexual men, 85 (13%) were heterosexuals, 6 (1%) were believed to have been infected by blood products. There were a large number of women (191 or 31%) offering a rare opportunity to look at gender differences in HIV disease progression and survival.

The average age of patients at enrolment was 28.6 (SD 7.3) years and 563 patients (91%) were aged between 20 and 40, so that the cohort members were mostly young. However there were significant age differences between exposure categories. Whilst IDUs had an average age of 27.1 (SD 5.2) years at enrolment, homosexual men were an older group with an average age of 34.8 (SD 8.8) years.

Follow-up Summary

The total number of visits made to the clinic at which **laboratory monitoring** was undertaken up to 31st December 1992 was 10940 with an average of 17.6 (SD 14.5) visits per patient. If follow-up time is defined as the time between first and last clinic visits the average follow-up period was 1120 days or 3.1 years. 63% of the cohort had more than two years of follow-up, 50% had more than three years and 23% had more than five years; 76% of the cohort made at least five clinic visits, 61% made at least ten clinic visits and 35% made at least 20 visits.

Against this background of long follow-up, a drop-out phenomenon also took place. Many cohort members became "lost-to-follow-up" (in the sense that they were not seen at the clinic for long time periods); although a subset of these cohort members later reappeared at the clinic. 112 patients had not been seen for a year at 31st December 1992 (and were not believed to be dead). However, over the years, 145 patients returned to the clinic after gaps greater than one year in their follow up. Considering long term lost-to-follow-ups; 49 patients had not been seen for three years although 21 patients returned to the cohort after gaps of three years; 29 had not been seen for four years although nine returned to the cohort after gaps of four years. Some of these long gaps in follow-up can be attributed to imprisonment or living away from Edinburgh in order to avoid the drug scene.

Diagnoses and Mortality

A diagnosis of AIDS was made on 154 individuals (25% of cohort) during the period of this study; whilst 349 (56%) received an AIDS or CDC Stage IV diagnosis; 316 (51%) were eligible for a diagnosis of CD200. Some 38% of the total AIDS diagnoses and CD200 diagnoses and 40% of the total CDC Stage IV diagnoses were made at the enrolment visit (table 14.1). However, over the years 1987 to 1992, a decreasing proportion of diagnoses were made at enrolment.

The initial AIDS diagnoses made on the 154 patients were as follows; 83 (54%) Pneumocystis carinii pneumonia, 21 (14%) oesophageal candida, 10 (6.5%) Kaposi's sarcoma, 5 (3%) atypical mycobacteriosis, 3 (2%) disseminated tuberculosis, 4 (2.5%) cerebral toxoplasmosis, 5 (3%) AIDS dementia complex, 3 (2%) lymphoma, 13 (8%) more than one opportunistic infections and 7 (5%) other opportunistic infections such as cytomegalovirus (CMV), herpes simplex virus (HSV) and progressive multi focal leucoencephalopathy (PML).

149 members of the cohort (24%) died during the period of follow-up; 97 (65%) of the deaths were considered to be AIDS deaths and a further 19 (13%) were as a result of medical conditions which occurred before the patient formally satisfied a diagnosis of AIDS. A number of deaths 21 (14%) were caused by drugs overdose and 12 (8%) of the deaths were from causes as yet undetermined.

Table 14.1: Clinical endpoints for cohort

Year	Deaths	AIDS cases	*Enrolments at AIDS*	*%*	CDC stage IV	*Enrolments at CDC IV*	*%*	CD200	*Enrolments at CD200*	*%*
1984	1	1	*1*		1	*1*		1	*1*	
1985	0	2	*2*		5	*5*		2	*2*	
1986	4	2	*0*		9	*7*		11	*2*	
1987	7	11	*7*	*8*	32	*18*	*5*	24	*11*	*4*
1988	9	18	*13*	*7*	50	*21*	*4*	44	*19*	*4*
1989	14	33	*14*	*4*	74	*32*	*4*	66	*29*	*4*
1990	29	32	*10*	*3*	64	*19*	*3*	59	*21*	*3*
1991	46	33	*7*	*2*	63	*21*	*3*	74	*24*	*3*
1992	39	22	*5*	*2*	51	*14*	*2*	35	*11*	*3*
Total	149	154	*59*	*3*	349	*138*	*4*	316	*120*	*3*

Enrolment Pattern

An enrolment CD4 count was available for 563 patients in the cohort. Regression analysis (table 14.2) showed gender, risk group, age and enrolment year effects on initial presentation at the clinic: women enrolled earlier in their HIV disease than men; homosexuals enrolled later than IDUs; younger adults enrolled earlier than older adults and enrolments in recent years were at a much more advanced point than enrolments in the early years of the cohort. This is consistent with the fact that the cohort was initially made up from a group of young IDUs enrolled shortly after the Edinburgh epidemic first became apparent.

Table 14.2: Regression of root of enrolment CD4 count on cofactors

Cofactor	Number	Coefficient	Std. error	t-statistic	p-value
Intercept	NA	21.4	0.9	NA	NA
Female	172	2.3	0.7	3.2	**0.00**
Homosexual	81	-4.2	0.9	-4.6	**0.00**
Heterosexual	76	-1.2	0.9	-1.3	0.19
Age < 25	171	1.4	0.8	1.9	**0.06**
Aged in 30s	168	-0.5	0.7	-0.7	0.47
Aged in 40s	39	-2.6	1.3	-2.0	**0.04**
Enrolled 87	107	-0.7	1.0	-0.7	0.49
Enrolled 88	102	-2.9	1.0	-2.9	**0.00**
Enrolled 89	106	-4.6	1.0	-4.6	**0.00**
Enrolled 90	61	-5.4	1.2	-4.6	**0.00**
Enrolled 91-92	92	-7.2	1.1	-6.6	**0.00**

N = 563; R-square = 0.26; F statistic = 17.8 on 11,551 df; p = 0.00.

Progression from enrolment

Progression rates to AIDS, CDC stage IV and CD200 at five years (figure 14.1 and table 14.3) were 36% (SE 2.8), 74% (2.5) and 67% (2.7). The mortality rate from enrolment was 33% (2.6). Progression rates in the IDUs alone were lower; at five years the rates to AIDS, CDC IV and CD200 were 28% (2.8), 71% (3.0) and 63%(2.7) and the mortality rate was 28% (2.8). In the IDUs the mortality rate exceeded the AIDS rate four years after enrolment; overdoses and non-AIDS deaths may account for this phenomenon.

367 patients were included in the analyses of progression to CDC stage IV of whom 177 were diagnosed with the endpoint; the AIDS analysis included 375 patients, of whom 49 progressed to AIDS; the analyses of mortality post-enrolment included 506 patients of whom 126 died. Larger risk sets were possible for the more advanced endpoints because there was more chance of finding baseline marker measurements between enrolment and endpoint.

Figure 14.1: Kaplan Meier Plot of Progression to AIDS, CDC stage IV and CD200

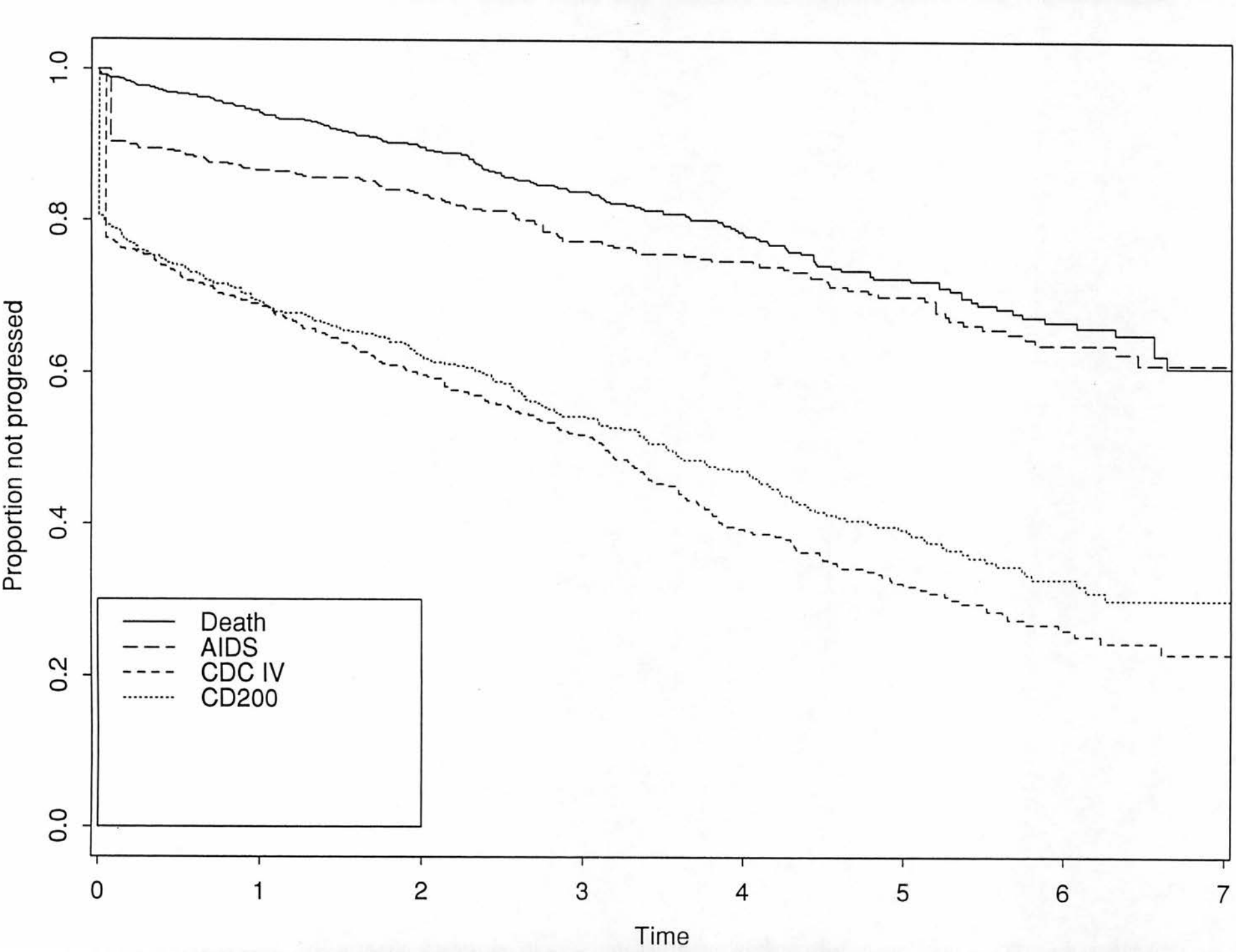
Proportion not progressed
0.0
0.2
0.4
0.6
0.8
1.0
Death
AIDS
CDC IV
CD200
0
1
2
3
4
5
6
7
Time

Table 14.3: Progression and mortality rates from enrolment for whole cohort and IDUs only

Endpoint (median survival *)	Year	Risk Set		Cumulative cases		Cumulative rate %		SE %	
Death	1	554	*409*	35	*18*	5.7	*4.2*	0.9	*1.0*
	2	468	*372*	60	*29*	10.3	*6.8*	1.3	*1.2*
	3	394	*318*	89	*48*	16.1	*11.9*	1.6	*1.6*
	4	285	*241*	112	*65*	21.7	*17.1*	1.9	*2.0*
	5	210	*183*	131	*78*	27.5	*22.1*	2.1	*2.3*
(3.8yrs)	6	107	*101*	143	*88*	33.3	*27.8*	2.6	*2.8*
AIDS	1	443	*357*	80	*20*	13.3	*4.8*	1.4	*1.0*
	2	364	*303*	95	*29*	16.6	*7.4*	1.6	*1.3*
	3	304	*257*	120	*48*	22.7	*13.5*	1.9	*1.8*
	4	237	*210*	129	*53*	25.3	*15.3*	2.0	*2.0*
	5	160	*144*	141	*64*	29.9	*20.7*	2.3	*2.4*
(2.8yrs)	6	90	*85*	152	*74*	36.3	*27.8*	2.8	*3.1*
CDC IV	1	361	*295*	188	97	31.2	*22.9*	1.9	*2.0*
	2	277	*226*	233	135	40.3	*33.4*	2.1	*2.4*
	3	211	*180*	267	*162*	48.2	*41.8*	2.2	*2.6*
	4	132	*115*	313	*202*	60.6	*55.9*	2.3	*2.8*
	5	77	*69*	334	*220*	68.1	*64.0*	2.4	*2.8*
(1.6yrs)	6	36	*35*	345	*231*	73.9	*71.0*	2.5	*3.0*
CD200	1	358	*296*	183	*91*	30.7	*21.7*	1.9	*2.0*
	2	281	*234*	218	*119*	38.0	*29.7*	2.1	*2.3*
	3	226	*192*	251	*144*	45.7	*37.6*	2.2	*2.5*
	4	158	*139*	278	*168*	52.9	*46.0*	2.3	*2.7*
	5	96	*87*	300	*188*	60.6	*55.0*	2.5	*2.9*
(1.6yrs)	6	55	*53*	313	*201*	67.2	63.1	2.7	*3.1*

NB figures for whole cohort in ordinary type; for IDUs alone in *reduced italicised* type . *median of observed and censored survival times

In all analyses (table 14.4) significant risk group effects emerged with homosexual men appearing to progress more quickly than IDUs. Relative risks were 2.9 ($p = 0.00$), 2.5 ($p = 0.01$) and 1.5 ($p = 0.1$) for progression from enrolment to CDC stage IV, AIDS and death respectively. Heterosexuals appeared to progress more slowly than IDUs and homosexuals with relative risks of 0.5 ($p = 0.02$), 0.4 ($p = 0.14$) and 0.4 ($p = 0.05$) for the three endpoints. There was no apparent gender effect and no pronounced age effects although the young (aged less than 25) appeared to progress significantly more slowly to AIDS (RR 0.4, $p = 0.00$). Calendar year effects were apparent in the analysis of mortality but in no other models. Enrolments in recent years seem to have died significantly more quickly, despite the fact that the analysis was controlled for CD4 count and IgA as well as other cofactors.

Table 14.4: Cofactor effects on progression from enrolment to CDC stage IV, AIDS and death

	CDC Stage IV N = 367				AIDS N = 435				Death N = 506			
Group	N	Cases	RR*	CI	N	Cases	RR*	CI	N	Cases	RR*	CI
Female	134	61	1.0	0.7-1.5	145	15	0.7	0.4-1.3	159	23	0.8	0.5-1.3
Male	233	116	1	Baseline	290	59	1	Baseline	347	99	1	Baseline
Homosexual	20	16	**2.9**	1.7-5.0	36	17	**2.5**	1.3-4.8	71	36	**1.5**	0.9-2.4
Heterosexual	52	12	**0.5**	0.2-0.9	59	3	0.4	0.1-1.4	68	4	**0.4**	0.1-1.0
Other risk	295	149	1	Baseline	340	54	1	Baseline	367	82	1	Baseline
Age < 25 (young)	134	64	1.0	0.7-1.4	148	11	**0.4**	0.2-0.7	161	26	0.7	0.5-1.2
Age 35+ (old)	53	21	0.8	0.5-1.3	69	16	0.9	0.5-1.6	90	29	1.1	0.7-1.7
Age 25-35	180	92	1	Baseline	218	47	1	Baseline	255	67	1	Baseline
Enrolled 90-92	67	18	1.5	0.8-2.6	100	14	1.9	0.8-4.2	122	20	**2.0**	1.0-4.0
Enrolled 88-89	133	60	1.0	0.7-1.5	157	22	0.8	0.5-1.5	194	55	1.4	0.9-2.3
Enrolled 84-87	167		1	Baseline	178	38	1	Baseline	190	47	1	Baseline

* Relative risk adjusted for other cofactors plus baseline CD4 count and IgA. **Bold** figures indicate significant and marginally significant associations ($p < 0.1$) with progression

Survival from diagnoses

Three year survival rates (figure 14.2 and table 14.5) post AIDS, CDC stage IV and CD200 were 25% (SE 4.3), 61% (3.3) and 58% (3.5) respectively. Equivalent rates in the IDUs alone were higher at 34% (6.3), 70% (3.7) and 64% (4.2).

Figure 14.2: Kaplan Meier Plot of Survival from Progression to AIDS, CDC stage IV and CD200

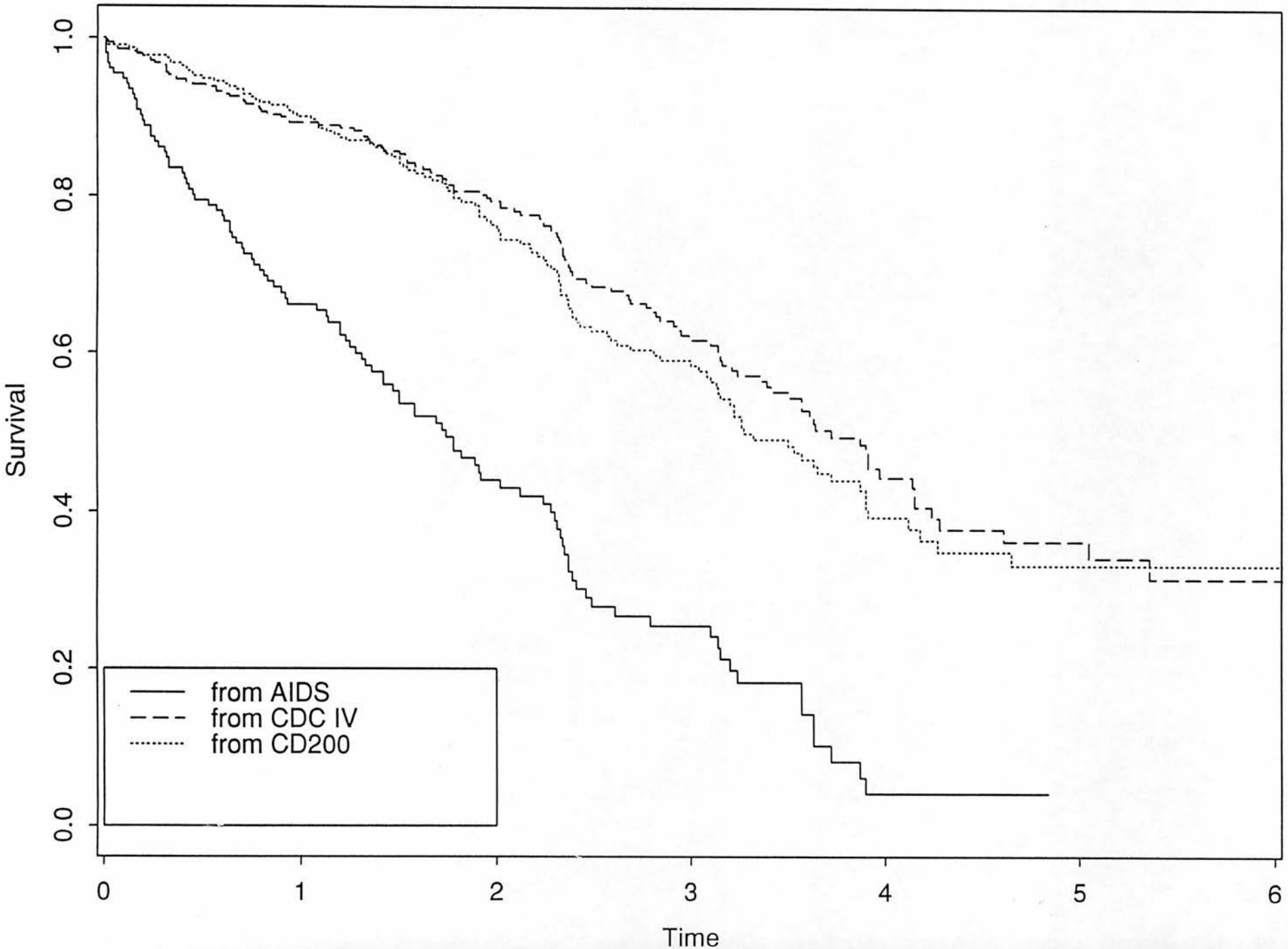
Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
6
Time
from AIDS
from CDC IV
from CD200

Table 14.5: Survival from AIDS, CDC stage IV and CD200

Survival from	Year	Risk set		Cumulative deaths (all causes)		Survival rate %		SE %	
AIDS	1	89	*43*	50	*27*	66.1	*62.9*	3.9	*5.7*
	2	48	*23*	77	*40*	43.9	*42.1*	4.4	*6.1*
	3	21	*9*	94	*47*	25.4	*33.8*	4.3	*6.3*
CDC IV	1	269	*187*	35	*19*	89.3	*91.4*	1.7	*1.9*
	2	187	*142*	61	*32*	79.4	*84.2*	2.4	*2.6*
	3	101	*79*	96	*51*	61.1	*69.7*	3.3	*3.7*
	4	38	*40*	118	*65*	44.3	*54.5*	4.0	*4.7*
CD200	1	253	*171*	30	*12*	90.1	*93.9*	1.7	*1.7*
	2	155	*112*	62	*29*	76.4	*82.9*	2.7	*2.9*
	3	87	*64*	94	*50*	58.4	*64.5*	3.5	*4.2*
	4	35	*30*	117	*64*	39.3	*47.7*	4.1	*5.1*

*figures for whole cohort in ordinary type; for IDUs alone in *reduced italicised* type

No gender effect (table 14.6) on survival from any of the three diagnoses was found. Homosexuals appeared to experience higher mortality after the two earlier diagnoses with relative risks of 1.8 ($p = 0.02$) for CDC stage IV and 1.6 ($p = 0.05$) for CD200. Heterosexuals showed poorer survival from CDC IV (RR 2.2, $p = 0.02$); however there were no risk group differences in survival from AIDS.

An age effect was found with men diagnosed with any diagnosis in their 40s showing poorer survival; relative risks of 1.6 ($p = 0.09$), 1.9 ($p = 0.03$) and 1.9 ($p = 0.04$) for survival from CD200, CDC IV and AIDS respectively. No statistically significant effect of year of diagnosis was found.

Table 14.6: Cofactor effects on survival from CD200, CDC stage IV and AIDS

	CD200 N = 316, deaths = 121				CDC IV N = 349, deaths = 126				AIDS N = 154, deaths = 106			
Group	N	Deaths	RR*	CI	N	Deaths	RR*	CI	N	Deaths	RR*	CI
Female	78	21	0.8	0.4-1.3	93	23	0.8	0.5-1.4	29	17	0.9	0.5-1.7
Male	238	100	1	Baseline	256	103	1	Baseline	125	89	1	Baseline
Homosexual	70	43	**1.8**	1.1-2.8	77	43	**1.6**	1.0-2.5	59	43	1.0	0.6-1.7
Heterosexual	38	11	1.6	0.8-3.2	34	11	**2.2**	1.1-4.4	18	10	1.0	0.5-2.2
Other risk	208	67	1	Baseline	238	72	1	Baseline	77	53	1	Baseline
Age in 40s at diagnosis	40	23	**1.6**	0.9-2.7	35	20	**1.9**	1.1-3.3	26	22	**1.9**	1.0-3.4
Age in 30s at diagnosis	126	45	1.1	0.7-1.6	124	47	1.3	0.9-2.0	67	44	1.2	0.8-1.9
Age < 30 at diagnosis	150	53	1	Baseline	190	59	1	Baseline	61	40	1	Baseline
Diagnosed 91-92	109	10	0.7	0.3-1.5	114	13	1.0	0.5-1.9	55	24	1.0	0.5-1.9
Diagnosed 89-90	125	58	1.1	0.8-1.7	138	49	0.9	0.6-1.4	65	49	0.8	0.5-1.5
Diagnosed 84-88	82	53	1	Baseline	97	64	1	Baseline	34	33	1	Baseline
AZT before diagnosis	87	28	**2.3**	1.2-4.4	87	21	1.7	0.9-3.3	77	56	1.2	0.6-2.4
AZT after diagnosis	177	78	**1.7**	1.0-3.1	197	86	**1.7**	1.0-2.8	55	37	**0.5**	0.3-1.1
No AZT	52	15	1	Baseline	65	19	1	Baseline	22	13	1	Baseline
Enrol at diagnosis	87	28	1.4	0.9-2.1	138	67	1.3	0.9-2.0	59	38	**0.5**	0.3-0.8
Enrol before diagnosis	229	93	1	Baseline	211	59	1	Baseline	95	68	1	Baseline

* Relative risks adjusted for other cofactors. Bold figures indicate significant and marginally significant associations ($p < 0.1$) with survival

For patients treated with zidovudine after an AIDS diagnosis, survival post-AIDS was marginally significantly lengthened (RR 0.5, $p = 0.08$). However, for patients treated with zidovudine after CD200 and CDC IV diagnoses, survival post-diagnosis was significantly shorter which probably merely shows an administration bias toward the sicker patients in the use of zidovudine (table 14.7). Also, patients treated with zidovudine before CD200 showed higher mortality post CD200 than untreated patients. This may also show administration bias to the sicker or it may show a postponement of the CD200 diagnosis due to prior treatment with zidovudine appearing as a shortening of survival after the diagnosis.

Moreover patients diagnosed with AIDS at the enrolment visit showed better post-AIDS survival than patients diagnosed at a later point in follow-up. This may again be caused by a postponed AIDS diagnosis for patients enjoying prior health care and or different AIDS defining events for those enrolling in clinical care.

Zidovudine Therapy

Zidovudine treatment was commenced in 379 patients (61%) although 17 subsequently came off the drug within 100 days and 48 came of the drug within a year. In total, 95 patients (25% of those commencing) have elected to stop taking zidovudine.

The proportion of eligible patients taking the drug in each of the three most advanced disease stages of table 14.7 (CD4 = 200-499 & non-AIDS, CD4 < 200 & non-AIDS, AIDS) increased steadily over the years 1987 to 1992. In the years 1990-1992 a great many patients in the first two of these bands commenced the drug. Only one patient categorised as having CD4 greater than 500 commenced the drug so that recipients of zidovudine were almost entirely immunodeficient.

Table 14.7: Use of zidovudine 1987 - 1992

Disease stage	AZT status	Number of cases in each category in											
		1987	%	1988	%	1989	%	1990	%	1991	%	1992	%
*CD4 ≥500+	Already on AZT	0		0		0		0		0		0	
	Newly on AZT	0		0		0		1	*3*	0		0	
	Not yet on AZT	57	*100*	52	*100*	33	*100*	31	*97*	16	*100*	5	*100*
	Total	**57**		**52**		**33**		**32**		**16**		**5**	
*CD4=200-499	Already on AZT	0		3	*2*	5	*3*	14	*8*	34	*22*	57	*42*
	Newly on AZT	2	*2*	2	*2*	16	*9*	33	*20*	35	*22*	11	*8*
	Not yet on AZT	93	*98*	128	*96*	156	*88*	121	*72*	87	*56*	69	*50*
	Total	**95**		**133**		**177**		**168**		**156**		**137**	
*CD4 ≤ 200	Already on AZT	0		9	*13*	21	*20*	37	*29*	80	*48*	120	*68*
	Newly on AZT	11	*31*	21	*30*	27	*25*	53	*42*	53	*32*	21	*12*
	Not yet on AZT	25	*69*	41	*57*	58	*55*	36	*29*	34	*20*	36	*20*
	Total	**36**		**71**		**106**		**126**		**167**		**177**	
AIDS	Already on AZT	0		7	*32*	23	*49*	41	*69*	35	*67*	35	*73*
	Newly on AZT	2	*20*	12	*55*	21	*45*	14	*24*	9	*17*	3	*6*
	Not yet on AZT	8	*80*	3	*13*	3	*6*	4	*7*	8	*16*	10	*21*
	Total	**10**		**22**		**47**		**59**		**52**		**48**	

Only patients alive in each year are included in the counts. *Immunological staging for non-AIDS cases only

Slopes of CD4 Loss

361 patients had ten or more CD4 determinations with which to calculate rates of CD4 decline. The mean rate of cell loss per year was 58; the median was 49; the 90% range was (-15,146) showing that a number of patients appeared to be gaining CD4 in the period for which measurements were available. When slopes were calculated by regression on the root scale the mean rate of loss per year was 2.1; the median was 1.6; the 90% range was (-0.4,5.5).

A regression of these slopes against cofactors showed significantly faster immune decay in homosexuals and in patients aged in their 40s at enrolment (table 14.8). It also showed significantly shallower slopes in enrolments in the most recent calendar years 1989-1992 which may show that people with the fast trajectories came in before 1989 and those enrolling more recently may be on slower trajectories, although they may still be at a later immunological point than the earlier enrolments as the enrolment analysis seemed to suggest. Or there may have been an ascertainment bias in the selection of patients from recent years for inclusion in this analysis whereby patients who obtained ten CD4 counts quickly (and were thus included) were patients receiving zidovudine and being closely monitored; such patients might show shallow slopes in response to treatment.

Table 14.8: Regression of slope of root CD4 decay on cofactors

Cofactor	Number	Co-efficient	Std. error	t-statistic	p-value
Intercept	NA	2.14	0.29	NA	**0.00**
Female	126	0.02	0.25	0.1	0.92
Homosexual	48	2.17	0.37	5.9	**0.00**
Heterosexual	34	-0.21	0.41	-0.5	0.61
Age < 25	126	-0.07	0.28	-0.3	0.79
Aged in 30s	100	-0.09	0.29	-0.3	0.76
Aged in 40s	21	1.31	0.52	2.5	**0.01**
Enrolled 87	87	-0.10	0.31	-0.3	0.75
Enrolled 88	66	-0.23	0.34	-0.7	0.50
Enrolled 89	67	-0.71	0.34	-2.1	**0.04**
Enrolled 90	27	-1.11	0.47	-2.4	**0.02**
Enrolled 91-92	17	-2.03	0.58	-3.5	**0.00**

N = 361; R-square = 0.17; F statistic = 6.47 on 11,349 df; p = 0.00.

Discussion

Methodological issues

There are important methodological considerations in documenting progression in a prevalent cohort i.e. one made up of individuals infected for varying lengths of time and recruited over time. These arise from the fact that clinical enrolment is not a meaningful event in the natural history of the disease but is rather an event which occurs after some unknown prior duration of infection which differs from individual to individual. These circumstances mean that it is difficult to make useful comparisons of progression from enrolment rates between cohorts and it is also difficult to assess cofactor effects on progression within a cohort because cofactors may be associated with different duration's of infection at enrolment. This latter problem is known as onset confounding and is the most serious of three potential biases in the assessment of cofactors in prevalent cohorts described by Brookmeyer and Gail [6].

In this analysis an attempt was made to extract as much information as possible about progression from a prevalent cohort. This was done by first seeking to understand the enrolment pattern in the cohort through a regression of root enrolment CD4 count against cofactors. This approach to analysis confirmed suspicions that there were great differences between typical enrolment times in different sections of the cohort. Thus for instance, homosexual men were found to enrol late in their HIV disease as compared to drug users which was consistent with the fact that the cohort was initially formed from a targeted group of IDUs who were known to be at risk.

Having verified that enrolment differences existed in the cohort an attempt was made to control for this in an analysis of cofactor effects on progression through the use of baseline CD4 count and IgA as surrogates for duration of infection. These two markers are well known to be powerful markers of disease progression[7,8]. While this method may not be the most desirable way of showing cofactor effects on disease progression it is one way of using the large volume of information that was available to obtain indications of the phenomena which were occurring. Verification of these results requires an analysis of progression from seroconversion in the 309 patients for whom accurate estimates of infection time are possible (although these patients are mainly a more homogeneous set of drug-users infected close to the start of the epidemic). This forms the subject of the next chapter.

The analysis of survival post-diagnosis of AIDS, CDC IV and CD200 was not affected by the use of a prevalent cohort and the results are likely to be generalizable, particularly in view of the careful censoring scheme applied in an attempt to minimise the effects of patients becoming lost-to-follow-up[9].

This analysis also undertakes a brief and preliminary investigation of immunological progression. Although some estimates of slope are erratic, due to the volatile nature of CD4[10], the results of this analysis are in agreement with the analysis of clinical progression in their suggestion that the homosexual men progress much more quickly than the IDUs. An analysis of CD4 slope, progression in HIV disease and their association with HLA haplotypes has been undertaken and is presented in detail in a Chapter 15[11]. In that analysis a more sophisticated but more difficult to fit random effects growth curve model was used to estimate slopes.

An exhaustive analysis of zidovudine effects was not made on progression instead the usage of the drug in the cohort was documented in order to look at possible effects on post-diagnosis survival. An analysis of progression from seroconversion is considered in Chapter 14 together with the question of beneficial effects of zidovudine on total survival or total AIDS-free time.

The Edinburgh cohort

The Edinburgh cohort of HIV patients has a number of unique features that make it worthy of study including a known start to the epidemic[4], detection of the epidemic within 2 years[1], a high proportion of women and a relatively homogenous and stable population. In addition, despite being largely composed of patients who acquired the infection via injection drug use there has been good clinical and immunological follow up with a relatively low drop out rate for this risk group[5,12](Chapters 6, table 6.9). The system of flagging defaulters with the Registrar General has provided us with reasonably accurate mortality rates. Since the epidemic was detected only 2.5 years after its onset it is unlikely that a large proportion of the symptomatic patients would have died without coming to the attention of the RIDU[1,3,13,14].

Progression to AIDS and CD200

Currently few cofactors for progression to AIDS among HIV infected individuals have been identified. An extensive review of progression from HIV to AIDS in cohorts of various risk groups with known seroconversion dates revealed rates of progression of 0-2% at 2 years, 5-10% at 4 years, 10-25% at 6 years, 30-40% at 8

years and 48% at 10 years[15]. Updated data on the San Francisco City Cohort published recently showed a progression rate of 51% by 10 years[16] although a haemophiliac cohort from London revealed a progression rate of 42% at 11 years[17]. The median time for progression to AIDS was initially around 7-10 years but has now risen to 11 years[16]. Despite this information on progression there are still a number of unanswered problems especially since the majority of the well studied cohorts have been based on relatively affluent white homosexual males and there have not been very many descriptions of similar well studied cohorts which include large numbers of injection drug users, heterosexuals or females.

In addition studies do not distinguish between those enrolling with AIDS or symptomatic disease and those developing disease under observation. Whilst one may assume that individuals with AIDS will present quickly to a health service this certainly may not be the case for patients with CDC stage IV disease. In Edinburgh a large percentage of those enrolling in the early years were unwell or symptomatic (Table 14.1); 56% of patients enrolled with symptomatic disease in 1987 but only 33% by 1991. It is likely that different HIV test seeking behaviour or more aggressive contact tracing procedures for drug users over the years might explain this effect.

By the 6th year **after** enrolment in the Edinburgh City Hospital cohort, 74% of the patients had become symptomatic and nearly 36% had developed actual AIDS (Table 14.3). It might be assumed that in the early years these rather high figures had been influenced by an initial influx of asymptomatic homosexuals who were about to become unwell . This was not the case however and the progression for drug users is not that different from the group as a whole with 71% being symptomatic by the 6th year and 28% having already progressed to AIDS. By comparison a 3 year follow up in San Francisco revealed progression to AIDS of only 22% and to AIDS or ARC of 41% after 3 years which is some what lower than our observations[18]. These differences between Edinburgh and San Francisco in the rates of progression from enrolment to symptomatic disease may be because of different ascertainment as a result of differences in the health care system (HIV test seeking behaviour, contact tracing methodology, publicity campaigns, combined medical and drug clinics).

Kaplan-Meier plots for fixed cofactors confirm that progression rates are slower for those under 25 years of age but there was no major difference for risk group or gender for survival from enrolment to an immunological endpoint (CD200), a clinical end point (CDC stage IV or AIDS) or to death for this cohort of mainly drug users

infected between 1983-85. Homosexual men appear to progress faster from enrolment but since they make up a minority of the cohort and the date of infection of homosexuals with HIV in Scotland is less clear, comparisons are more prone to error. It does however tend to confirm the suggestion that sexual transmission of HIV may result in faster progression than injection drug user transmission.

Injection Drug Users

Several reported studies have tried to assess the rate of progression to AIDS amongst drug users although most of these reports like the current report have related the onset of symptoms or AIDS to the length of follow up and not to the duration of HIV infection. Hence figures of progression must be interpreted carefully as differing results may merely reflect differing intervals between infection and the start of the assessment period.

A study of around 300 HIV positive drug users from the Montefiore Methadone Programme, Bronx, New York reported progression rates to AIDS of 16-17% over 2.5-3 years of follow up[19,20]. The results obtained in European studies show similar rates of progression; in a large Spanish survey of 646 IDUs, the actuarial incidence of AIDS was 15% at 3 years, with a similar incidence being found amongst homosexuals[21]. Other smaller scale studies showed an incidence of AIDS of 6-6.5% after 14-18 months and 6-7% after 3 years follow up but with wide confidence intervals[22-26].

The Edinburgh City Hospital cohort data reveals progression rates from enrolment to AIDS of 23% by 3 years, 30% by 5 years and 36% by 6 years of follow up. The progress of the Edinburgh cohort seems closer to the data from the USA when compared to other European data; this may be explained by closer follow up and flagging of defaulters to identify progressions or deaths. Thus Moss et al from San Francisco reported 22% progression to AIDS 3 years after enrolment with a further 19% progressing to ARC[18]. They estimated that this represented an average of 6 years post seroconversion in San Francisco. Whilst the progression rate to AIDS is similar the overall progression rate to CDC stage IV (basically ARC) is higher in Edinburgh at 65% rather than the 41% in San Francisco. The epidemic in Edinburgh occurred between 1983-85 suggesting that 6 years after enrolment perhaps represents Year 8 of HIV infection. The differing rates from enrolment may be explained by the error in determining the date of infection rather than a difference in risk activity.

This will be examined in more detail in Chapter 14 when considering the sub group in Edinburgh with a known date of seroconversion.

Women

As with injection drug users there are unfortunately not many cohort studies of progression in women. Gender was not reported as a significant factor in a study of progression in 58 male and 18 female Spanish injection drug users[18]. The Swedish blood transfusion study noted shorter progression times for men but this was not statistically significant[19]. The Italian follow up study of drug users with known seroconversion dates contained 127 women and no gender effect on progression was observed[28]. US data are confounded by the poor use of medical care facilities (see section on AIDS) and relatively late presentation to medical care. Despite this, a report on 318 HIV positive drug users followed prospectively via a Methadone Maintenance programme, 147 of whom were female, showed no effect of gender on progression[20].

The RIDU's experience, which may not even reflect the rest of the UK, is that women in Edinburgh present early for treatment. It is difficult to explain the reasons for this difference but it may be related to the close integration of obstetric, paediatric and HIV services in Edinburgh and the mother's concerns over their ability to care for their children. The Edinburgh cohort is made up of a substantial number of women of comparable age and risk activity to men and does not show a gender effect for progression from enrolment to symptomatic disease (CDC stage IV or AIDS).

Although this study and others have failed to demonstrate a major difference between the sexes in the rate of progression from HIV to AIDS, as with drug users, there is concern over whether AIDS accurately reflects the natural history of HIV in women since the initial definition, after all, was based largely on homosexual men. To date in Edinburgh a different spectrum of HIV disease for women has not been found. For instance in a retrospective survey of 612 HIV related admissions there was no excess of female admissions except for detoxification, investigation of episodes of loss of consciousness and urinary tract infections[29]. In addition the lack of an excess mortality for HIV infected women compared to men does not support the argument that the AIDS definition as applied in the UK is a poor reflection of overall time course of female HIV disease.

Age

There is evidence that age at the time of HIV infection is perhaps one of the most important factors affecting progression to AIDS. Studies among individuals infected through blood transfusion[27,30], injection drug use[28,31] and haemophilia[17,32] all suggests an adverse effect of age. In the Swedish transfusion study progression to AIDS at 5.5 years after infection was 48% in those over 60 compared to only 28% between 15 and 60 years of age[27]. In an Italian haemophiliac study after 5.5 years of infection 38% of those over 35 years of age had progressed to AIDS compared to only 19% of those under 35 years of age ($p<0.02$)[33]. There was no difference in the rate of progression however for those above and below 18 years of age. A haemophiliac cohort from the UK reported that age over 25 years had a relative hazard of 5[17]. The progression rate for US haemophiliacs was 5.66/100 person years for those aged 35-70 but only 2.39 for those aged 18-25[32]. An Italian study of IDUs with known dates of seroconversion also noted more rapid progression for those over 25 years of age[28].

This present study also confirms an age effect with a relative hazard of 0.4 (90% CI, 0.2-0.7) for those under 25 years of age progressing to AIDS and 0.7 (90% CI, 0.5-1.2) for overall mortality.

Survival from AIDS

In general without treatment around 50% of patients with AIDS survive one year but only 20% three years[34]. Survival after an immunological end point (CD200) or a clinical end point (AIDS/CDC stage IV) for the group as a whole is better for those under 25 years of age. There was a suggestion of shorter post AIDS survival for women but no significant differences for gender or risk activity.

Injection Drug Users

It is generally assumed that the survival for drug users with AIDS is shorter than other risk groups but a report on 5833 cases of AIDS from New York which adjusted for various factors found no difference between homosexuals and drug users in terms of survival[34]. Injection drug use itself was thought to be an adverse factor, however, since the combination of IDU and homosexuality did lead to a shorter survival. A proportional hazards model showed a significant interaction between IDU and PCP as factors shortening survival[34].

A cohort of 526 patients from a single medical centre in the Bronx, 47% of whom were drug users had a median survival of 12.8 months[35]. Again as with current study drug use was not found to be an adverse factor in survival but in fact it was associated with a more favourable prognosis($p<0.005$). A Spanish study of 289 patients with AIDS revealed a median survival of just over one year (385 days) and again IDU was associated with a more favourable prognosis (median survival; 744 days for drug users vs. 253 days for male homosexuals, $p<0.004$)[36]. In this latter study however, whilst 53% of the patients were injection drug users, 33% of the AIDS cases presented with extra pulmonary tuberculosis which may have a better prognosis than other opportunistic infections. This was not the case in Edinburgh where tuberculosis is an uncommon AIDS diagnosis and the majority AIDS defining condition in IDUs was PCP.

The one year survival rate for the Edinburgh cohort which was largely infected via IDU was 65% which is entirely comparable if not better than published data. In the present analysis as with the study from Spain, age was the most important determining factor for survival and this may explain the differences between the risk groups (see below)[36].

Women

As with IDU, the initial impression based on data from the USA suggested that women had a poorer survival from AIDS than men; significantly more women died at diagnosis of AIDS compared to men in both New York and San Francisco (16% vs. 11% in New York and 5.6% compare to 1.7% in San Francisco, $p<0.01$)[34,37]. Women were at greater risk of respiratory failure with PCP as well as having a two fold increase in mortality compared to a matched group of men[38]. In New Jersey amongst 345 women, 95% of whom were Black and 63% drug users, the mean survival for women was only 14.5 weeks[39]. Overall the prognosis for women from the USA does seems to be poorer since in the New York series the cumulative probability of survival at one year was 75.4% for white males with KS but only 37% for Black, female drug users with PCP[34]. A follow up study of patients in a MMTP in the Bronx presenting with PCP also noted better survival for males with a relative hazard of 0.59[35].

This reduced survival may well however be related to access to medical services rather than gender since those studies with good access to care have shown women to have equivalent if not better survival. A series of 24 women, all white from Rhode

Island had a mean length of survival of 19 months[40]. Survival analysis of 4323 patients with AIDS in San Francisco, between July 1981-December 1987 did not confirm a poorer prognosis for women and IDUs[34,37]. Interestingly recent figures from San Francisco for the period July 1981-June 1990 did show a significant difference in survival between men and women[41], the overall median survival was significantly shorter at 11.1 months for women compared to 14.2 months for men ($p<0.01$). When survival was stratified by year there had been a significant improvement for men since 1986 but not so for women ($p<0.01$). However survival for women who had used zidovudine or dideoxydidanosine (DDI) was not significantly shorter than men (20.1 months compared to 24.2). The fact that a significant difference in survival for men and women disappeared when controlled for anti-retroviral drug use, suggests that socio-economic factors, delays in diagnosis, poor utilisation of, or poor access, to medical services are more important than gender[41]. Access to health care would seem to explain much of the differences in studies from the USA where women tend to present late for medical care; for instance in Minnesota two thirds of women with HIV were detected by neonatal screening rather via medical care[42]. It would also appear that use of anti-retroviral therapy may be a surrogate marker for overall utilisation of medical services.

As far as European studies are concerned the Spanish study of 289 patients only contained 43 women but noted a longer survival for women which just fell short of statistical significance (median survival of 436 days for women and 366 days for men)[36]. In a study from France of 1,816 HIV infected patients, 483 women (106 with AIDS) looked at the effect of gender on survival. A comparison was made of incident AIDS cases only (25 women and 103 men) and this showed a median survival of 23.5 months for women and only 13 months for men which yielded a relative risk of 2.7[43]. The European data supports the suggestion that other factors are more important in survival than gender.

Unlike the other European studies and as with the reports from the Bronx, USA the Edinburgh City Hospital cohort analyses gave a suggestion of a shorter post AIDS survival for women drug users but the difference was not significant. Post AIDS survival may be heavily influenced by early or late presentation of patients even when good medical care is available. For instance early presentation to medical services may increase the use of prophylaxis for opportunistic infections thus delaying the diagnosis of AIDS. This may however paradoxically shorten post AIDS survival if there is no reduction of immunological decline. Equally, late presentation

to medical services may result in an AIDS diagnosis with a relatively well preserved immunological state as a consequence of a lack of prophylaxis for the common opportunistic infection and thus a paradoxically prolonged post AIDS survival. The earlier presentation of women to the clinic, with possible earlier use of prophylaxis, may explain the slightly shorter survival post AIDS for women.

The lack of any excess in the overall mortality for HIV infected women compared to men does not support the argument that the AIDS definition as applied in the UK is a poor reflection of female HIV disease.

Age

The large New York study reported by Rothenberg noted an age effect with the median survival of those under 30 years of age being 371 days compared to 300 days for those over 40 years of age[34]. The Spanish study reported median survival for those over 45 years of 135 days and for those under 45 years 625 days ($p<0.0001$)[36]. The Bronx cohort only noted an age effect for men with men under 35 years surviving 3 months longer than men over 35 years[35]. Survival from AIDS in this study is related to age. For instance relative to patients aged 25 or younger, patients aged 26-35 had an adjusted relative risk of 2.2 (90% CI, 1.5-3.3) and patients aged over 35 had a risk of 4.1 (CI, 2.6-6.6).

Survival from CD200

An analysis of survival from the immunological end point of CD200 noted that this was distinct and longer (a 30 month difference in the median survival) than from the 1987 definition of AIDS(Chapter 12 and [44]). It tends to represents survival from symptomatic HIV, whether defined as ARC or CDC stage IV and this is an earlier stage than that represented by the term AIDS. The consecutive definition is also advocated by Hoover et al and has been adopted for the 1993 UK predictions of severe HIV related immunodeficiency[45]. Unfortunately at present there is little if anything in the literature for comparison especially amongst a group predominantly drug user in composition.

Non AIDS related Deaths

There is evidence that, amongst drug users especially, mortality data collected on AIDS cases greatly under represents the toll of serious HIV disease. In New York, Stoneburner reported that amongst narcotic drug users there had been a rapid increase

in both AIDS and non AIDS related deaths such that by 1986, for every AIDS related death in a drug user, there was one other as a consequence of conditions such as tuberculosis, endocarditis and bacterial pneumonia[46]. Similar data have been reported from Europe[47]. More recently this effect was again reported from drug users prospectively followed via a Methadone maintenance programme where 57% of the deaths were attributed to AIDS[20].

The Edinburgh City Hospital cohort data also supports this phenomenon but to a lesser degree than noted in the USA or Europe with only 37% of deaths being non AIDS related. The majority of non AIDS deaths after the development of AIDS were related to hepatitis and in fact hepatitis accounts for 18% of the drug user deaths. By comparison in New York the major cause of non AIDS death was bacterial pneumonia or sepsis and no excess of deaths for liver disease was noted by comparison to HIV negative drug users on the same programme. The absence of a substantial number of deaths in the cohort attributed to bacterial pneumonia or sepsis may be as a consequence of access to primary health care and earlier use of antibiotics. This has been the experience in Amsterdam drug users which noted an increase in morbidity for conditions such a bacterial pneumonia, the relative risk being 4 compared to non infected controls but there was no increase in mortality from these conditions[48]. Paradoxically the excessive non AIDS related mortality for drug users results in little difference between drug users and homosexuals in overall death rate despite a lower progression rate in drug users and shorter survival for homosexuals after AIDS. Overall survival for HIV as opposed to progression rates may well be the same for the two risk groups suggesting perhaps that the majority of non AIDS deaths in drug users are HIV related rather than drug related.

Zidovudine

Zidovudine therapy was commenced in 61% of the patients in this cohort and obviously therefore may have had some effect on outcome . The use of zidovudine was for the most part not randomised (50 patients participated in Concorde[49]) and was a clinical decision made in the light of then currently available evidence of efficacy. Despite the fact that zidovudine use was not via a controlled trial, retrospective observations on its effect in this cohort of patients are a relevant consideration.

For patients treated with zidovudine after an AIDS diagnosis, survival post-AIDS was lengthened (RR 0.5, $p = 0.08$). However, for patients treated with zidovudine

after CD200 and CDC IV diagnoses, survival post-diagnosis was significantly shorter which probably indicates an administration bias toward the sicker patients in the use of zidovudine. It might also be caused by a postponed AIDS diagnosis for patients enjoying prior health care and or different AIDS defining events for those enrolling early or late for clinical care. Also, patients treated with zidovudine before CD200 showed higher mortality post CD200 than untreated patients. This may also show administration bias to the sicker or it may show a postponement of the CD200 diagnosis due to prior treatment with zidovudine appearing as a shortening of survival after the diagnosis.

The phenomenon of a shortened post AIDS survival following treatment with zidovudine has been recently noted by others. An analysis of 6578 European case of AIDS revealed in a proportional hazards model that one of the independent predictors of shortened survival was zidovudine therapy prior to an AIDS diagnosis[50]. This raises the possibility that zidovudine is in fact deleterious for health. However the recent MRC/Inserm Concorde showed no difference in survival or progression depending upon when zidovudine was commenced[49]. There are obvious concerns over conclusions based on the non-randomised use of zidovudine. These concerns are increased in patients with differing lengths of HIV infection and this factor is examined in more detail in the next chapter.

Conclusions

Progression to AIDS or an immunological end point such as CD200 is affected by age but not apparently by having acquired the infection via drug use whether judge by local or international comparisons. Similar effects were noted for survival after the clinical or immunological end points. An analysis of the deaths to date confirms that as noted previously a significant number of HIV patients die before developing AIDS although the magnitude of the effect is not as great as that reported from the USA or Europe. The effect of zidovudine on survival appeared to be equally effective for drug users as for other risk groups.

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CHAPTER 15

Progression of HIV disease in injection-drug-users: a follow-up of the Edinburgh City Hospital IDU seroconverters

Introduction

Many of the published reports on progression relate the onset of symptoms or AIDS to the length of follow up (a prevalent cohort analysis) and not to the duration of HIV infection (an incident cohort analysis). Data from either type of cohort may be influenced by ease of access to medical care. Hence, figures from different type of cohorts must be interpreted carefully as differing results may merely reflect differing intervals between infection and the start of the assessment period. For instance amongst prevalent IDUs cohort's progression rates from enrolment vary from 6% at one year to 25% at 3 years[1-7]. Data from the prevalent cohort in Edinburgh reveals progression rates from enrolment to AIDS of 21% by 3 years, 29% by 5 years and 37% by 6 years of follow up(Chapter 13)[8]. Amongst a recently reported incident IDU cohort there was a 18% progression to AIDS after four years of HIV infection[9].

From within the prevalent cohort, an incident sub-cohort of infections from 1983-1985 in IDUs has been identified and since Edinburgh has a stable, homogenous population with relative ease of access to medical care, the incident progression rates are of relevance. It should be noted that since zidovudine was licensed in 1987 in the UK, access to anti-retroviral therapy has been relatively easy and therefore the data presented here are essentially a treated cohort and reflect the general sequelae of HIV infection when patients have good access to medical care.

Methods

Study Setting and Design

The voluntary self referral HIV clinic (Chapter 5), the subsequent HIV medical clinics (Chapter 7) and the recruitment of the Edinburgh City Hospital cohort (624 seropositives at 31st December 1992) have been described previously as has the enrolment, progression and survival characteristics(Chapter 14)[8].

Retrospective testing of stored sera and knowledge of injecting behaviour provided accurate estimates of seroconversion times for 309 patients. From stored sera one patient was retrospectively found to have seroconverted for HIV in January 1983 soon after returning from Southern Europe[10] (and Chapter 4). This is the earliest

known date for an injection drug user in Edinburgh to have seroconverted for HIV. This individual went on to share with other known Edinburgh based injection drug users, who are now known to have seroconverted for HIV later in 1983 .

The 309 patients with accurate seroconversion estimates fell into four categories (figure 15.1): (1) those experiencing a seroconversion illness (13 patients); (2) those with negative and positive HIV tests not more than two years apart (95 patients); (3) those with positive tests not more than two years after the estimated epidemic start in January 1983 (169) and (4) those whose drug injecting behaviour during the epidemic was sufficiently well known to allow accurate estimates of seroconversion (32). For interval estimates, the seroconversion time was taken as the midpoint so that such estimates were subject to a year's error at most. 276 of 309 patients were IDUs; 10 were homo/bisexuals, 20 were heterosexuals and three were infected by blood products (figure 15.2).

Attention was focused on the 260 IDUs who were infected in 1983 to 1985, of whom 61 had negative and positive tests, 168 had positive tests within two years of 1st January 1983 and 31 had seroconversions estimated by knowledge of their injecting behaviour; no patients in the study group had observed seroconversion illness. These patients (the Edinburgh City Hospital IDU seroconverters) were believed to form a homogeneous group. Prior evidence emerged from an analysis of progression from enrolment that heterosexuals and particularly homosexuals might have quite different progression characteristics to the IDUs in the Edinburgh City Hospital Cohort[8].

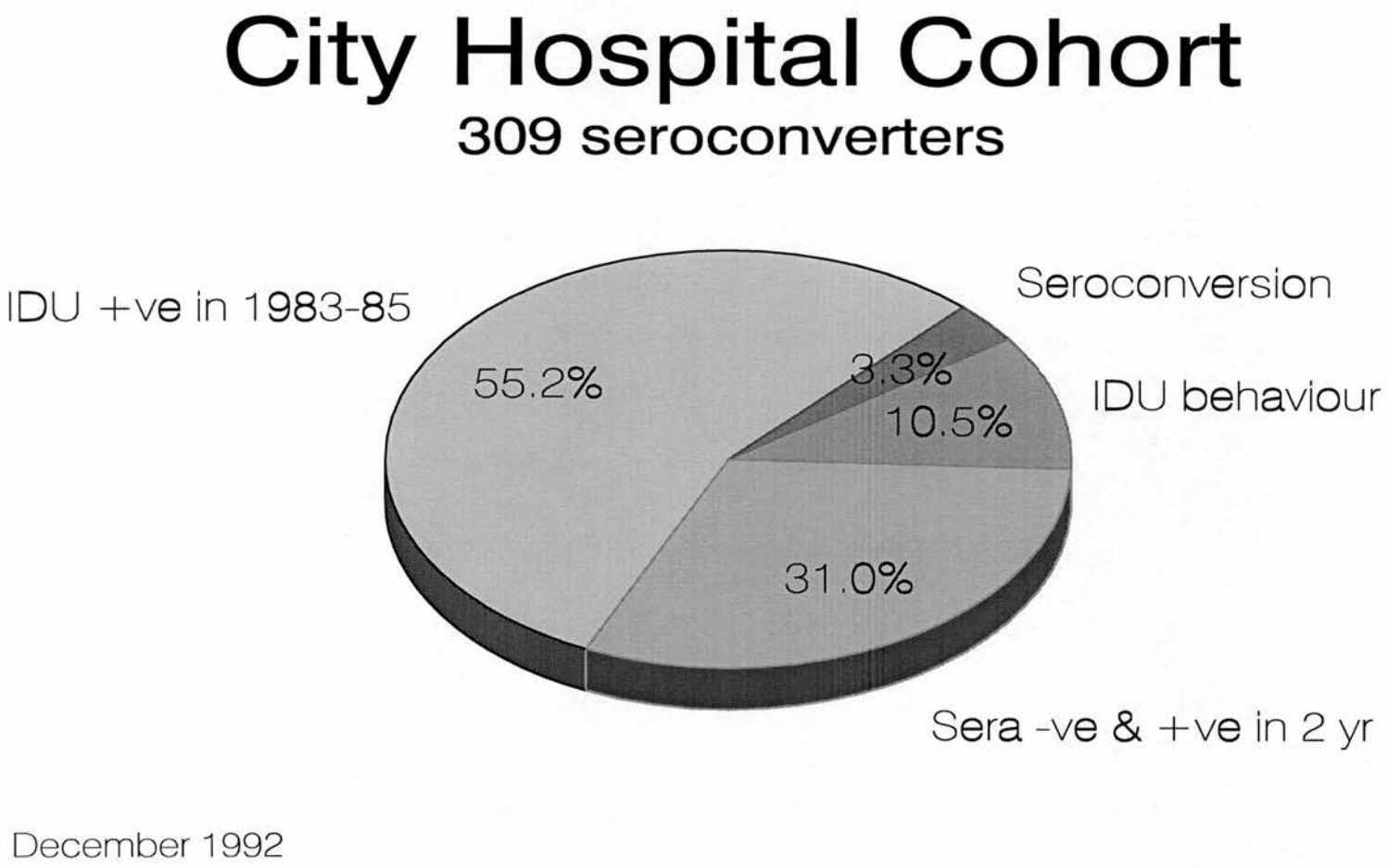


Figure 15.1: Frequency of the different methods of determining the length of HIV infection in 309 seroconverters

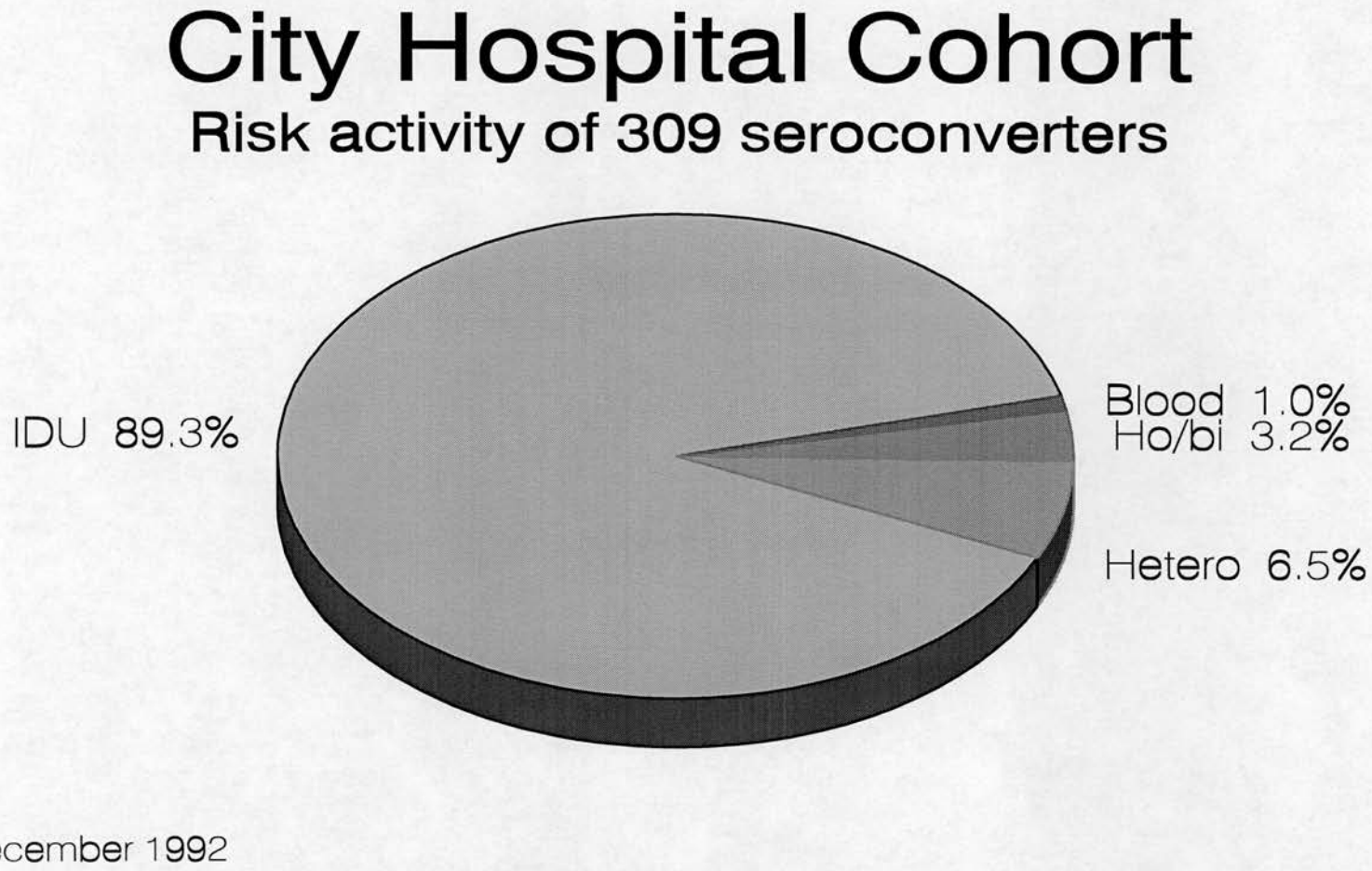


Figure 15.2: Risk activity of the 309 seroconverters

Laboratory Methods

The methods employed in the measurement of lymphocyte surface markers including the CD4 count were as described in Chapter 13 whilst the method of estimating serum IgA levels was as described in Chapter 14. HLA typing was by a standard two-stage complement-dependent microlymphocytotoxicity technique[10].

Statistical Methods

Progression rates to Centers for Disease Control (CDC) stage IV, AIDS and CD200 were calculated using the Kaplan Meier method. The definitions of CD200 and the censoring methods were as described in Chapter 13. Mortality rates were calculated from enrolment and survival was tabulated from AIDS, CDC stage IV and CD200 diagnoses, again by the Kaplan Meier method. Mortality from all causes, including drugs overdose, was included in the endpoint definition.

The effect of fixed covariates age, gender, method of determination of seroconversion and HLA type A1-B8-DR3 on progression were analysed using the Cox proportional hazards model; endpoints of AIDS, CDC stage IV, CD200 and mortality from all causes were considered. For endpoints of AIDS, CDC IV and death a further analysis was performed assessing the effect of early and late AZT treatment (before and after CD4 levels of 200 and 100) through the use of binary switch covariates in the Cox proportional hazards model. CD4 level at intervention was taken as the nearest CD4 count to the start of treatment.

Parametric estimates of the AIDS incubation distribution and the total survival distribution for the Edinburgh IDUs (including the effect of treatment) were derived by fitting Weibull and generalised gamma regression models in SAS. (The generalised gamma model is a three parameter model which contains the familiar gamma and Weibull distributions as special cases.) Fitted Weibull curves were compared with the survival functions previously estimated by the Kaplan Meier method.

Patients with ten or more serial CD4 determinations were assigned a rate of root CD4 loss from linear regressions of CD4 count against time on the root scale. Covariate effects on rate of CD4 loss were investigated through a regression model.

Results

Cohort Description

The 260 IDU seroconverters who formed the IDU seroconverter sub cohort included 82 women (32%); the mean age at seroconversion was 22 years (SD 4.8); 198 patients (76%) were younger than 25 and only three were older than 35. The numbers estimated to be infected in the years 1983 to 1985 were 218 (84%), 34 (13%) and eight. 168 (65%) commenced courses of zidovudine at some time although 40 (24%) eventually came off the drug, 20 within a year. The numbers enrolling each year from 1984 to 1992 were respectively three, 13, 66, 54, 43, 48, 19, 11 and three.

There were 5233 visits made to the clinic at which **laboratory monitoring** was undertaken for an average of 20 visits per person (SD 14.2). 218 patients (84%) had more than five visits; 186 (72%) had more than ten, 116 (45%) had more than 20 and 56 (22%) had more than 30. If follow-up time is defined as the time between first and last clinic visits them the mean period of follow-up was 3.9 years (SD 2.1). 205 (79%) patients had more than two years of follow-up, 127 (49%) had more than four and 53 (20%) had more than six. 40 (15%) patients were considered lost-to-follow-up at 31st December 1992, since they had not been seen for a year and were believed to be still alive. However it was noted in Chapter 13 that many patients return to the clinic after gaps of longer than a year.

During the period of follow-up, 45 members of the seroconverter cohort (17%) received a diagnosis of AIDS and 146 (56%) received a CDC stage IV diagnosis. There were 59 (23%) deaths of which 28 (47%) were AIDS deaths, 11 (20%) were for medical reasons before a formal AIDS diagnosis, 13 (22%) resulted from overdoses and seven were from causes as yet undetermined. 129 cohort members received a CD200 diagnosis.

Progression and Mortality Rates

The estimated cumulative progression rate to AIDS at nine years was 19% (SE. 2.6) (table 15.1 and figure 15.3). The estimated cumulative mortality rate at nine years was also 19% (SE. 2.5). However the mortality curve appeared to overtake the AIDS curve in the tenth year post-seroconversion, showing the effect of a great deal of excess mortality from overdoses and non-AIDS medical causes before an AIDS diagnosis could be given. It is probable that this heavy censoring due to deaths before AIDS in patients experiencing advanced immunodeficiency violates the assumption

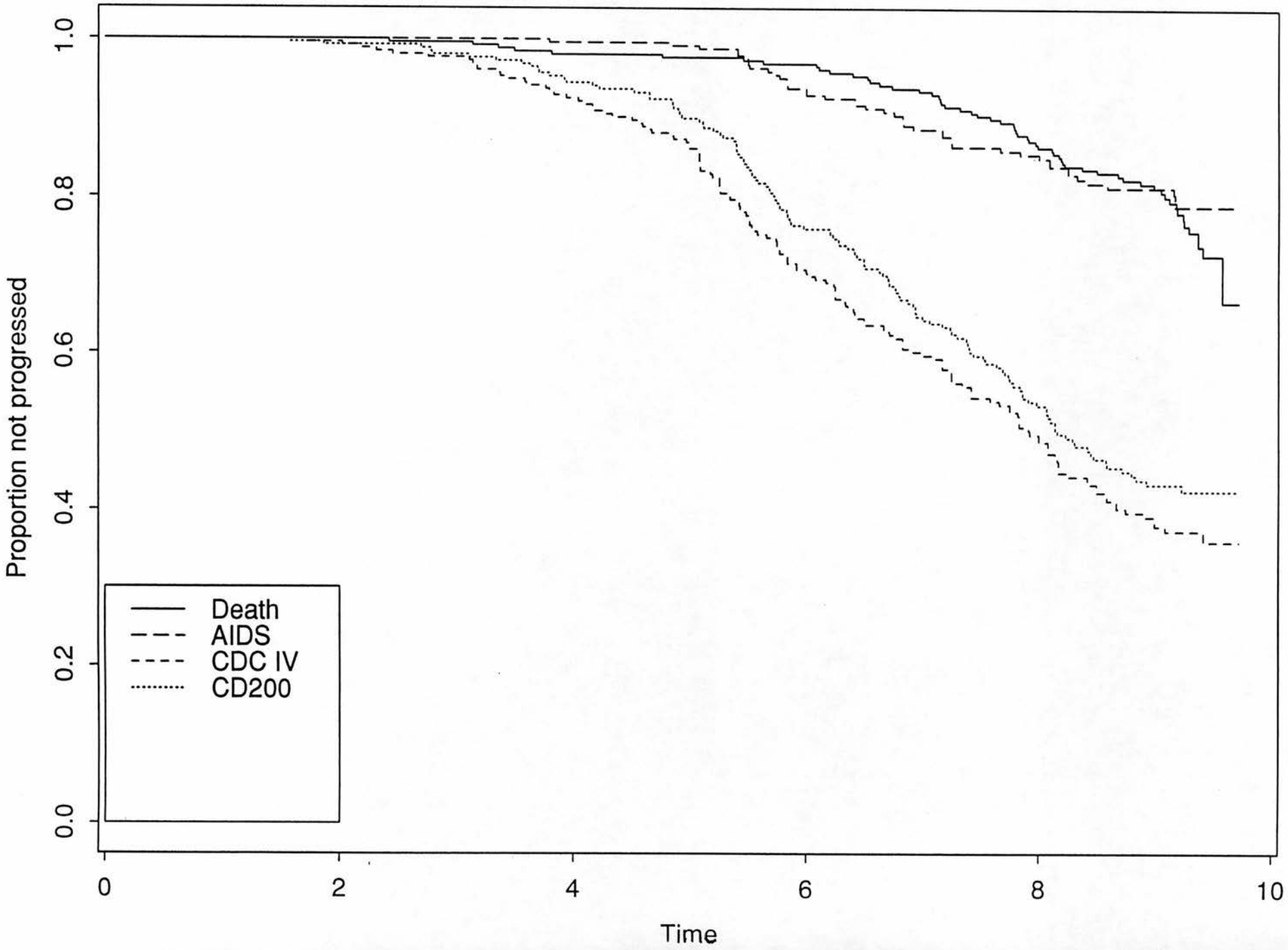
of independent censoring which survival analysis makes, and causes the AIDS rate to be underestimated.

The nine year CDC IV and CD200 rates were 62% (SE. 3.3) and 57 % (SE. 3.4); the CD200 curve lay between the AIDS and CDC stage IV curves but followed the CDC stage IV more closely.

Table 15.1: Progression and mortality rates for Edinburgh City Hospital IDU seroconverters

Endpoint (Median progression)	Year	Risk Set	Cumulative cases	Cumulative rate %	SE %
Death (9.1 years)	5	255	6	2.3	0.9
	6	253	8	3.1	1.1
	7	244	17	6.5	1.5
	8	218	35	13.6	2.1
	9	150	47	18.7	2.5
AIDS (9.0 years)	5	245	2	0.8	0.6
	6	225	17	7.0	1.6
	7	202	27	11.3	2.1
	8	171	35	15.0	2.3
	9	145	42	18.7	2.6
CDC IV (7.2 years)	5	216	35	13.8	2.2
	6	171	74	29.8	2.9
	7	138	99	40.4	3.1
	8	104	123	51.3	3.3
	9	66	144	62.1	3.3
CD200 (7.5 years)	5	222	25	10.0	1.9
	6	182	59	24.1	2.7
	7	145	86	35.8	3.1
	8	108	109	46.7	3.3
	9	75	128	56.7	3.4

Figure 15.3: Kaplan Meier plot of progression rate to AIDS and death in Edinburgh City Hospital IDU seroconverters


Proportion not progressed
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
Time
Death
AIDS
CDC IV
CD200

Influence of cofactors on progression

Gender and age effects on progression were not found; however the study group was very homogeneous with respect to age. A clear significant association with progression was shown by the 14 patients who were HLA typed A1-B8-DR3. Relative to the baseline group who were HLA-typed negative for A1-B8-DR3, these patients had relative risks of 7.1 (95% CI 3.2-15.8), 5.9 (2.5-13.4), 2.3 (1.2-4.2) and 2.6 (1.3-5.0) for progression to death, AIDS, CDC IV and CD200 respectively (Table 15.2). The untyped patients showed significantly reduced relative risks of progression to CDC stage IV and CD200, consistent with the fact that typing was initiated in the most seriously ill patients (while such patients were still alive).

It was also found that method of seroconversion estimation had a bearing on subsequent progression. The 168 patients whose seroconversions were determined as the midpoint of January 1983 and a positive HIV test showed significantly slower progression to all endpoints when compared to the baseline group whose seroconversions were determined from pairs of negative and positive HIV tests. The relative risks were 0.4 (0.2-0.8), 0.5 (0.2-0.9), 0.5 (0.3-0.7) and 0.5 (0.3-0.7) for endpoints of death, AIDS, CDC IV and CD200 respectively. This could indicate that the putative epidemic start in January 1983 was a little too early for most IDUs (simply subtracting six months or a year from follow-up for these patients largely eliminates the effect), or it could show that the group with negative and positive tests were disposed to progress more quickly for some reason such as co-infection with Hepatitis B.

Table 15.2: Covariate effects on mortality and progression to AIDS, CDC stage IV, AIDS and CD200

Risk set = 260		To **Death** (Cases = 49)			To **AIDS** Cases = 45)			To **CDC stage IV** (Cases = 146)			To **CD200** (Cases =129)		
Group	N	Cases	RR	CI	Cases	RR	CI	Cases	RR	CI	Cases	RR	CI
Female	82	16	0.9	0.5-1.6	10	0.6	0.3-1.3	47	0.9	0.6-1.3	38	0.8	0.5-1.2
Male	178	43	1	Baseline	35	1	Baseline	99	1	Baseline	91	1	Baseline
Age 30+	26	4	0.6	0.2-1.8	2	0.4	0.1-1.8	12	0.7	0.4-1.2	13	1.1	0.6-2.1
Age 25-30	36	10	1.0	0.5-2.2	9	1.5	0.7-3.3	26	1.2	0.7-1.9	21	1.3	0.8-2.2
Age < 25	198	35	1	Baseline	34	1	Baseline	108	1	Baseline	95	1	Baseline
Knowledge of IDU	31	9	1.2	0.5-2.8	4	0.5	0.2-1.6	20	0.9	0.5-1.7	17	0.7	0.4-1.4
Positive test only	168	34	**0.4**	0.2-0.8	27	**0.5**	0.2-0.9	85	**0.5**	0.3-0.7	74	**0.5**	0.3-0.7
Negative and positive tests	61	6	71	Baseline	14	1	Baseline	41	1	Baseline	38	1	Baseline
A1-B8-DR3	14	10	**7.1**	3.2-15.8	9	**5.9**	2.5-13.4	12	**2.3**	1.2-4.2	11	**2.6**	1.3-5.0
Incompletely typed	6	1	1.1	0.1-8.6	2	2.4	0.5-10.4	5	1.7	0.7-4.2	6	**5.0**	2.1-11.8
Untyped	143	30	1.3	0.7-2.3	14	0.6	0.3-1.1	63	**0.7**	0.5-0.9	56	**0.7**	0.5-1.0
Not A1-B8-DR3	97	8	1	Baseline	20	1	Baseline	66	1	Baseline	56		Baseline

* Relative risk adjusted for other covariates. **Bold** figures indicate significant and marginally significant associations ($p < 0.1$) with progression

Influence of zidovudine on progression

Simple use of a binary switch cofactor in the Cox model to investigate treatment effects merely showed the bias in the administration of the drug toward sicker individuals. Of 168 individuals who took AZT at some time 41 died, 43 had AIDS or developed AIDS and 126 had CDC stage IV symptoms or reached CDC stage IV. Of 92 patients who never took zidovudine 18 died, two developed AIDS and 20 developed CDC stage IV illnesses. Not surprisingly use of zidovudine was associated with elevated relative risks of disease progression.

However, using a second binary switch for patients who took zidovudine with a CD4 count greater than 100 (which is to say intervention before full immunosuppression) whilst controlling for the administration bias via the first switch showed that some reduction of progression risk resulted from the use of zidovudine. Relative to those patients who did not take zidovudine, those who took zidovudine only after endpoint and those who took zidovudine before endpoint but with counts less than 100, patients who took zidovudine with counts above 100 had relative risks of 0.2 (0.1-0.3), 0.2 (0.1-0.3) and 0.5 (0.2-1.1) for progression to death, AIDS and CDC IV respectively (Table 15.3).

When the analysis was repeated with a binary switch for patients taking zidovudine with CD4 counts above 200 a significant reduction in the risk of mortality was found (RR 0.1, 0.0-0.5) but it was not possible to show significant reductions in the risk of progression to clinical endpoints AIDS and CDC IV relative to other patients. This may be because later interventions are also effective at postponing clinical endpoints or it may be because the numbers of patients taking zidovudine before such endpoints with counts above 200 are too few to show significant results.

Table 15.3: Effect of zidovudine on mortality and progression to AIDS and CDC stage IV

Risk set = 260	To **Death** Cases = 59				To **AIDS** Cases = 45				To **CDC stage IV** Cases = 146			
Group	N	Cases	RR	CI	N	Cases	RR	CI	N	Cases	RR	CI
No AZT	92	18	1	Baseline	92	1	1	Baseline	92	20	1	Baseline
AZT only after endpoint	NA	NA	NA	NA	11	11	1	Baseline	85	85	**1**	Baseline
AZT before endpoint (100)	168	41	**7.6**	3.7-15.6	157	33	**12.7**	5.8-27.7	83	41	**5.2**	2.6-10.6
(AZT at CD4 > 100)	(119)	(12)	**0.2**	0.1-0.3	(116)	(11)	**0.2**	0.1-0.3	69	(30)	**0.5**	0.2-1.1
(AZT at CD4 <= 100)	(49)	(29)	1	Baseline	(41)	(22)	1	Baseline	14	(11)	1	Baseline
AZT before endpoint (200)	168	41	**4.0**	2.0-7.8	157	33	**5.5**	2.6-11.8	83	41	**3.4**	2.1-5.6
(AZT at CD4 > 200)	(48)	(2)	**0.1**	0.0-0.5	(47)	(6)	0.6	0.2-1.5	(31)	(9)	0.6	0.3-1.3
(AZT at CD4 <= 200)	(120)	(39)	1	Baseline	(110)	(27)	1	Baseline	(52)	(32)	1	Baseline

* Relative risk adjusted for other covariates

Bold figures indicate significant and marginally significant associations ($p < 0.1$) with progression

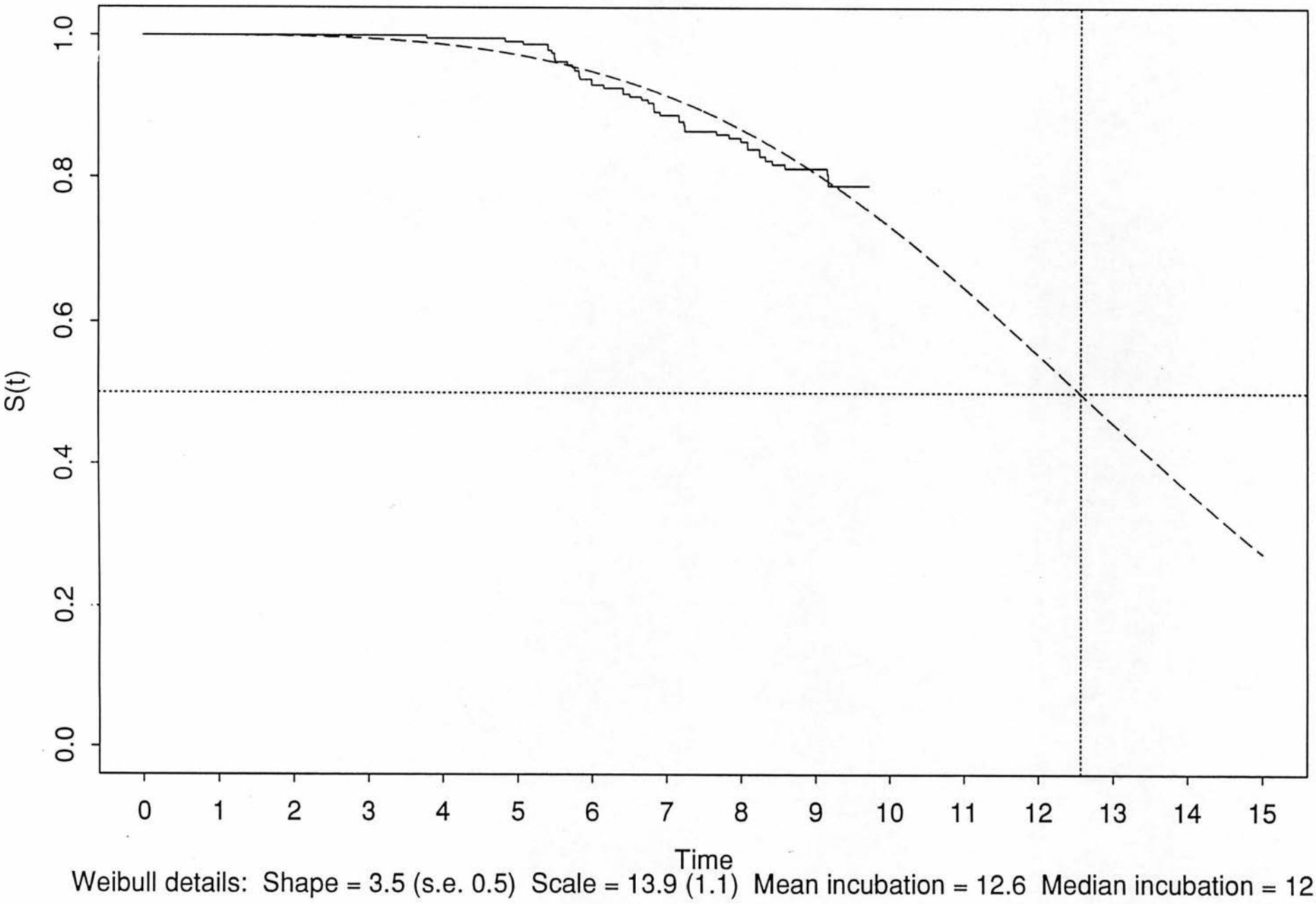
Parametric Estimates of AIDS and Mortality Curves

Under the Weibull assumption the estimated shape parameter of the AIDS incubation distribution was 3.5 (SE. 0.5) and the estimated mean and median AIDS incubation times were both 12.6 years (figure 15.3). In the case of the total survival distribution the shape parameter was 4.3 (SE. 0.5) and the estimated mean and median were 11.5 and 11.6 years (figure 15.5).

The Weibull curve appeared to be a very good fit to the survival distribution, but a less adequate fit to the AIDS incubation distribution; the AIDS progression curve may well be underestimated because of near diagnosis censoring due to death. The three parameter generalised gamma model gave negligible improvement in fit for the survival distribution (log likelihood's of -115.2 and -114.6 for the Weibull and generalised gamma respectively) but a slight improvement for the AIDS incubation distribution (log likelihood's of -105.5 and -99.1).

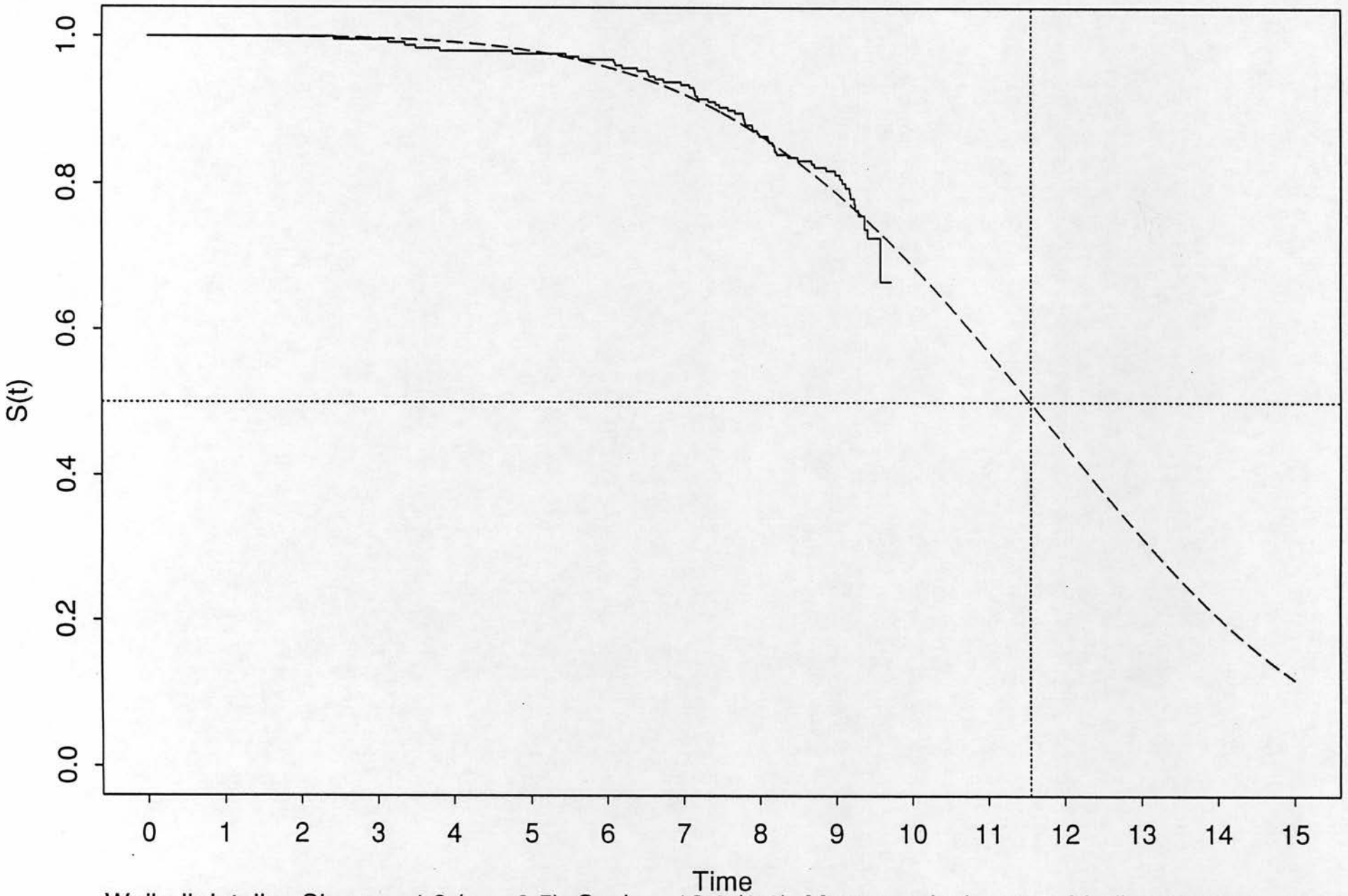
The total survival distribution seems to be the most accurate guide to the duration of HIV disease in IDUs because of the phenomenon of non-AIDS mortality. However application of both these distributions beyond the range of the data should be done with great circumspection because the fitted Weibull has a sharply increasing hazard rate beyond 10 years. It should also be noted that these estimates relate to treated HIV disease and no attempt has been made to estimate survival in untreated patients.

Figure 15.4: Survival functions to AIDS: estimated and fitted Weibull



Weibull details: Shape = 3.5 (s.e. 0.5) Scale = 13.9 (1.1) Mean incubation = 12.6 Median incubation = 12.6

Figure 15.5: Survival functions to Death: estimated and fitted Weibull



Weibull details: Shape = 4.3 (s.e. 0.5) Scale = 12.6 (0.6) Mean survival = 11.5 Median survival = 11.6

Survival

The three year survival rates (table 15.4) after diagnoses of AIDS, CDC stage IV and CD200 were 20% (se 7.4), 70% (4.7) and 65% (se 5.3) respectively. The median survival times were 1.3, 2.3 and 2.3 years.

Table 15.4: Survival from AIDS, CDC stage IV and CD200

Survival from (Median survival)	Year	Risk set	Cumulative deaths (all causes)	Survival rate %	SE %
AIDS	1	27	16	63.5	7.3
(1.3 years)	2	13	25	39.2	7.9
	3	6	30	19.9	7.4
CDC IV	1	123	10	92.8	2.2
(2.3 years)	2	94	18	86.1	3.1
	3	53	32	69.7	4.7
	4	29	42	54.0	5.7
CD200	1	112	8	93.6	2.2
(2.3 years)	2	75	16	85.4	3.4
	3	43	31	65.4	5.3
	4	26	41	47.9	6.1

CD4 loss

178 patients had ten or more serial CD4 determinations by which to estimate slopes of CD4 loss. On the untransformed scale the mean rate of loss per annum was 59 and the median was 52; the range was (-20, 243). On the root scale the mean rate was 1.9 and the median was 1.5; the range was (-0.7,6.1). In a regression analysis of the effect of gender, age, method of determination of seroconversion and A1-B8-DR3 status on slope on the root scale, only A1-B8-DR3 had a significant effect on slope. Patients with this HLA combination (usually received as a complete haplotype) were

estimated to lose CD4 on the root scale 1.8 times as fast as patients without these antigens ($p = 0.00$).

Discussion

Edinburgh cohort

The Edinburgh HIV seroconverter cohort was initiated retrospectively as a result of a number of opportune coincidences. The epidemic of injection drug use in Edinburgh came to light because of the concurrent epidemic of Hepatitis B[12]. The medical profession in Edinburgh were sensitised to the dangers of Hepatitis B as a result of the dramatic nosocomial outbreak that had occurred in 1970 with the deaths of a number of health care workers. Consequently, many drug users had sera sent for Hepatitis B testing because of obvious or minimal symptoms or signs. Combined with the Regional Virus Laboratory's (RVL) policy of storing all sera for 7 years, the fact that the RVL is the repository for all ante-natal rubella specimens resulted in substantial amounts of stored sera which were subsequently available to determine seroconversion dates for a number of patients. The sharp onset of the epidemic in Edinburgh amongst injection drug users, which was believed to have taken place in January 1983, meant that, for drug users with stored sera soon after this date, fairly accurate dates of seroconversion could be determined retrospectively for those who attended the self-referral HIV clinic at the Regional Infectious Diseases Unit (RIDU)[10,12-17]. The combined effect of the above allowed a reasonable numbers of drug users, one third of them women, to form the basis for an incident cohort.

The Edinburgh HIV cohorts, both incident or prevalent, have a number of other unique features that make them important for study. These are: a high proportion of women; a relatively homogenous and stable population; ease of access to medical services and the 'flagging' of defaulters to determine their dates of death. In addition, despite being largely composed of patients who acquired the infection via injection drug use, there has been good clinical and immunological follow up with a relatively low drop out rate for this risk group[8,18,19]. The epidemic was detected only 2.5 years after its onset and therefore it is unlikely that a large proportion of the symptomatic patients would have died of HIV before 1985 without coming to the attention of the Unit[13-17]. It also seems likely that the great majority of patients infected in the needle-sharing epidemic of 1983-85 will by now have come to the attention of the clinic. 11 patients estimated to be infected in this period enrolled in

1991 and only three enrolled in 1992 so that new enrolments from this era have dwindled.

Despite these advantages the IDU patients included in this cohort of seroconverters may still not necessarily be representative of the IDUs in the larger cohort from which they were drawn. The selection for these analyses was mainly from those people who had sera stored in 1984-1985. It is possible that those suffering symptomatic Hepatitis B may have a different course of illness with HIV than asymptomatic and therefore undetected Hepatitis B seroconversion.

Progression to AIDS and CD200

Currently few cofactors for progression to AIDS among HIV infected individuals have been identified. An extensive review of progression from HIV to AIDS in cohorts of various risk groups with known seroconversion dates revealed rates of progression of 0-2% at 2 years, 5-10% at 4 years, 10-25% at 6 years, 30-40% at 8 years and 48% at 10 years[20]. Updated data on the San Francisco City Cohort revealed a progression rate of 51% by 10 years although a haemophiliac cohort from London revealed a progression rate of 42% at 11 years[21,22]. The median time for progression to AIDS was initially around 7-10 years but has now risen to 11 years possibly because of the advent of anti-retroviral therapy[21].

Despite this information on the course of HIV disease there are still a number of problems. The majority of the well studied cohorts have been based on relatively affluent white homosexual males and there have not been very many descriptions of well studied cohorts which include injection drug users, heterosexuals or females. In Edinburgh data from both the prevalent and incident cohort, homosexual men appear to progress faster but since they make up a minority of the cohort they may not be representative of homosexual groups in general[8](and Chapter 13). It does however raise the question of whether sexual transmission of HIV may result in faster progression than injection drug user transmission.

Estimates presented are more likely to be underestimates of progression rates for Edinburgh HIV positives than overestimates because there may be long term infected patients in the community who have never come to the attention of the cohort. There are unlikely to have been many progressions before the cohort was assembled. Whilst only 19% had reached the end point of AIDS by 9 years 62% had dropped below a CD4 count of 20 cells/cumm. The fact that by 9 years 60% of individuals had

dropped below CD200 indicates that amongst this group there are unlikely to be many long term survivors since the majority have already developed serious immunodeficiency.

Non AIDS related Deaths

There is evidence that amongst drug users especially, data collected on AIDS cases greatly under represents serious HIV disease as a consequence of a substantial non AIDS mortality from conditions such as TB, endocarditis and bacterial pneumonia[23,24,25,29]. The data from the Edinburgh prevalent cohort also supports this phenomenon but to a lesser degree than noted in the USA or Europe with only 37% of deaths being non AIDS related instead of the figure of 50%[8,23,24,25,29]. The majority of non AIDS deaths after the development of AIDS were related to hepatitis and in fact hepatitis accounts for 18% of drug user deaths in the cohort rather than bacterial pneumonia. Thus for drug users the end point of AIDS may not be a particularly reliable event and overall survival may be a better indicator of the effect of HIV.

Injection Drug Users

Several studies have tried to assess the rate of progression to AIDS amongst drug users although most of these reports have related the onset of symptoms or AIDS to the length of follow up and not to the duration of HIV infection. Hence figures of progression must be interpreted carefully as differing results may merely reflect differing intervals between infection and the start of the assessment period.

An Italian study for which seroconversion dates were available, estimated that there was a 5% progression rate by year 3-4 and a 21% progression rate to AIDS after 6-7 years of HIV infection[26]. The Edinburgh cohort study reveals progression rates to AIDS of 20.4% by 9 years with an estimated median time to AIDS of 11.1 years. Thus the progress of the Edinburgh cohort seems closer to the data from the USA when compared to other European data. This may be explained by closer follow up and flagging of defaulters to identify progressions or deaths and or an effect of medical treatment including zidovudine.

Women

As with injection drug users there are unfortunately not many cohort studies of progression in women particularly those with seroconversion dates. Gender was not

reported as a significant factor in a study of progression in 58 male and 18 female Spanish injection drug users[27]. The Swedish blood transfusion study noted shorter progression times for men but this was not statistically significant[28]. The Italian follow up study of drug users with known seroconversion dates contained 127 women and no gender effect on progression was observed[26]. A report on 318 HIV positive drug users followed prospectively via a methadone maintenance programme, 147 of whom were female, showed no effect of gender on progression[29].

The lack of any gender effect on mortality for this group is an important observation because of the debate over whether or not the AIDS definition is suitable for women. Since this study and others have failed to demonstrate a major difference between the sexes in the rate of progression from HIV to AIDS it would appear that the lack of any excess mortality for HIV infected women compared to men does not support the argument that the AIDS definition as applied in the UK is a poor overall reflection of female HIV disease.

Age

Whilst there is evidence that age at the time of HIV infection is perhaps one of the most important factors affecting progression to AIDS this was not the case in this incident cohort. Other incident cohorts with a larger spread of age have clearly demonstrated an age effect and one might consider this incident cohort as one controlled for age[27].

Studies among individuals infected through blood transfusion[28,30], intravenous drug users[26,31], haemophiliacs[22,32] all suggests an adverse effect of age. In the Swedish transfusion study progression to AIDS at 5.5 years after infection was 48% in those over 60 compared to only 28% between 15 and 60 years of age[28]. In an Italian haemophiliac study after 5.5 years of infection 37.7% of those over 35 years of age had progressed to AIDS compared to only 18.5% of those under 35 years of age ($p<0.02$)[33]. There was no difference in the rate of progression however for those above and below 18 years of age. A haemophiliac cohort from the UK reported that age over 25 years had a relative hazard of 5[22]. The progression rate for US haemophiliacs was 5.66/100 person years for those aged 35-70 but only 2.39 for those aged 18-25[32]. An Italian study of IDUs with known dates of seroconversion also noted more rapid progression for those over 25 years of age[26].

Survival from CD200 and AIDS

The three year survival rates after diagnoses of AIDS, CDC stage IV and CD200 were 20%, 70% and 65% respectively with median survival times of 1.3, 2.3 and 2.3 years which are broadly comparable with data from the prevalent cohort. This gave 3 year survival rates of 25%, 61% and 58% for AIDS, CDC stage IV and CD200. Thus survival from clinical and immunological end points may vary depending upon length of infection confirming the fact that there is individual variation in achieving clinical and immunological end points. This confirms the fact that it is the rate of immunological decline that varies between individuals and is the more important determinant of survival than the actual end points themselves.

HLA Haplotypes

The clearest significant association with progression in the incident cohort was shown by the 13 patients who were HLA typed A1-B8-DR3. Relative to the baseline group who were typed negative for A1-B8-DR3 these patients showed relative risks of progression *of 2.3, 5.9 and 7.1 for progressio*n to CDC stage IV, AIDS and death respectively. The untyped patients showed reduced relative risks of progression to CDC stage IV and AIDS, probably since typing was initiated in the most seriously ill patients (while such patients were still alive); the untyped patients showed elevated risks of mortality, probably because a number had died before typing was initiated.

The issue of HLA associations is described in more detail in the next chapter in a further analysis of seroconverters drawn from the Edinburgh City Hospital cohort[34].

Zidovudine

The use of zidovudine at the RIDU was not in any way randomised (50 patients participated in the MRC/Inserm Concorde trial[35]) and was a clinical decision made in the light of then currently available evidence of efficacy. This bias towards sicker patients can be seen by the fact that not surprisingly the decision to prescribe zidovudine was associated with an elevated risk of progression. However if this bias was controlled for in the analysis it appeared that taking zidovudine before a CD4 count of 100 reduced the risk of progression to a clinical end point (CDC stage IV or AIDS) as well as reducing the risk of dying. By comparison taking zidovudine before a CD4 count of 200 only reduced the risk of dying and had no effect on the risk of progression to a clinical end point.

Thus this analysis does indicate that use of zidovudine for those patients with quite low counts who have not yet developed a substantial clinical end point between a CD4 count 100-200 cells/cumm does have an effect of delaying progression and reducing the risk of dying and is consistent with previous work on early symptomatic HIV infection[36]. The recently announced Concorde trial which was set up to test the decision whether earlier therapy increased the benefit of zidovudine noted no increased benefit of early therapy at any level of initial CD4 count[35]. However as yet no analysis around an entry level of a CD4 count of less than or equal to 100 cells/cumm has been published and this might explain the apparent contradiction between the present analysis and Concorde[35].

Conclusion

Edinburgh drug users do not seem to progress more rapidly than other risk groups although the total survival distribution seems to be the best guide to the duration of HIV disease in IDUs rather than the AIDS distribution because of the phenomenon of non-AIDS mortality. Unlike the data from the prevalent cohort, there was no apparent age effect on progression. this is likely to be as a consequence of the fact that the patients were very homogeneous with respect to age. Similarly there was no gender effect apparent and the clearest significant association was with the HLA haplotype A1-B8-DR3.

Under the Weibull assumption the estimated shape parameter of the AIDS incubation distribution was 4.2 and the estimated mean and median AIDS incubation times were 11.0 and 11.1 years which is similar to a number of homosexual cohorts[37]. The estimated shape of the survival distribution was 4.5 and the estimated mean and median survival times were 10.7 and 10.8 years.

For the majority of patients the use of zidovudine at the RIDU was not randomised and this can be seen by the fact that not surprisingly the decision to prescribe zidovudine was associated with an elevated risk of progression. However if this bias was controlled for in the analysis it appeared that taking zidovudine before a CD4 count of 100 reduced the risk of progression to a clinical end point (CDC stage IV or AIDS) as well as reducing the risk of dying. By comparison taking zidovudine before a CD4 count of 200 only reduced the risk of dying and had no effect on the risk of progression to a clinical end point.

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CHAPTER 16

The association of HLA types with rapid and slow progression of HIV disease

Introduction

Whilst there could be many factors influencing disease progression of HIV, because of the intimate association between HIV and the immune system, one important influence to consider is the effect if any of HLA antigens. A number of studies have previously reported associations between HIV disease progression and HLA antigens.

For instance the antigens DR2 and DR5 were initially reported to be more prevalent in populations with AIDS and Kaposi's sarcoma but some of these findings were not confirmed in other studies[1-3]. DR3 and Cw7 antigens were also found early on in a high proportions of AIDS patients with opportunistic infections[4,5]. In a study of 102 HIV seropositive men with a mean follow up time of 43 months, AIDS developed more frequently in HLA-DR1 positive men than in those with other HLA-DR phenotypes; however, with longer follow-up times the difference diminished[6,7].

The antigen combination A1-B8-DR3 (usually identified as a haplotype) was reported from the haemophilic cohort in Edinburgh to be weakly associated with an increased risk of seroconversion (relative risk or RR 2.9) while, in those who seroconverted, it was strongly associated with rapid decline in CD4 cells and development of HIV-related symptoms (RR 28)[8]. Confirmation of this result came from a second group that reported A1-B8-DR3 to be significantly more common in rapid progressors (odds ratio 3.8)[9]. This latter study did not show any association between rapid decline in CD4 cells with the presence of HLA-DR1[9]. The B8-DR3 combination was also found to be significantly associated both with progression to AIDS (RR 10.6) and with a six-month CD4 lymphocyte loss of greater than 20% (RR 2.2)[10].

The B35 antigen has also been reported as a factor influencing HIV disease progression. It was found to be significantly associated with AIDS in Italian patients with lymphadenopathy and with progression from enrolment to AIDS in US homosexual men, although in both these studies the numbers of patients studied were small[11,12]. In addition B35 was recently reported to be a factor for fast progression from seroconversion to AIDS (RR 2.7) in a study of 144 French haemophiliacs,

where seroconversion times were estimated using the midpoints of negative and positive HIV tests[13].

In view of these finding the influence of HLA type on progression and rate of loss of CD4 in the Edinburgh City Hospital seroconverter cohort was examined. In addition to the above listed antigens, a possible associations with B27, because of its known association with other immunological diseases (ankylosing spondylitis, Reiter's syndrome) was also investigated. This was important also because of recent work suggesting similarities exist between HLA class 2 DR B1 chain and the carboxyterminus of the HIV-1 envelope gp120, when presented as peptides by B27, which leads to the hypothesis that B27 might be associated with slower progression[14].

Methods

Study Setting and Design

This analysis is based on the 301 patients from the Edinburgh City Hospital seroconverter cohort already described in Chapter 15 at first January 1992. One hundred and thirty one of these patients had been HLA typed by first March 1993 when the data was analysed. The HLA typing exercise was initiated in the sickest patients so that the information could be obtained whilst they were still alive.

Laboratory Methods

HLA typing was by a standard two-stage complement-dependent microlymphocytotoxicity technique[15]. The methods employed in the measurement of lymphocyte surface markers including the CD4 count were as described in Chapter 12.

Statistical Methods

The data was analysed by proportional hazards models to CDC stage IV or AIDS, to AIDS and to death with covariates controlled for gender, exposure category, age at seroconversion and year of seroconversion to explore associations with progression rate.

To test the effect of HLA antigens three indicator variables were constructed for patients who were: (1) positive for the antigen or antigen combination in question; (2) untyped; (3) typed in insufficient detail to judge whether they had, or had not, the

antigen or antigen combination in question. Thus the baseline group was taken to be the patients who were definitely negative for the antigen of interest.

To see whether HLA was associated with rate of loss of CD4 a subset of 164 of the seroconverters were ranked by decreasing rate of CD4 loss. A random effects decay curve model for root of CD4 count was used to estimate individual rates[16]. The 164 patients selected all had at least ten CD4 counts, which was considered the minimum number which would allow an accurate estimate of the individual rate of CD4 loss.

A Wilcoxon rank sum test leading to the calculation of a z-score was used to test the hypothesis that rates of CD4 decline were not different for the antigen-positive and -negative subgroups of the patients who were fully typed for each antigen or antigen combination.

Results

The numbers of patients typed for HLA antigens and the proportions typed positive for various single antigens and antigen combinations are shown in Table 16.1. Of the 131 typed patients, 13 had the antigens A1, B8 and DR3 in their phenotype (which is most likely to mean that they received the combination as a complete haplotype) and seven were typed in insufficient detail to tell whether they were A1-B8-DR3 or not. Thus about 10% of the fully typed individuals were A1-B8-DR3 which was a lower proportion than expected. From previous reports the expected frequency of occurrence of A1-B8-DR3 was 25% in Scotland whilst Jazwinska and Kilpatrick reported a frequency of 20% in parents of 132 babies born at an Edinburgh maternity unit (see final column of table)[17]. The frequencies of the other antigens were more in line with those expected, with the exception of DR1 which was slightly over represented.

Table 16.1: Numbers typed positive for various antigens

HLA combination	Number Positive	% positive	Number Negative	Incompletely typed	Expected frequency % [17]
A1-B8-DR3	13	10	111	7	20
DR1	21	19	91	18	10
DR2	34	30	79	18	29
B35	16	14	98	17	12
B27	8	7	106	17	8

In a proportional hazards analysis of progression to clinical endpoints only A1-B8-DR3 emerged as a significant predictor of faster progression to either of the advanced endpoints AIDS or death (see table 16.2). A1-B8-DR3 was associated with adjusted relative risks of 2.1 (p=0.05) of reaching CDC stage IV, 4.4 (p=0.00) of developing AIDS and 8.6 (p=0.00) of dying.

The analysis also showed the bias inherent in the typing of the cohort. The untyped patients had a significantly lowered risk of progression to CDC stage IV and AIDS consistent with the fact that typing began with the most seriously ill patients. Conversely the untyped patients showed a significantly elevated risk of dying, probably indicating that some patients died before they could be typed.

B35 was not significantly associated with progression to AIDS or death but was significantly associated with rapid development of symptomatic disease (relative risk 2.0, p=0.03). 12 of 16 patients typed positive for B35 reached CDC stage IV; six developed AIDS and four died.

In the case of B27 the proportional hazards form of analysis was not appropriate since there were only eight typed patients possessing the antigen and none of them developed AIDS or died. Three reached CDC stage IV but no significant effect on progression to this endpoint was demonstrable.

Table 16.2: Results of a proportional hazards analysis of the effect of A1-B8-DR3 on progression to clinical endpoints

Group	Number	CDC-IV	RR*	CI	AIDS	RR*	CI	Dead	RR*	CI
Whole cohort (N=301)										
A1-B8-DR3	13	9	**2.1**	1.0-4.3	8	**4.4**	1.9-10.3	9	**8.6**	3.4-21.6
Not A1-B8-DR3	111	56	1	Baseline	20	1	Baseline	10	1	Baseline
Undetermined	7	5	**1.7**	0.7-4.3	2	**1.9**	0.4- 8.3	1	1.6	0.2-12.4
Untyped	170	59	0.7	0.5-1.0	17	0.5	0.3- 1.1	27	2.1	1.0- 4.5
IDUs only (N=269)										
A1-B8-DR3	13	9	**2.1**	1.0-4.3	8	**4.2**	1.8- 9.8	9	**8.7**	3.4-21.9
Not A1-B8-DR3	106	55	1	Baseline	20	1	Baseline	10	1	Baseline
Undetermined	6	5	**1.9**	0.8-4.8	2	**2.2**	0.5- 9.4	1	**1.7**	0.2-13.0
Untyped	144	48	0.7	0.5-1.0	11	0.4	0.2- 0.9	23	2.1	1.0- 4.4

* Relative risk adjusted for gender, age, risk group and year of infection

In the group of 164 selected for the analysis of rate of CD4 loss there were nine patients with the A1-B8-DR3 haplotype. An association with rapid loss of CD4 was readily apparent: when the patients were ranked by decreasing rate of CD4 loss seven of the nine individuals were found in the top quarter of the list (see table 16.3). Moreover four of the seven most rapid decliners (one untyped) were A1-B8-DR3. The Wilcoxon rank sum z-score was -3.45 ($p = 0.00$).

Of six patients who were B27 positive, five were found to be in the half of the group of 164 who declined most slowly. The z-score was 2.21 ($p = 0.02$).

Of the 12 patients who were B35 positive in the group of 164, seven were found in the quarter of the list who lost CD4 most quickly; a further three were found in the next quarter and only two were in the lower half of the list. However the Wilcoxon z-score was not statistically significant at -1.4 ($p=0.16$). Neither DR1 nor DR2 displayed a significant association with rate of CD4 loss.

Table 16.3: Rates of CD4 loss in 164 patients: 41 patients per quarter

Group	Fastest quarter	Intermediate	Intermediate	Slowest quarter
A1-B8-DR3	7	1	1	0
Not A1-B8-DR3	25	21	19	21
Undetermined	2	2	2	0
Untyped	7	17	19	20
B35	7	3	1	1
Not B35	24	14	19	16
B27	0	1	2	3
Not B27	31	16	18	14
Undetermined	3	7	2	4
Untyped	7	17	19	20
Ranks A1-B8-DR3*	1,2,4,6,12,14,23	45	69	
Ranks B35**	6,11,16,19,23,28,29	33,42,48	66	83
Ranks B27**		40	60,64	71,74,78

* Ranks from top of list out of 105 for whom A1-B8-DR3 status was known , ** Ranks from top of list out of 85 for whom B locus was known

Discussion

These results support previous studies which have shown A1-B8-DR3 to be associated with more rapid progression of HIV disease[8,9]. This is a large study of the influence of HLA antigens in the setting of a cohort which is homogenous with respect to race and risk group. This cohort has the additional advantage of accurately estimated lengths of HIV infection. Although the number typed definitely positive for A1-B8-DR3 was not high (13 out of 131), the analysis nonetheless gave striking evidence of very fast clinical and immunological progression in patients carrying this haplotype. Given the rapidity of progression associated with this particular HLA haplotype consideration should be given to HLA typing before randomisation of patients into prospective clinical trials. The ability to identify rapid progressors might make it possible to accelerate clinical trials by focusing attention on fast-progressing patients. Small trials involving only rapid progressors could be organised with the knowledge that clinically significant endpoints would be reached within one to two years. This would allow more drugs to be evaluated and would also have the benefit of concentrating therapy on those at greatest risk.

The homogeneity of the City Hospital cohort is due primarily to the rapid spread of the virus among a young group of needle-sharing IDUs in 1983-1985[18-21](and Chapter 3). The majority of the 301 eligible patients in the study group were from this initial explosive epidemic. To maximise numbers, a number of heterosexual and homosexual transmissions (32) were included in the study; however results for the analysis of clinical progression were very similar when the IDUs were analysed alone (table 14.2 for A1-B8-DR3 analysis).

The principal eligibility criterion for inclusion in the study was the availability of an accurate estimate of seroconversion time. In seroconversions estimated from interval data (85% of cases) the maximum possible error in the estimate was one year; in the remaining cases estimated through seroconversion illness and knowledge of drug-using behaviour the estimates were also likely to be accurate. It was possible to make accurate interval seroconversion estimates for so many people because of the availability of stored sera.

Survival analysis methods, such as the proportional hazards model, with survival measured from seroconversion time are the most appropriate means of estimating the influence of HLA antigens, or any other covariates, on clinical progression. As has been previously pointed out simple studies of HLA associations with clinical

diagnoses without regard for duration of infection are less conclusive, and studies which measure progression times from first known occasion of HIV-positivity (so-called prevalent cohort studies) are prone to a series of biases in estimation of covariate effects, especially onset confounding[13,22]. The present study, like that of others benefited greatly from accurate knowledge of seroconversion[23].

A further strength of the study was the ability to make accurate estimates of rates of CD4 loss for 164 members of the study group (54%). CD4 monitoring is performed regularly in the Edinburgh cohort (every three months for most patients, more frequently for the sicker patients and patients on zidovudine). If the requirement of ten serial CD4 counts had been relaxed and individuals with five or more counts had been included then rates of CD4 loss could have been done in 226 patients (75% of study group). However five counts may be insufficient to characterise individual rates of decline. This is particularly important since five counts could display great variability and could also span fairly short periods of time of less than a year for those patients seen frequently.

The low prevalence (10%) of A1-B8-DR3 in the fully typed individuals in this study by comparison to local controls was initially puzzling, particularly since typing was biased toward the faster progressors in whom a higher than average prevalence of the haplotype might have been expected. It is possible that a large proportion of those who died rapidly before typing began carried the haplotype, although this hypothesis cannot now be verified. However, it could also be argued that the expected population frequencies are not appropriate comparisons since the study group is not a random sample from the general population since many of the needle-sharing IDU networks included substantial numbers of family members. The group under study also exemplified this phenomenon: among the group of 164 patients with 10 CD4 determinations alone it was possible to count 17 patients in eight families with first order relationships (sibling, parent-child) to other cohort members. This estimate of family relationships was the minimum since in this group there may be second order relationships of which the Unit was not aware because of the need to maintain confidentiality even within families.

The underlying biological basis for the association of A1-B8-DR3 with rapid progression of HIV-related disease and CD4 loss remains obscure. The haplotype A1-B8-DR3 is well known to be associated with a wide range of auto immune disorders and individuals bearing this haplotype could be considered to be immunologically "hyper-responsive" [8]. This suggests that auto immunity may be

involved in part or in whole in the progressive immunodeficiency characterising HIV disease. This is an alternative explanation for the development of immunodeficiency via a direct cytopathic effect of HIV on CD4 lymphocytes. However at present the mechanism of development of immunodeficiency at the molecular level remains unclear.

The second major association noted by this analysis was between B27 and slow progression. None of eight patients typed positive for this antigen reached AIDS or died and it seemed that these patients were experiencing slow immunological decay. There has been recent interest in the phenomenon of long term survival in HIV patients and in the explanation for the differences between such patients and rapid progressors[24-26]. One suggestion that has been put forward is that differences are due to a less virulent strain of HIV-1[24]. However the HLA data from the Edinburgh cohort but this data as well as the work of others raise the possibility that it could also be as a result of decreased susceptibility in the host[26]. In two recent reports the number of long term survivors (10-15 years) infection varied from 5-15% of cohorts[25,26]. The latter study noted that long term survivors with known length of infection had better immunological parameters at their first visit; higher total white blood cell counts, lymphocyte counts, haemoglobin, CD4 counts and lower IgG levels suggesting that such individuals are already different soon after infection[26]. One of the cohorts reported on HLA associations and noted greater frequencies of A32, B4 and C2 (19% vs. 4%[p=0.03], 73% vs. 51%[p=0.05], and 27% vs. 4% [p=0.004] respectively) in the long term survivors[25]. The report of an association with B27 adds further to the suggestion that there may be an immunological as well as, or instead of, a virological explanation of the phenomenon of long term survival.

B35 was not found to be as important as A1-B8-DR3 in influencing clinical progression to the advanced endpoints of AIDS or death. However there was an effect on progression to symptomatic disease and a suggestion of an association with fast CD4 loss. It is possible that when further HLA typing is performed and follow-up is longer a stronger B35 effect in line with other studies will be found[16].

Conclusion

The HLA haplotype A1-B8-DR3 was associated with a rapid development of immunodeficiency after HIV infection in a cohort of homogenous individuals with known length of infection with HIV. In addition the HLA haplotype B27 was associated with a slow development of HIV immunodeficiency. HLA typing of

patients with HIV should be of use in identifying patients at risk of rapid onset of immunodeficiency and therefore at priority for anti-retroviral therapies.

Appendix

z-score for rank sum test

$$\text{z-score} = [\text{observed rank sum} - \text{expected rank sum}] / s$$

$$= [\text{observed rank sum} - n1 \times \text{integer}(n1+n2+1) / 2)] / \sqrt{[n1 \times n2 \times (n1+n2+1) /12]}$$

where n1 is number antigen-positive and n2 is number antigen-negative

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CHAPTER 17

Clinical features of HIV in Edinburgh

Introduction

Whilst there has been considerable experience of the clinical problems of homosexual cohorts, much less is known about the clinical presentation and features associated with drug users in the UK. Equally geographical variations in the clinical problems of cohorts of patients have been reported; for instance disseminated fungal infections are relatively common in the USA as is tuberculosis in Southern Europe but both these are rarely seen in the UK. This chapter details the clinical features of patients with HIV attending the RIDU at the City Hospital, Edinburgh.

Method

The recruitment of the Edinburgh City Hospital cohort has been described in Chapter 14 as has the enrolment, progression and survival characteristics of the cohort. All HIV positive patients visiting the clinic at the Regional Infectious Diseases Unit of the City Hospital, Edinburgh over the 8 year period between its inauguration in October 1985 and September 1993 (plus a small number of HIV positives seen in 1984 and 1985 before the opening of the clinic) were included in this analysis. The patients were coded by the physicians caring for the patients initially using the CDC classification at each outpatient clinic and admission to the ward[1]. From January 1992 all clinical events were also coded prospectively utilising a locally modified coding system, based on the WHO classification, suitable for storage in a computer database as shown in the appendix[2,3]. Past events were retrospectively coded utilising the modified WHO system. An analysis of these clinical events was undertaken at 30/9/93. The follow up time was expressed as person years of follow up and was calculated by subtracting the date of the initial clinic visit from the last date of a clinic visit or the death of the patient. The follow up time for AIDS was calculated using a similar method (subtracting the month of AIDS diagnosis from the month of the last clinic visit or the month of death) and expressed as person years AIDS.

Results

By 30/9/93, 8 years after a dedicated HIV clinic was commenced, a total of 680 patients had attended, 204 (30%) women (table 17.1 and figures 17.1-3). The risk activities for acquisition of HIV infection were as follows; 462 (68%) heterosexual

injection drug use [IDU], 99 (14.5%) heterosexual [het], 95 (14%) homosexual, 9 (1%) bisexual [ho/bi] and 15 (2.5%) others [8 blood products or Bp, 3 homosexual IDU or ho/IDU and 4 unknown or UK].

Pattern of referral

The pattern of referral over the 10 years reflects what is known about the Edinburgh epidemic. Substantial numbers of patients entered the medical system in the early years (1986-1989), the majority infected via IDU. In the later years (post 1989) the absolute numbers enrolling fell and the distribution of risk activities also changed (table 17.1). In 1989, 70% of the new patients were infected via IDU, 16% via homo/bisexual activities and 13% by heterosexual activities whereas by 1992 only 45% were infected via IDU, 21% by homo/bisexual activities and 25% via heterosexual activities. The M/F ratio for those infected heterosexually reflects the M/F ratio of the largest group of infected heterosexuals i.e. IDUs. The M/F ratio for those infected heterosexually was 0.52 close to the reciprocal (0.42) of the M/F ratio for IDU of 2.37.

Table 17.1: Risk activity of the Edinburgh City Hospital cohort analysed by year of first attendance

Year	IDU		Het		Ho	Ho/ID	Bi	Bp		UK		Total		Total
	M	F	M	F	M	M	M	M	F	M	F	M	F	
'84	1	0	0	0	1	0	0	0	0	0	0	2	0	2
'85	14	5	0	0	5	0	0	0	0	0	0	19	5	24
'86	54	42	0	3	6	0	0	0	1	0	0	60	46	106
'87	57	33	3	9	9	0	0	0	0	0	0	69	42	111
'88	53	22	2	8	14	0	1	3	0	0	0	73	30	103
'89	53	21	3	11	17	0	1	0	0	0	0	74	32	106
'90	27	4	4	10	12	1	3	0	0	0	0	47	14	61
'91	26	3	10	9	12	2	1	0	0	1	0	52	12	64
'92	16	5	7	4	8	0	3	2	0	1	1	37	10	47
'93	23	2	4	11	11	0	1	2	0	2	0	43	13	56
Total	324	137	33	65	95	3	10	7	1	4	1	476	204	680
M/F	2.37	-	0.51	-	NA	NA	NA	7	-	4	-	2.33	-	

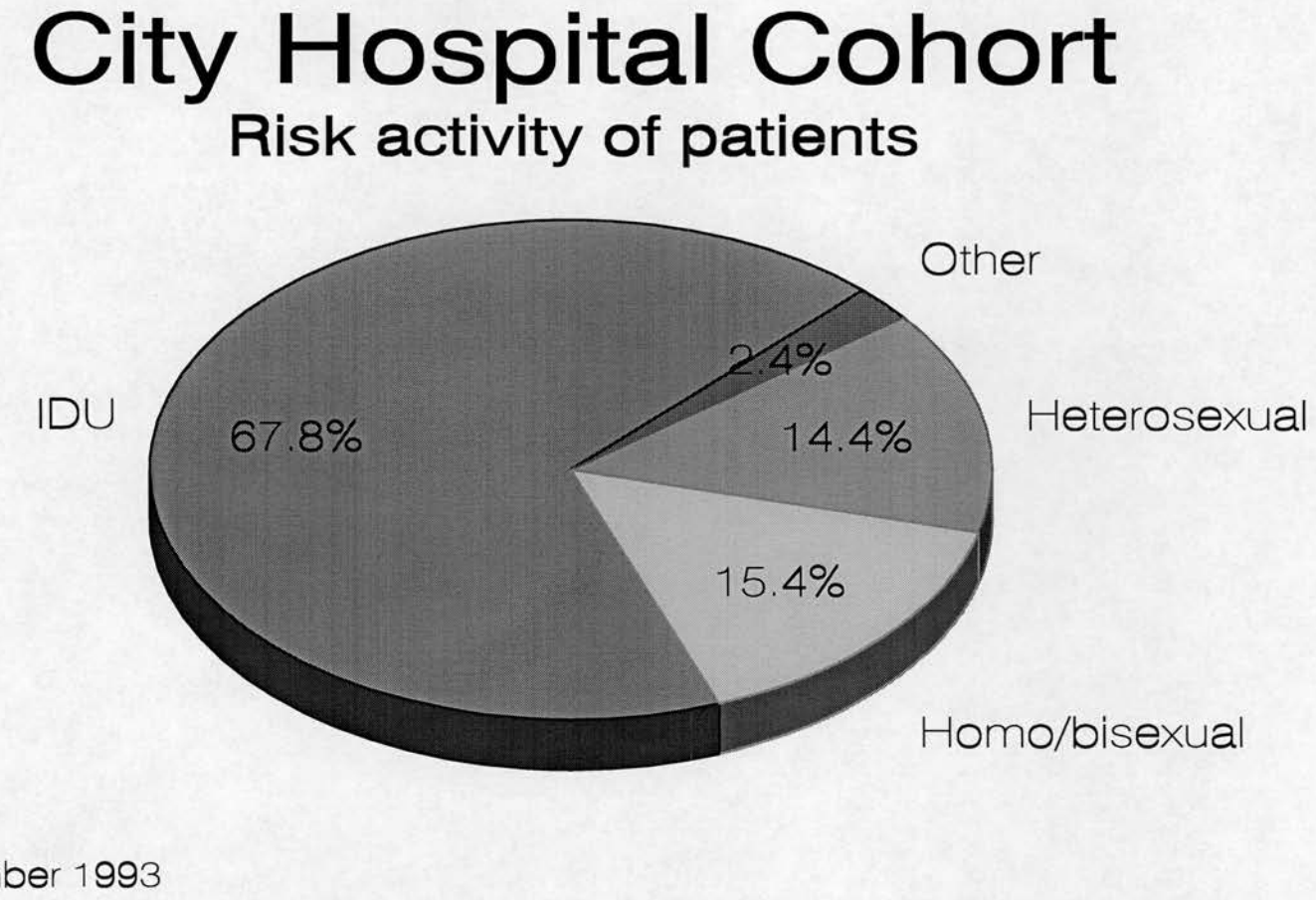

Figure 17.1: Risk activity of the Edinburgh City Hospital cohort

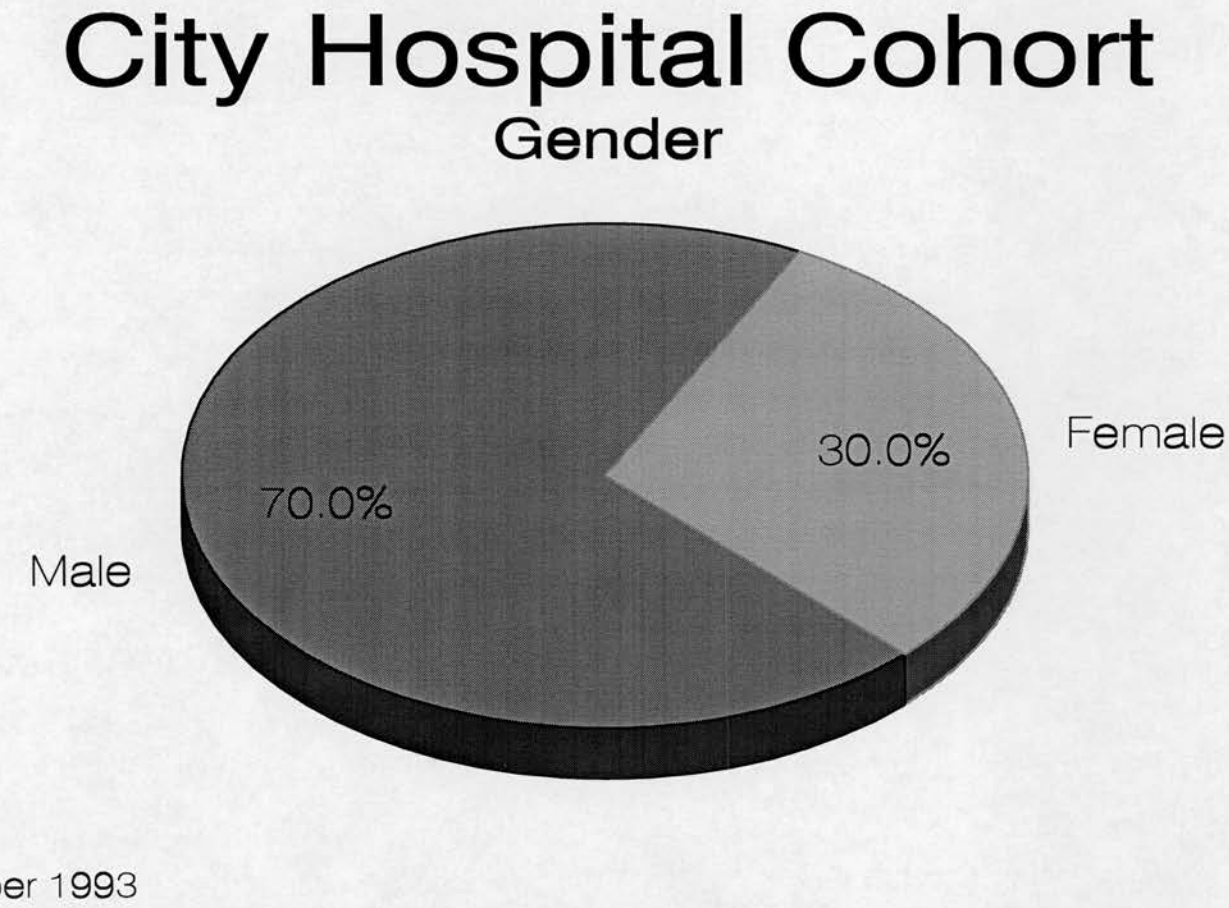

Figure 17.2: Gender of the Edinburgh City Hospital cohort

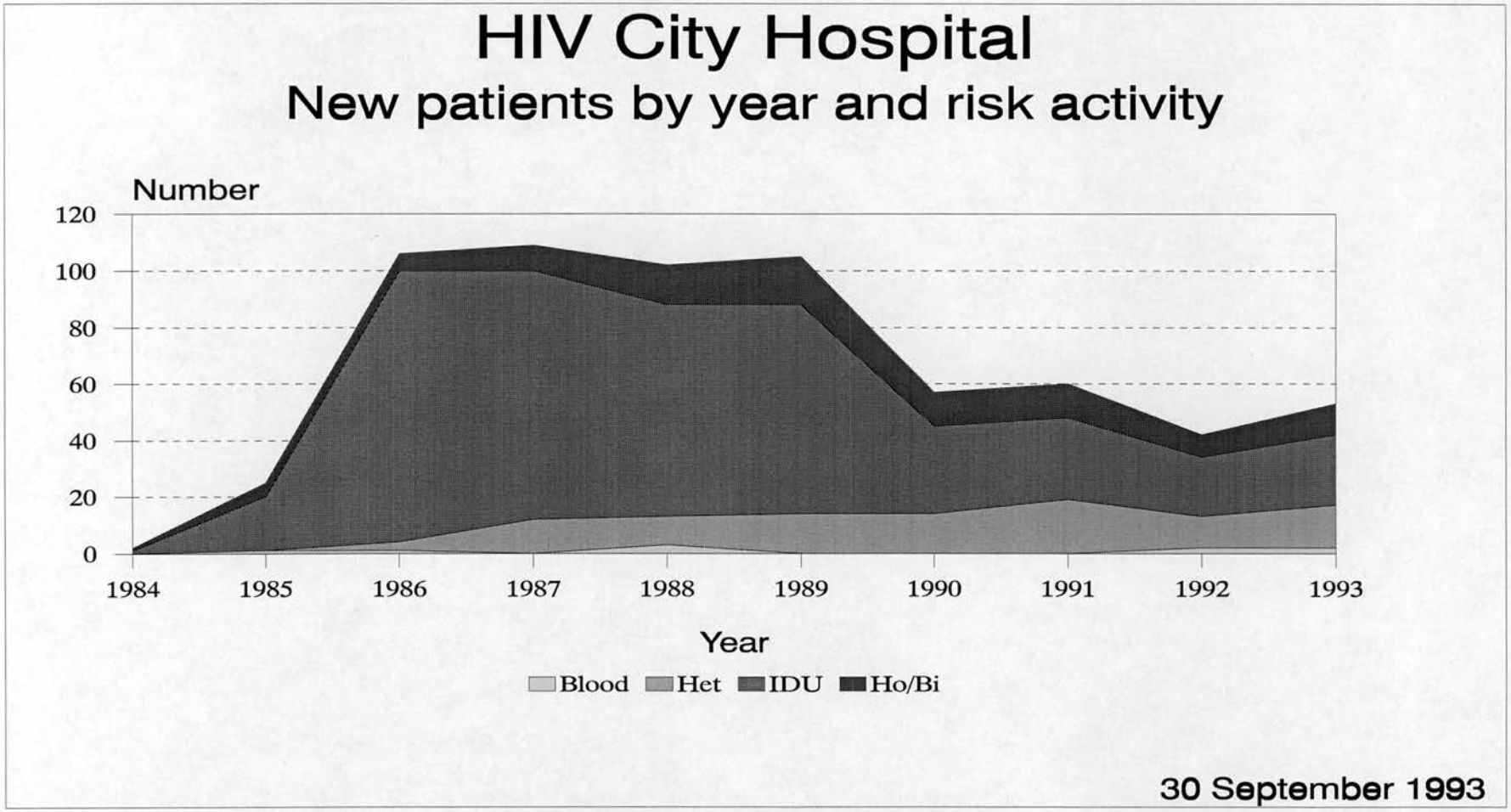

Figure 17.3: Risk activity of the Edinburgh City Hospital cohort between 1984 and 1993

Morbidity

Clinical status at initial visit

The clinical status of the patients at their first visit (Tables 17.2, 17.3, figures 17.4 and 17.5) was as follows; 476 or 70% were essentially well (WHO stage 1), 110 or 16% were symptomatic (21 or 3% were in WHO stage 2 and 89 or 13% in WHO stage 3) and 77 or 11% had AIDS (WHO stage 4). A small number of patients, 17 or 2%, presented with conditions such as thrombocytopaenia and myopathy which do not at present fit into the original WHO classification system. However the percentage of patients presenting each year with AIDS rose from 7% in 1987 to 27% in 1993.

The significant initial non AIDS clinical presentations (Table 17.2) to the clinic were as follows; minor skin problems (code 202) 2%, HIV related thrombocytopaenia (code 507) 2%, weight loss (code 301) 3%, oral thrush (code 304) 4.5%, oral hairy leucoplakia (code 306) 3.5% and severe bacterial sepsis (code 308) 1.5%.

Table 17.2: Non-AIDS clinical features (modified WHO code) at first visit by calendar year

Code	'84	'85	'86	'87	'88	'89	'90	'91	'92	'93	Total
Stage 1											
101	1	8	41	56	48	33	20	26	12	20	**265**
102								1	1		**2**
103		11	57	28	27	41	18	8	12	7	**209**
Sub total	**1**	**19**	**98**	**84**	**75**	**74**	**38**	**35**	**25**	**27**	**476**
Stage 2											
202			1	2	1	4	1	2	3	1	**15**
203		1		1				1		1	**4**
204				2							**2**
Sub total		**1**	**1**	**5**	**1**	**4**	**1**	**3**	**3**	**2**	**21**
Stage 3											
301		1	1	1	1	3	2	2	3	7	21
304		1	1	2	4	8	2	8	2	2	30
306				6	2	5	5	3	5	1	27
308					6	1	1	2		1	11
Sub total		**2**	**2**	**9**	**13**	**19**	**10**	**15**	**10**	**11**	**89**
Others											
504								1			**1**
506									1		**1**
507		1	4	1	2	2	1	2		1	**14**
509						1					1
Sub total		**1**	**4**	**1**	**2**	**2**	**1**	**3**	**1**	**1**	**17**
Total	**1**	**23**	**105**	**99**	**91**	**98**	**50**	**56**	**39**	**41**	**603**

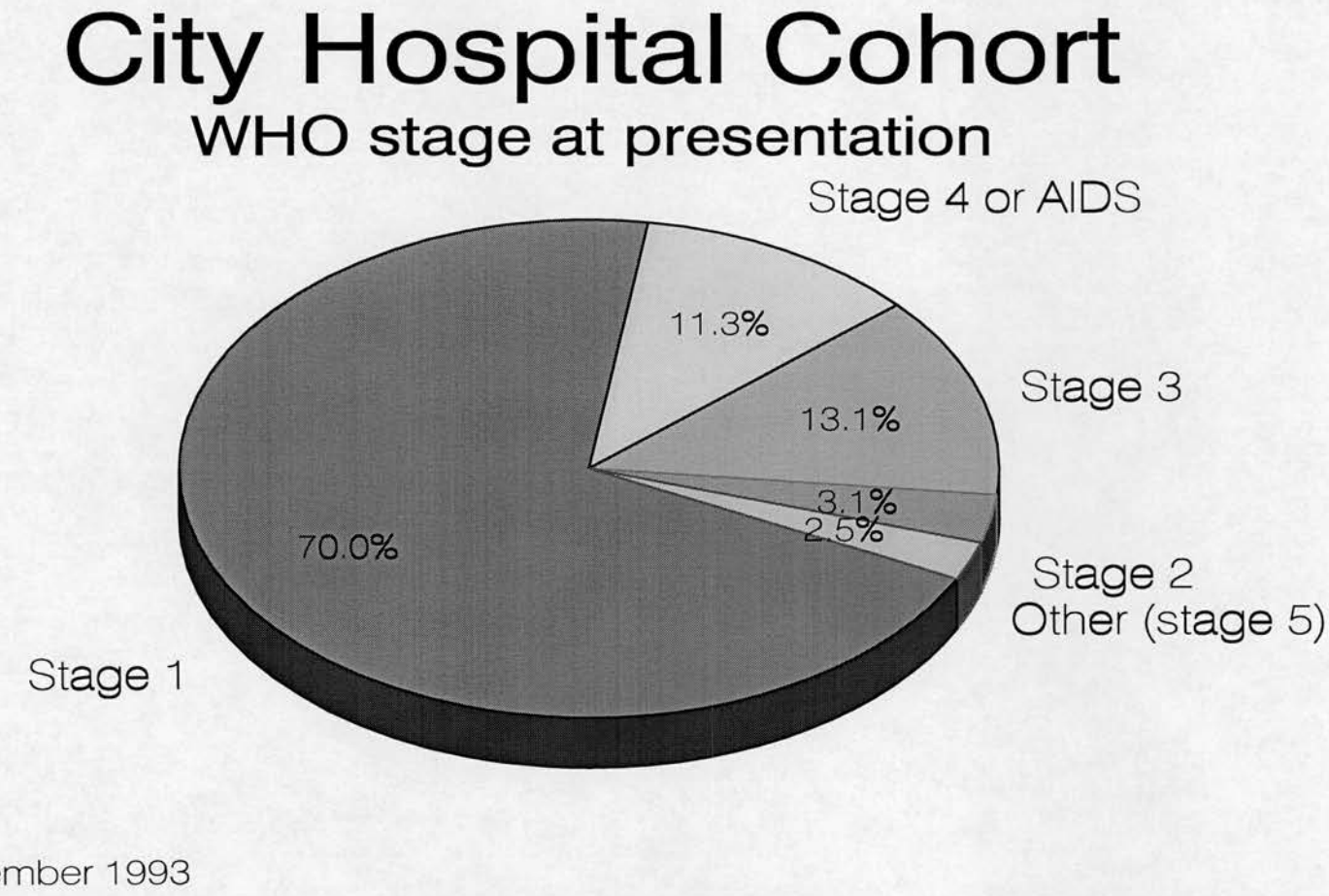

Figure 17.4: Clinical features (WHO stage) of patients at first visit to City Hospital

Table 17.3: Clinical features (modified WHO code, AIDS) at first visit by year of presentation

WHO code	'84	'85	'86	'87	'88	'89	'90	'91	'92	'93	Total
402				2	1	1		1	2	2	**9**
409	1			1	2		1		1	3	**9**
414		1	1	3	6	9	9	7	4	8	**48**
Others				1	3	2	1		2	2	**11**
Total	**1**	**1**	**1**	**7**	**12**	**12**	**11**	**8**	**9**	**15**	**77**

There were significant risk activity differences in the clinical features at enrolment according (Tables 17.4); 79% of drug users, 77% of heterosexuals but only 32% of homo/bisexuals enrolled when asymptomatic ($\chi^2_{(1)}= 87.5$, $p<0.001$). There were no significant differences between heterosexuals and drug users in terms of their initial presentation. Oral thrush (code 304) was commoner in homo/bisexuals than IDUs or heterosexuals (10% vs. 4 and 3%, $\chi^2_{(1)}= 6.6$, $p<0.05$) as was OHL (code 306; 9% vs. 1 and 2%, $\chi^2_{(1)}= 6.9$, $p<0.01$). A presentation with weight loss (code 301) was equally common in the major risk groups. HIV related thrombocytopaenia (code 507) was not seen in homo/bisexuals and accounted for only 2.5% of presentations for IDUs and 1% of heterosexuals, perhaps suggesting that it is essentially an early clinical problem.

Table 17.4: Clinical features (modified WHO code, Non-AIDS) at first visit by risk activity

WHO code	IDU	Het	Ho/bi	Blood	Ho/IDU	Unknown	Total
Stage 1							
101	193	48	19	3	1	1	**265**
102		1	1				**2**
103	172	24	13				**209**
Sub total	**365**	**73**	**33**	**3**	**1**	**1**	**476**
Stage 2							
202	12	1	2				**15**
203	1	1	1	1			**4**
204	2						**2**
Sub total	**15**	**2**	**3**	**1**			**21**
Stage 3							
301	14	3	2	1	1		**21**
304	17	1	10	1		1	**30**
306	14	2	10		1		**27**
308	6	2	2	1			**11**
Sub total	**51**	**8**	**24**	**3**	**2**	**1**	**89**
Others							
504	1						**1**
506			1				**1**
507	12	1				1	**14**
509	1						**1**
Sub total	**14**	**1**	**1**			**1**	**17**
Total	**445**	**84**	**61**	**7**	**3**	**3**	**603**

The frequency of an AIDS diagnoses at first clinic visit for the cohort as a whole were as follows; oesophageal candida (code 402) 1%, Kaposi's sarcoma (code 409) 1% and PCP (code 414) 7%. By year of presentation, PCP (code 414) was the initial AIDS diagnosis in 43% of those presenting with AIDS in 1987, 88% in 1991 and 53% in 1993 (Table 17.3). Of the 77 patients with AIDS at their first clinic visit (Table 17.3 and figure 17.5), 22 (29%) were referred with a pre-existing diagnosis of AIDS. The common presentations were; oesophageal candida (code 402) 12%, Kaposi's sarcoma (code 409) 12% and PCP (code 414) 62%.

Risk activity differences for those presenting with AIDS at there initial visit were not pronounced. The analysis was complicated by whether or not individuals with a prior diagnosis of AIDS were included (Tables 17.5 and 17.5a). No significant differences were observed for clinical presentation to the RIDU with AIDS (Table 17.5a). PCP with or without other OI's (69%) was the commonest clinical problem

for patients presenting to RIDU with AIDS followed by oesophageal candida (7%) and malignant disease (5.5%).

Table 17.5: Clinical features (modified WHO code, AIDS) at first visit by risk activity

WHO code	IDU	Het	Ho/bi	Blood	Ho/IDU	Unk	Total(%)
402	2	2	3				**7(9)**
404			1				**1**
406			1				**1**
409			6				**6**
410		1					**1**
411			1				**1**
412+405	1		2				**2**
414	9(56)	8(71)	21(48)			1	**39(51)**
414+402	1	1					**2**
414+407	1						**1**
414+407+405		1					**1**
414+409			2				**2**
414+410	1		1				**2**
414+412	1		1	1			**3**
414+416+410+403		1					**1**
414+417			2				**2**
414+417+407						1	**1**
414 sub total	**13(81)**	**11(79)**	**27(61)**	**1**		**2**	**54(70)**
415	1						**1**
417			1				**1**
417+409			**2**				**2**
Total	**16(21)**	**14(17)**	**44(58)**	**1(1.5)**	**0**	**2(2.5)**	**77(100)**

Table 17.5a: Clinical features (modified WHO code, AIDS) at first visit by risk activity excluding AIDS events prior to first visit at the City Hospital

WHO code	IDU	Het	Ho/bi	Blood	Ho/IDU	Unk	Total(%)
402	2(15)	1(9)	1(3)				**4(7)**
404			1				**1**
406			1				**1**
407+405		1					**1**
409			1				**1**
410		1	1				**2**
411			1				**1**
412			1				**1**
412+405			1				**1**
414	6(46)	6(55)	18(60)				**30(55)**
414+402	1	1					**2**
414+407	1						**1**
414+409			1				**1**
414+410	1	1					**2**
414+412	1			1			**2**
414 sub total	**10(77)**	**8(73)**	**19(63)**	**1**			**38(69)**
415	1						**1**
417			2				**2**
417+409			**1**				**1**
Total	**13**	**11**	**30**	**1**	**0**		**55**

The effect of gender on presentation is shown in Table 17.6. More females presented when asymptomatic (84%) compared to males (64%) and this difference was significant ($\chi^2_{(1)}$= 28.4, p<0.001). There was no difference in HIV related thrombocytopaenia (code 507) at 2% for men and 1% for women.

Twelve or 6% of women (2 with oesophageal candida and 10 with PCP) presented with AIDS at their first clinic visit compared to 65 or 14% of men. Oesophageal candida (1.5% of men and 1% of women) and PCP (11% for men and 5% of women) showed differences but not as previously reported. The lower numbers of women presenting with these two problems may reflect the fact that women tend to present when asymptomatic in Edinburgh and may therefore be more likely to utilise prophylaxis which is available for both PCP and thrush. If expressed as a percentage of AIDS cases at first visit for women PCP was the commonest presentation at 83% compared to 68% for men.

Table 17.6: Clinical features (modified WHO code AIDS and Non-AIDS) at first visit by gender

Modified WHO code code	Male(%)	Female(%)	Total(%)
Stage 1			
101	148	117	**265**
102	2		**2**
103	154	55	**209**
Sub total	**304(64)**	**172(84)**	**476(70)**
Stage 2			
202	14	1	**15**
203	2	2	**4**
204	1	1	**2**
Sub total	**17(3.5)**	**4(2)**	**21(3)**
Stage 3			
301	17	4	**21**
304	25	5	**30**
306	26	1	**27**
308	8	3	**11**
Sub total	**76(16)**	**13(6)**	**89(13)**
Others			
504	1		**1**
506	1		**1**
507	11	3	**14**
509	1		**1**
Sub total	**14(3)**	**3(1)**	**17(2.5)**
Stage 4	**65(13.5)**	**12(5)**	**77(11)**
Total	**476(100)**	**202(100)**	**680(100)**

Cumulative clinical events (Non AIDS)

By the 30/9/93 a total of 482 (71%) patients had been noted to have become symptomatic i.e. had moved into WHO stage 2 or higher; 104 (15%) patients remained in WHO stage 2, 293 (43%) had been in WHO stage 3, 35 (5%) in WHO stage 5 and 197 (30%) in WHO stage 4.. The percentages relate to the cohort as a whole and the frequency of ever having had a condition. Consequently their sum exceeds 100% since the patients may progress through many of these conditions.

The distribution of these symptomatic events by risk activity are shown in Table 17.7. In view of what is known about the Edinburgh epidemic considerable differences in the clinical conditions associated with risk groups were observed. For instance only 5% of the 104 homo/bisexuals were ever diagnosed in WHO stage 2

compared to 13% of the heterosexuals and 18% of those infected via IDU. By comparison 60.5% homo/bisexuals had developed WHO stage 4 or AIDS compared to only 21% of heterosexuals and 22.5% of IDUs (Table 17.11).

Important clinical problems (Table 17.7) observed for the cohort as a whole (680 patients) were; minor skin problems (code 202, 62 or 9%), minor bacterial infections (code 204, 27 or 4%), major bacterial problems (code 308, 44 or 6.5%), oral thrush (code 304, 110 or 16%), OHL (code 306 82 or 12%), significant weight loss of >10% (code 301, 58 or 8.5%), HIV related thrombocytopaenia (code 507, 30 or 4%).

Significant differences were observed in the frequency of clinical conditions depending upon risk activity (Tables 17.7 and 17.8); between IDU and homo/bisexuals for OHL (15% vs. 54%, $\chi^2_{(1)}= 34.5$, $p<0.001$) and weight loss (14% vs. 5%, $\chi^2_{(1)} = 6.1$, $p< 0.05$) but not severe bacterial infections (9% vs. 2%, $\chi^2_{(1)}=1.1$); between IDU and heterosexuals for oral candidiasis (23% vs. 9%, $\chi^2_{(1)} = 4.8$, $p<0.05$), weight loss (14% vs. 5%, $\chi^2_{(1)}= 4.3$, $p<0.05$), OHL (25% vs. 15%, $\chi^2_{(1)}= 4.0$, $p<0.05$) and thrombocytopaenia (9% vs. 1% $\chi^2_{(1)}= 5.7$, $p<0.05$); between homo/bisexuals and heterosexuals for weight loss (34% vs. 11%, $\chi^2_{(1)}= 12.4$, $p<0.001$), oral thrush (82% vs. 25%, $\chi^2_{(1)}= 46.6$, $p<0.001$) and OHL (62% vs. 15%, $\chi^2_{(1)}= 34.5$, $p<0.001$).

The rate of development of clinical conditions (Table 17.8 and figure 17.5) according to risk activity was calculated for the most important clinical events; weight loss (code 301), oral thrush (code 304), oral hairy leucoplakia (OHL or code 306) and severe bacterial infections (code 308).

Table 17.7: Cumulative number of clinical events (modified WHO codes , Non AIDS) by risk activity

WHO code	IDU (%) N=445	Het (%) N=84	Ho/bi (%) N=61	Blood (%) N=7	Ho/IDU N=3	Unknown N=3	Total(%) N=603
101	197(44)	50(59)	21(34)	3(4)	1(33)	1(33)	**273**(45)
102	1	3(4)	2(3)				**6**(1)
103	262(59)	35(41)	15(25)	1(14)			**313**(52)
201	4(1)						**4**
202	159(36)	20(24)	25(41)	1(14)	3(100)		**208**(34)
203	32(7)	4(5)	12(20)	1(14)	1(33)		**50**(8)
204	58(13)	11(13)	10(16)	2(29)	2(67)	1(33)	**84**(14)
301*	91(20)	9(11)	21(34)	2(29)	1(33)		124(21)
302	9(2)	1(1)	6(10)		1(33)		**17**(3)
303		2(2)					**2**
304*	165(37)	21(25)	50(82)	3(43)	2(67)	3(100)	**244**()40
305	3	1(1)		1(14)			**5**
306*	113(25)	13(15)	38(62)	2(29)	2(67)	1(33)	**169**(28)
307	4(1)						**4**
308*	118(27)	17(20)	20(33)	4(57)			**159**(26)
504	8(2)		2(3)				**10**(2)
505			1(2)				**1**
506	9(2)	1(1)	9(15)	1(14)			**20**(3)
507	38(9)	1(1)	1(2)	1(14)		1(33)	**42**(7)
508	1						**1**
509	8(2)		1(2)		1(33)		**10**(2)

** Significant on a chi squared test with one degree of freedom; 301 IDU vs. ho/bi $\chi^2 = 6.1$, $p<0.05$, IDU vs. het $\chi^2 = 4.5$, $p<0.05$, ho/bi vs. het $\chi^2 = 12.4$, <0.001 ; 304 IDU vs. het $\chi^2 = 4.8$, $p<0.05$, IDU vs. ho/bi $\chi^2 = 44.2$, $p<0.001$, ho/bi vs. het $\chi^2 = 46.6$, $p<0.001$; 306 IDU vs. ho/bi $\chi^2 = 34.9$ $p< 0.001$, ho/bi vs. het $\chi^2 = 34.5$, $p<0.001$; 308 IDU vs. ho/bi $\chi^2 = 1.1$ NS, IDU vs. het $\chi^2 = 1.6$, NS, ho/bi vs. het $\chi^2 = 3.1$, NS; 507 IDU vs. het $\chi^2 = 5.7$, $p<0.05$.*

Table 17.8: Rate (per 100 person years) of common clinical conditions (Non AIDS) by risk activity

WHO code	IDU (1674.7 person yrs)	Het (196.8 person yrs)	Ho/bi (96.4 person yrs)	Others (19.3 person yrs)	Total (1987.2 person yrs)
201	0.24				**0.2**
202	9.5	10.2	25.9	20.7	**10.5**
203	1.9	2.0	12.4	10.4	**2.5**
204	3.5	5.6	10.4	25.9	**4.2**
301*	5.4	4.6	21.8	15.5	6.2
302	0.54	0.5	6.2		**0.86**
303		1.0			**0.1**
304*	9.9	10.7	51.9	41.5	**12.3**
305	0.18	0.5		5.2	**0.25**
306*	6.7	6.6	39.4	25.9	**8.5**
307	0.24				**0.2**
308*	7.0	8.6	20.7	20.7	**8.0**
504	0.48		2.1		**0.5**
505			1.0		**0.05**
506	0.54	0.5	9.3	5.2	**0.1**
507	2.3	0.5	1.0	10.4	**2.1**
508	0.06				**0.05**
509	0.48		1.0	5.2	**0.5**

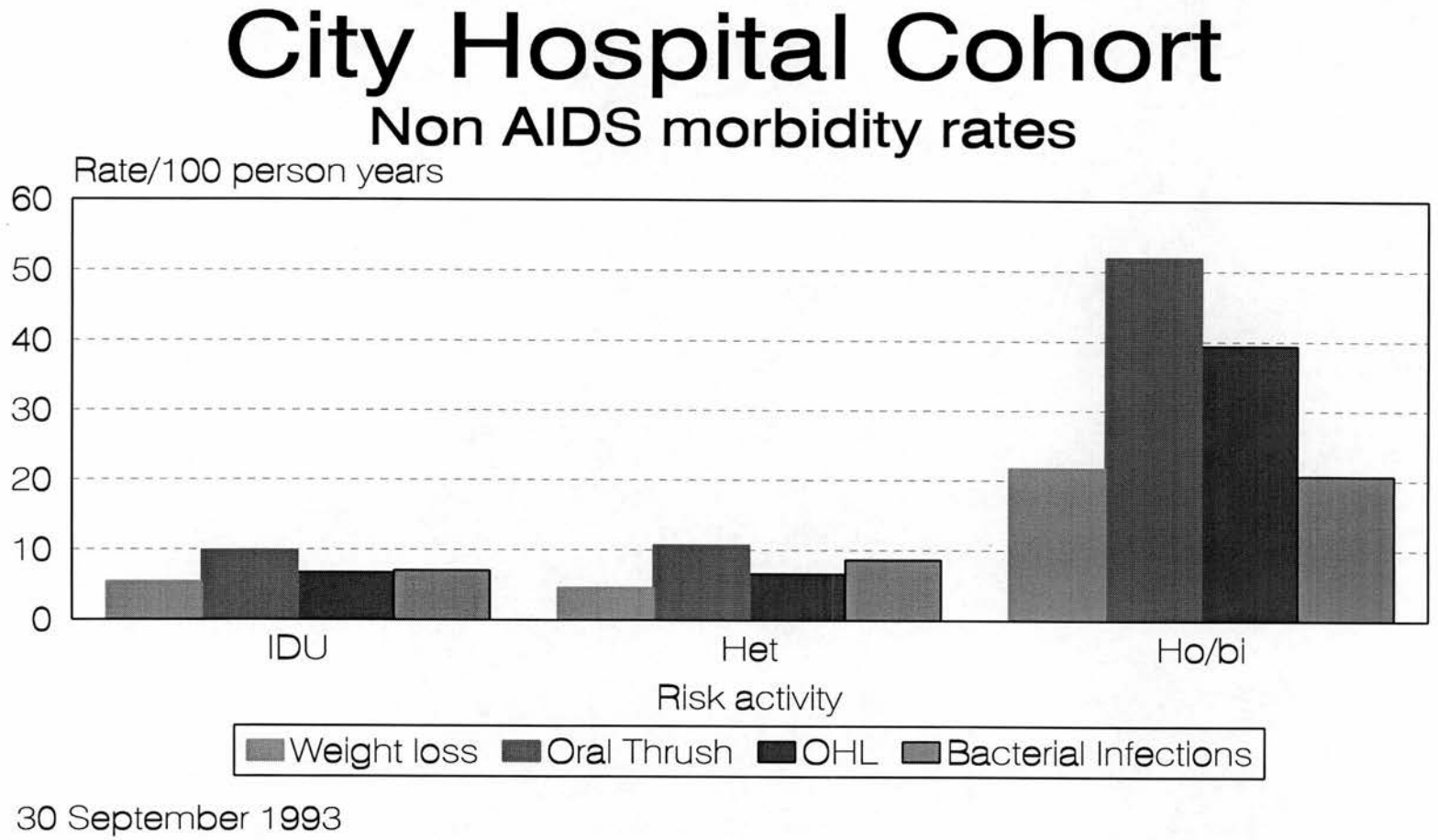

Figure 17.5: Rate of some common clinical conditions (Non AIDS) by risk activity

The analysis for gender differences was undertaken without homo/bisexuals (Table 17.9) . Significant differences were noted only for the fact that women were more likely to have had recurrent upper respiratory tract infections ($\chi^2_{(1)} = 6.3$, $p<0.05$). All other differences including thrush or OHL were not significant.

Table 17.9: Cumulative number of clinical events (modified WHO codes, Non-AIDS) by gender with and without homo/bisexuals

WHO code	Complete cohort (%)			Cohort without homo/bisexuals (%)		
	Male N=411	**Female N=192**	**Total N=603**	**Male N=350**	**Female N=192**	**Total N=542**
201	4(1)		**4**	4(1)		**4(1)**
202	145(4)	63(33)	**208(34)**	120(34)	63(33)	**183(34)**
203	36(9)	14(7)	**50(8)**	24(7)	14(7)	**38(7)**
204*	51(12)	33(17)	**84(14)**	41(12)	33(17)	**74(14)**
301	85(21)	39(20)	**124(21)**	64(18)	39(20)	**103(19)**
302	13(3)	4(2)	**17(3)**	7(2)	4(2)	**11(2)**
303	1	1	**2**	1	1	**2**
304	180(44)	64(33)	**244(40)**	130(37)	64(33)	**194(36)**
305		5(3)	**5(1)**		5(3)	**5(1)**
306	134(33)	35(18)	**169(28)**	96(27)	35(18)	**131(24)**
307	4(1)		**4**	4(1)		**4**
308	108(26)	51(26)	**159(26)**	88(25)	51(26)	**139(26)**
504	9(2)	1	**10(2)**	7(2)	1	**8(2)**
505	1		**1**			**1**
506	19(5)	1	**20(3)**	10(3)	1	**11(2)**
507	25(6)	17(9)	**42(7)**	24(7)	17(9)	**41(8)**
508	1		**1**	1		**1**
509	9(2)	1	**10(2)**	8(2)	1	**9(2)**

** Significant on a chi squared test with one degree of freedom; 204 males vs. females excluding ho/bisexuals $\chi^2 = 2.5$ NS; 204 males vs. females excluding ho/bisexuals $\chi^2 = 6.3$ $p<0.05$*

AIDS as an index diagnosis

The frequency of particular conditions as index diagnoses in 198 patients with AIDS (table 17.10 and figure 17.6) was as follows; 22 or 11% had multiple index conditions at presentation; the commonest was PCP (code 414) in conjunction with other OI's (single and double) and this occurred in 7% of the index diagnoses. For the rest the diagnosis of AIDS was made via a single event; PCP (code 414) alone 51%, oesophageal candidiasis (code 402) 15%, Kaposi's sarcoma (code 409) 5.5%, HIV dementia (code 407) 4%, atypical mycobacteria (code 412) 4%, cerebral toxoplasmosis (code 417) 2.5%, lymphoma (code 410) 2%, CMV disease (code 405) 1.5% and extra pulmonary tuberculosis (code 411) 1.5%. Thus PCP was involved in 58% of the AIDS index conditions. The incidence of AIDS for the cohort as a whole, by risk activity and gender is shown in table 17.11 and figure 17.7. Not surprisingly Kaposi's sarcoma was significantly commoner as a presentation in homo/bisexuals than in drug users. Oesophageal candidiasis was commoner in drug users than homosexuals ($\chi^2_{(1)}= 4.6$, $p<0.05$). There were no significant gender differences.

Table 17.10: Clinical features of patients with an index diagnosis of AIDS by risk activity

WHO code	IDU (%)	Het(%)	Ho/bi(%)	Blood	Ho/IDU	Unknown	Total (%)
Single							
402	20(19)	3(14)	5(7)				**28(15)**
405			3(5)				**3**
406			2(3)				**2**
407	7(7)	1					**8(4)**
409		1	10(15)				**11(5.5)**
410	1	1	1	1			**4**
411	2		1				**3**
412	7		1				**8(4)**
414	53(51)	9(41)	35(52)	1	1	2	**101(51)**
415	2	1					**3**
416		1					**1**
417		2	3				**5**
Subtotal	**92(88)**	**19(86)**	**61(91)**	**2**	**1**	**2**	**177(89)**
Multiple							
402+405	1						**1**
411+407	1						**1**
412+405	1		1				**2**
414+402	2	2					**4**
414+405			1				**1**
414+407	1						**1**
414+409	1		2				**3**
414+410	1						**1**
414+412	1			1			**2**
414+417				1			**1**
417+405	1						**1**
417+409	1			1			**2**
414+412+404		1					**1**
Sub total for >1 code	**11(11)**	**3(14)**	**6(9)**	**2**	**0**	**0**	**22(11)**
Total	**103**	**22**	**67**	**3**	**1**	**2**	**198(100)**

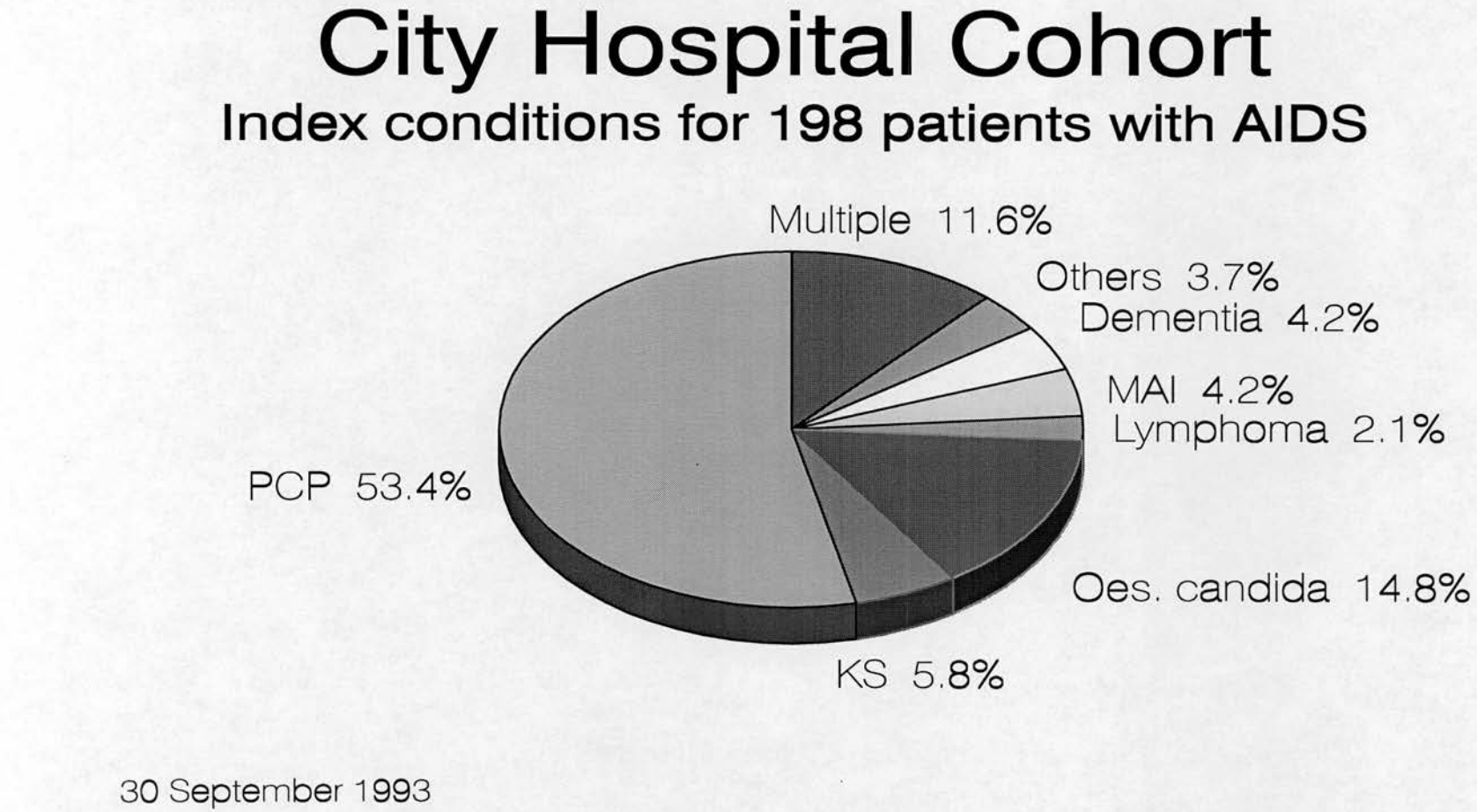

Figure 17.6: Clinical features of patients with an index diagnosis of AIDS

Table 17.11: AIDS incidence/100 person years for risk groups

Risk Group	Follow up (person years)	No. cases of AIDS	Rate/100 person years
IDU	1798.7	103	**5.7**
Het	221.3	22	**9.9**
Ho/bi	203	67	**33.0**
Others	23.4	6	**25.6**
All Males	1454.5	157	**10.8**
Non Ho/bi males	1251.5	94	**7.5**
Female	791.9	41	**5.2**
Total	2246.4	198	**8.8**

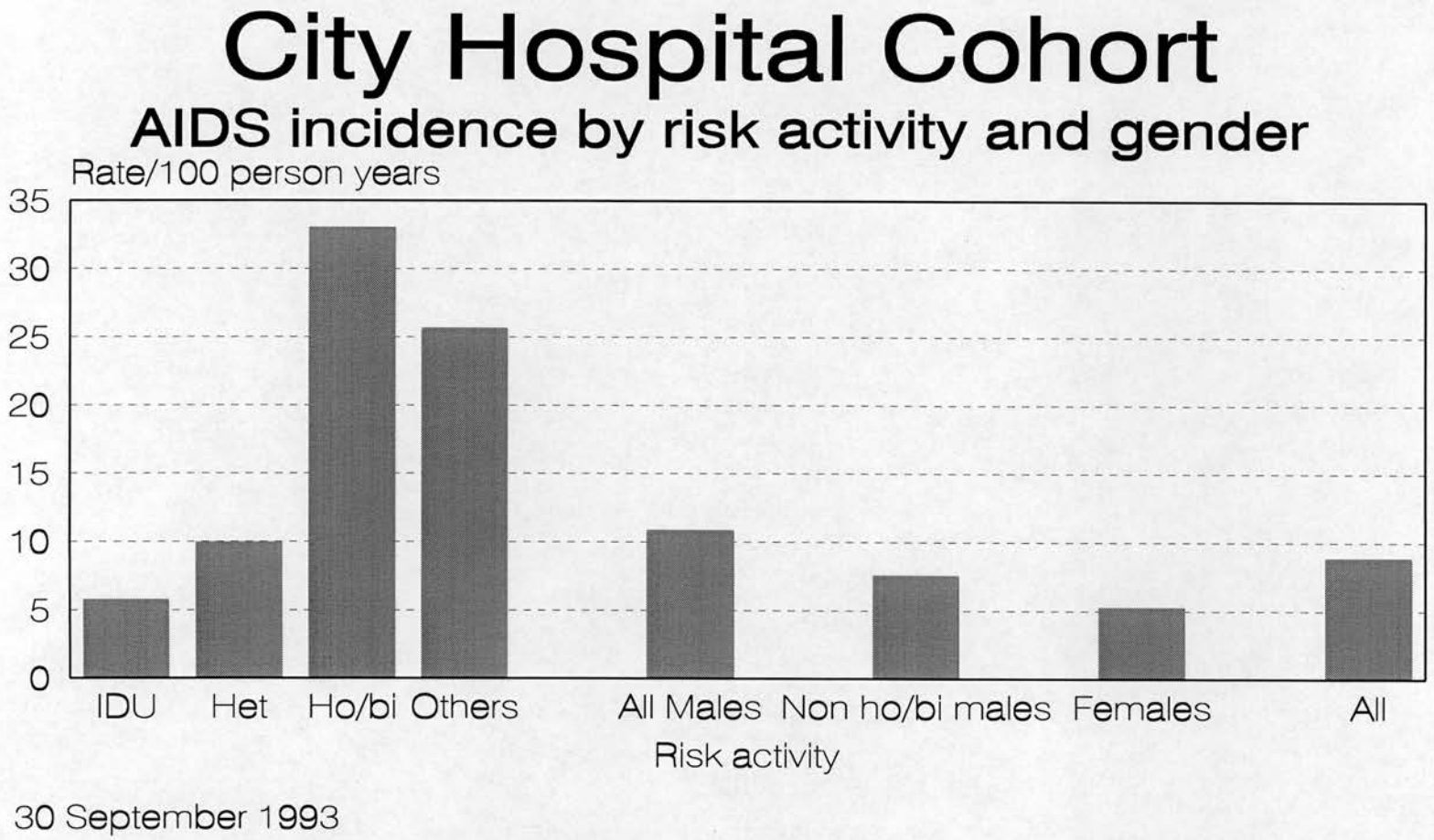

Figure 17.7: AIDS incidence by risk activity and gender

Cumulative AIDS events

The 198 patients with AIDS had more than one WHO stage 4 condition over the study period. The number of patients ever having particular clinical events were as follows (table 17.12 and figure 17.8); PCP (code 414, 180 or 91%), oesophageal candidiasis (code 402, 56 or 28%), Kaposi's sarcoma (code 409, 22 or 11%), disseminated MAI (code 412, 58 or 29%), HIV dementia (code 407, 19 or 10%), CMV disease (code 405, 41 or 21%), extra-pulmonary tuberculosis (code 411, 4 or 2%). The percentages relate to the cohort as a whole and the frequency of ever having had a condition. Consequently they exceed 100% since the patients progress through many of these conditions.

As expected KS (code 409) was significantly commoner in homo/bisexuals (28%) compared to the other risk groups (2-5%). One female, an African heterosexual from Zaire and 2 heterosexual drug users (2%) developed biopsy proven KS.

Significant differences were observed for risk group however; between IDU and homo/bisexuals for oesophageal candida (40% vs. 13%, $\chi^2_{(1)}=13.5$, $p<0.01$), CMV (14% vs. 34%, $\chi^2_{(1)} = 10.3$, $p< 0.001$), KS (2% vs. 28%, $\chi^2_{(1)}= 26.2$, $p<0.001$) and toxoplasmosis (7% vs. 28%, $\chi^2_{(1)}= 14.5$, $p<0.001$); between homo/bisexuals and heterosexuals for KS (28% vs. 5%, $\chi^2=5.4$, $p<0.05$) and PCP (84% vs. 100%, $\chi^2_{(1)} = 4.1$, $p<0.05$)

Table 17.12: Cumulative number of clinical events for AIDS (modified WHO code) by risk activity

WHO code	IDU(%) N=103	Het(%) N=22	Ho/bi(%) N=67	Blood N=3	Ho/IDU N=1	Unknown N=2	Total(%) N=198
402*	41(40)	6(27)	9(13)				**56(28)**
403	3(3)	1(5)	1(2)				**5(2.5)**
404	3(3)	3(14)	2(3)				**8(4)**
405*	14(14)	4(18)	23(34)				**41(21)**
406			4(6)				**4(2)**
407	14(14)	2(9)	2(3)			1	**19(10)**
409*	2(2)	1(5)	19(28)				**22(11)**
410	8(8)	3(14)	10(15)	2			**23(12)**
411	3(3)		1(2)				**4(2)**
412	31(30)	4(18)	22(33)	1			**58(29)**
414*	93(90)	26(100)	56(84)	2	1	2	**180(91)**
415	2((2)	1(5)					**3(1.5)**
416	1(1)	1(5)					**2(1)**
417*	7(7)	3(14)	19(28)			1	**31(16)**

** Significant on a chi squared test with one degree of freedom; 402 IDU vs. ho/bi* $\chi^2=13.5$ *p<0.001; 405 IDU vs. ho/bi* $\chi^2=10.3$, *p<0.001; 409 IDU vs. ho/bi* $\chi^2=26.2$ *p< 0.001, ho/bi vs. het* $\chi^2=5.4$, *p<0.05; 414 ho/bi vs. het* $\chi^2=4.1$ *p< 0.05; 417 IDU vs. ho/bi* $\chi^2=14.5$ *p<0.001.*

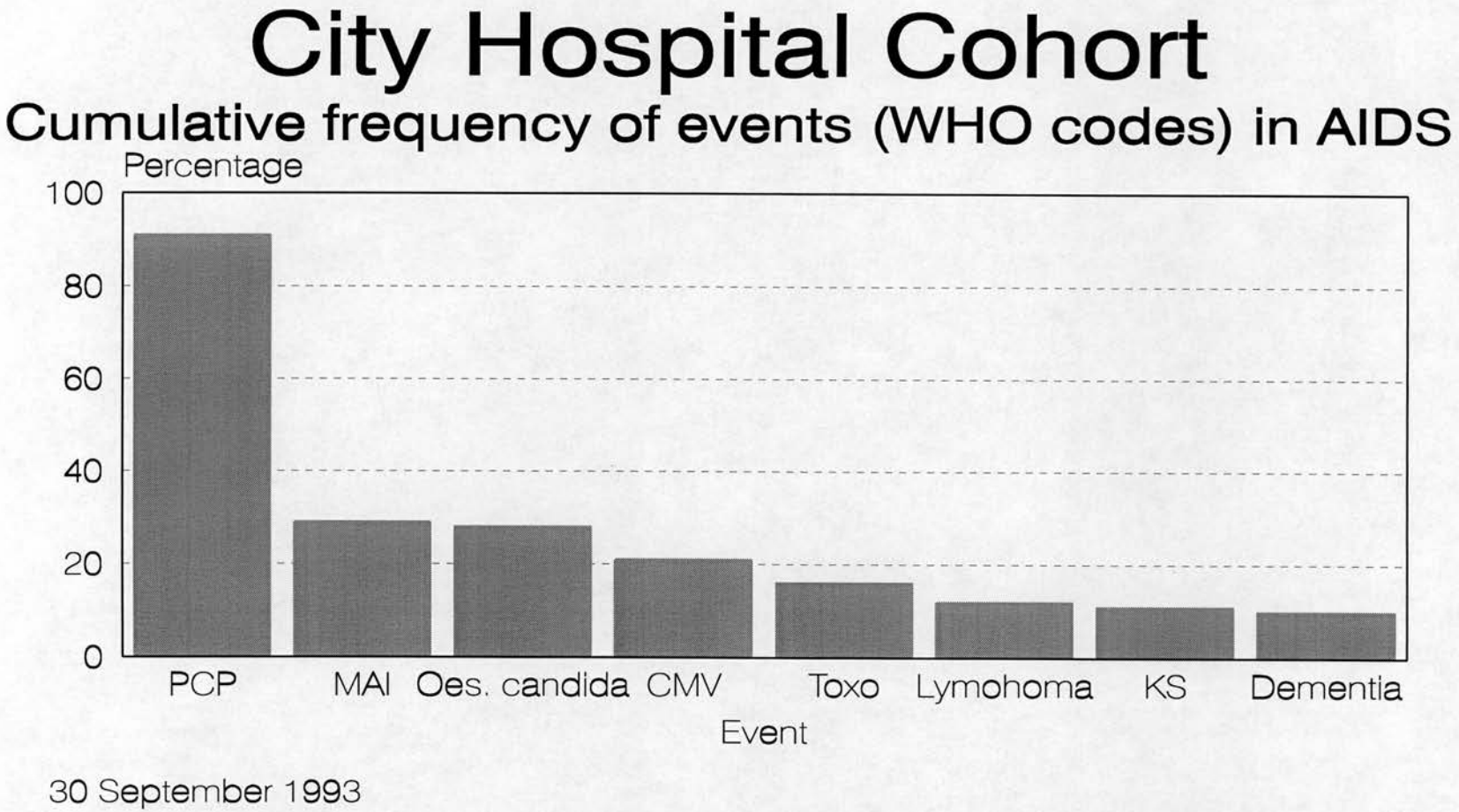

Figure 17.8: Cumulative frequency of clinical events (modified WHO codes) for patients with AIDS by risk activity

Table 17.13: Cumulative number of clinical events (AIDS) expressed as rates/100 person years of follow up (modified WHO codes) by risk activity

WHO code	IDU (124 person yrs.)	Het (24.6 person yrs.)	Ho/bi (106.6 person yrs.)	Others (4.08 person yrs.)	Total (259.3 person yrs.)
402	33	24.4	8.4		**21.6**
403	2.4	4.1	0.9		**1.9**
404	2.4	12.2	1.9		**3.1**
405	11.3	16.3	21.6		**15.8**
406			3.8		**1.5**
407	11.3	8.1	1.9	24.5	**7.3**
409	1.6	4.1	17.8	24.5	**8.5**
410	6.5	12.2	9.4	49	**8.9**
411	2.4		0.9		**1.5**
412	25	16.2	20.6	24.5	**22.4**
414	75	105.7	52.5	122.5	**69.4**
415	1.6	4.1			**1.2**
416	0.8	4.1			**0.8**
417	5.6	16.3	17.8	24.5	**11.9**
Total	**179**	**227**	**135**	**245**	**176**

An assessment of the morbidity of patients with AIDS was obtained by expressing the WHO events observed as a rate/100 person years of follow up both for all the patients and by risk activity (Table 17.13 and figures 17.9-11).

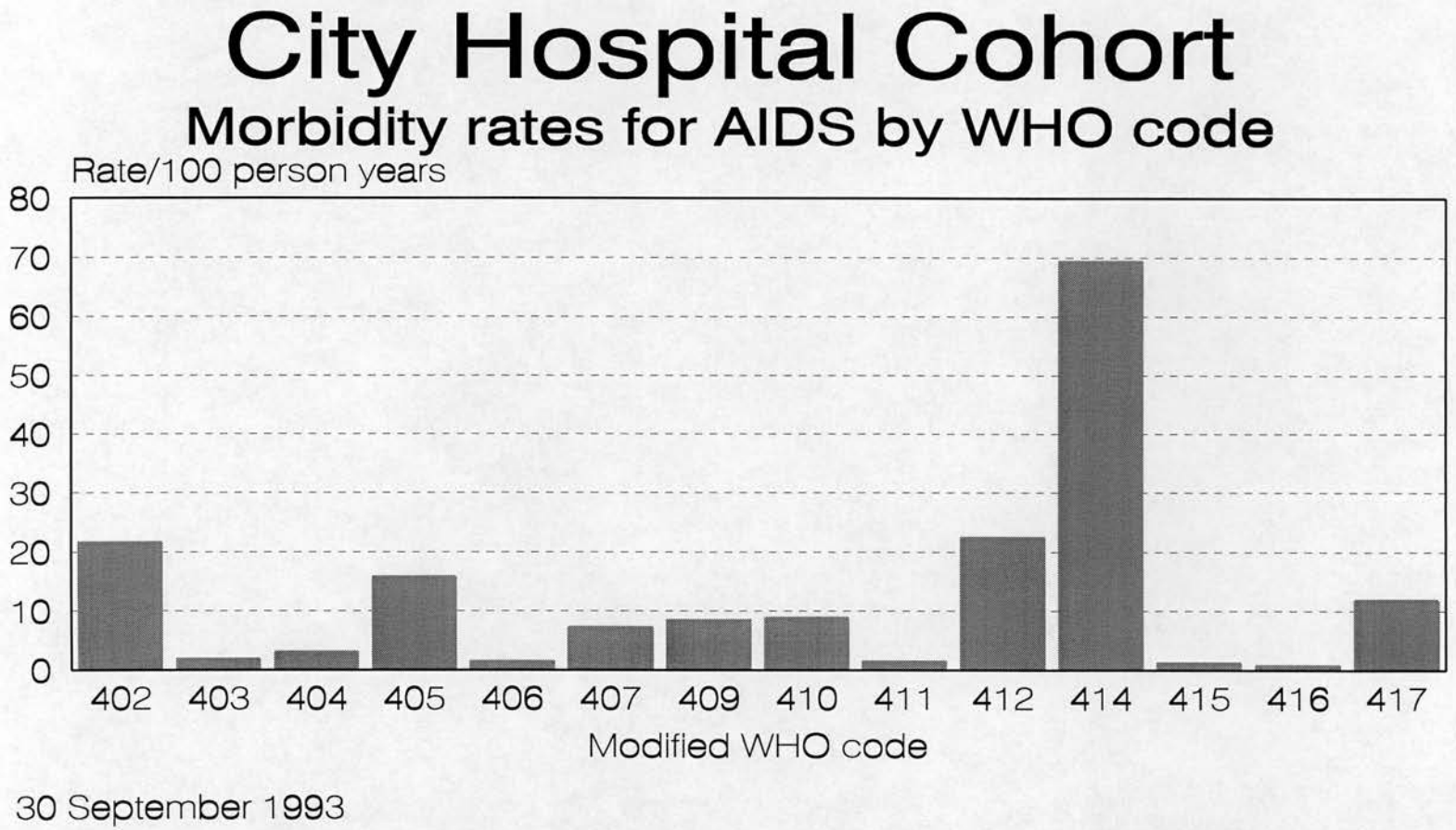

Figure 17.9: Cumulative morbidity or number of clinical events (AIDS) expressed as rates/100 person years of follow up by modified WHO codes

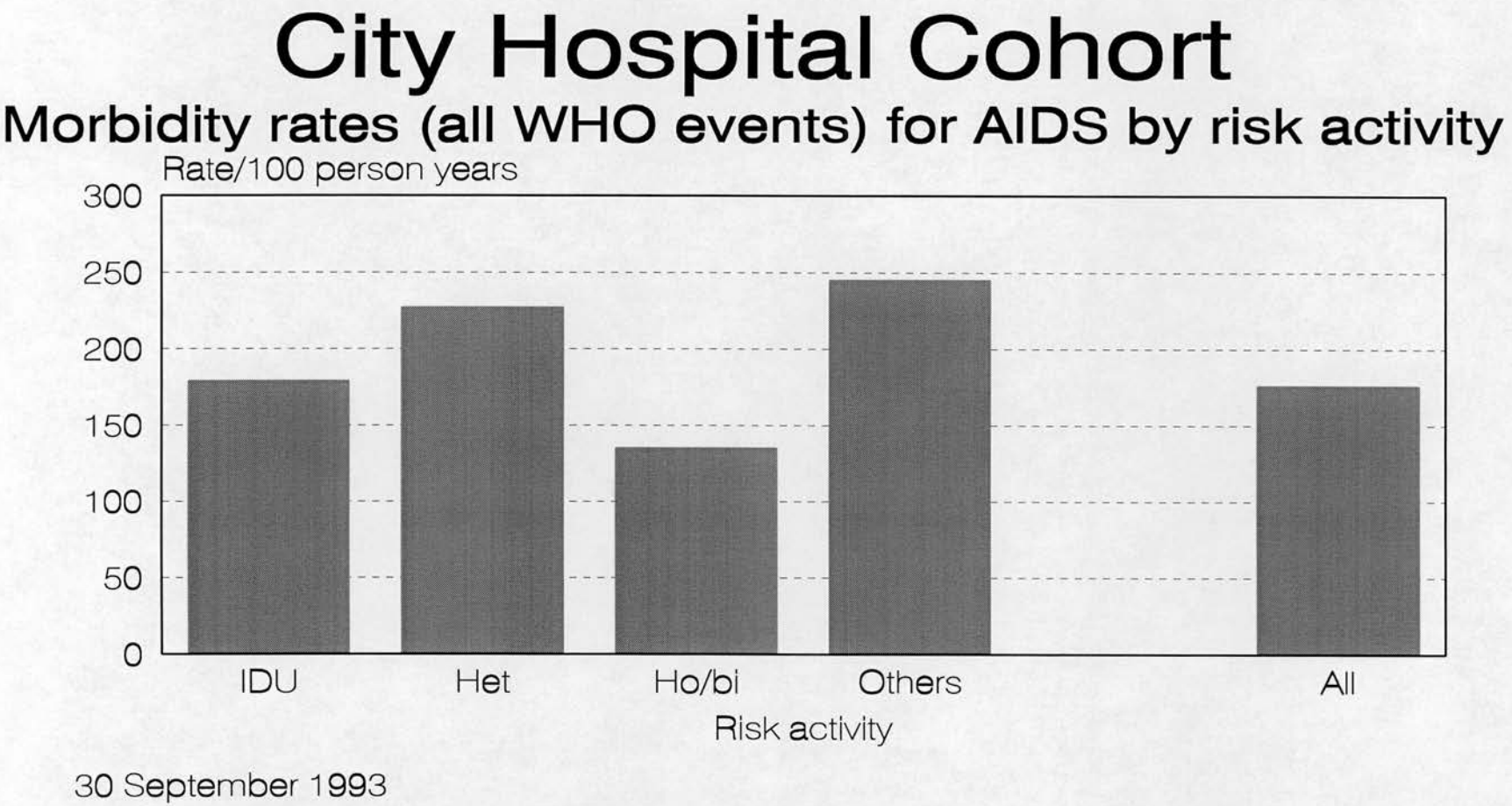

Figure 17.10: Cumulative morbidity or number of clinical events (AIDS) expressed as rates/100 person years of follow up by risk activity

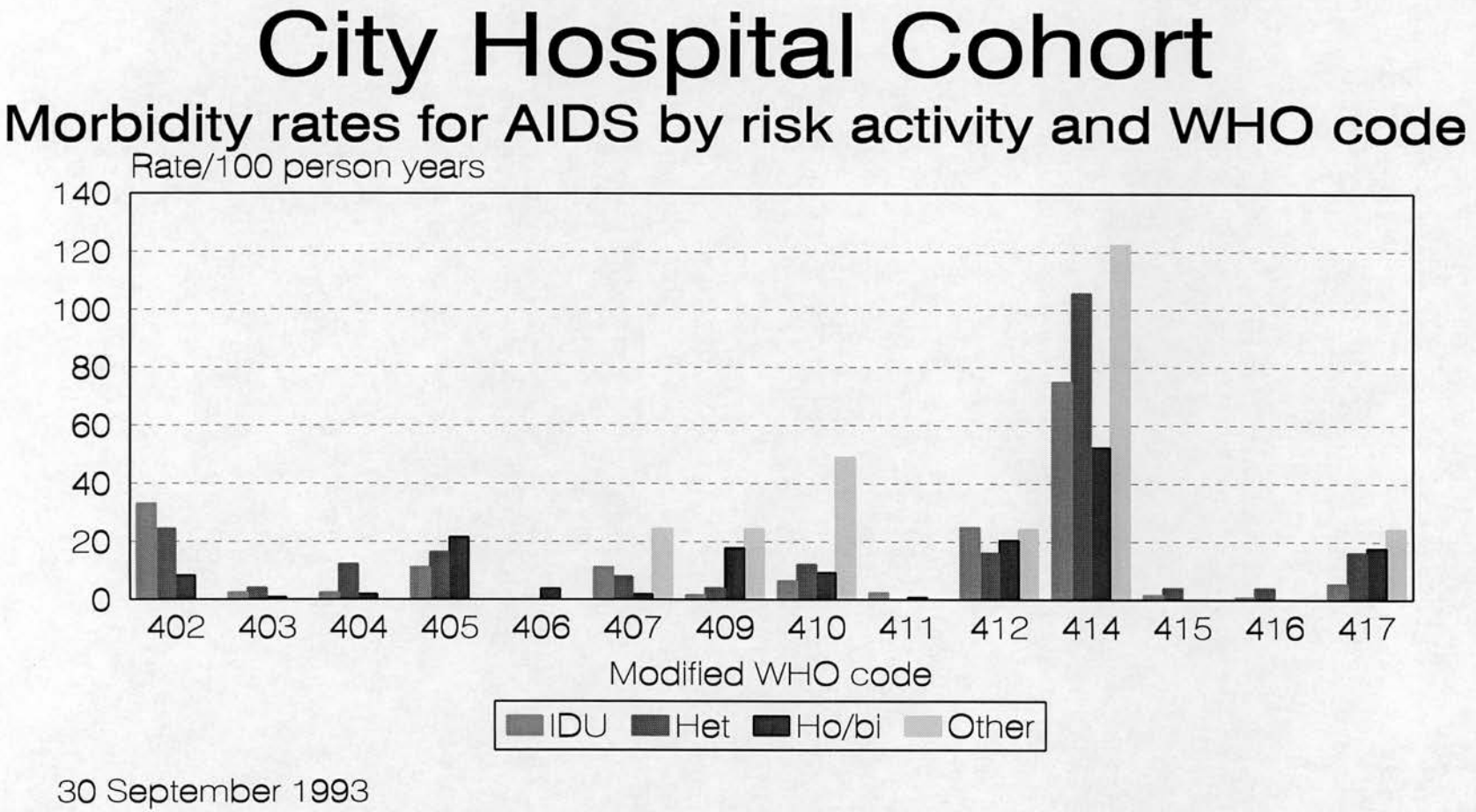

Figure 17.11: Cumulative morbidity or number of clinical events (all WHO AIDS events) expressed as rates/100 person years of follow up by risk activity and modified WHO codes

No significant gender differences were noted with the homo/bisexuals excluded from the analysis (Table 17.14).

Table 17.14: Cumulative number of clinical events (modified WHO codes, AIDS) by gender with and without homo/bisexuals

WHO code	All patients with AIDS (%)			Excluding homo/bisexuals (%)		
	Male N=157	Female N=41	Total N=198	Male N=94	Female N=41	Total N=135
402	36	14	**50**	28	14	**42**
403	5	0	**5**	4	0	**4**
404	4	4	**8**	2	4	**6**
405	28	9	**37**	7	9	**16**
406	4		**4**	4		**4**
407	14	3	**17**	12	3	**15**
409	22	1	**23**	2	1	**3**
410	21	2	**23**	11	2	**13**
411	4		**4**	3		**3**
412	39	5	**44**	20	5	**25**
414	103	31	**134**	57	31	**88**
415	3		**3**	3		**3**
416	2		**2**	2		**2**
417	19	3	**22**	7	3	**10**

Mortality

A total of 181 (27%) of 680 patients had died, 131 (72%) after a diagnosis of AIDS. Only 6 (%) patients died in the same month as the diagnosis of AIDS was made, whilst a total of 11 (%) patients died in the two months after the diagnosis of AIDS was made. Ten patients with AIDS died after the diagnosis of AIDS but not of an obvious AIDS related problem; 3 died of liver failure, 2 of drug overdoses, 4 of unknown causes without post mortem information and one of pulmonary hypertension which could have been either as a consequence of HIV or IDU.

Overall the patients had a mortality rate of 8.1/100 person years (Table 17.15 and figure 17.12). The mortality rate for those developing AIDS was 5.8/100 person years compared with 2.2/100 person years for those dying before a diagnosis of AIDS. There were significant differences in mortality when analysed by risk group. When mortality rates were examined for drug users alone the rates were 5.9/100 persons years (3.4 after AIDS and 2.5 before AIDS). The rates for other risk groups

were as follows; heterosexuals 6.3/100 person years (5.4 after AIDS and 0.9 before AIDS), homo/bisexuals 27.5/100 person years (26.6 after AIDS and 0.9 before AIDS) and others 17.1/100 person years (12.8 after AIDS and 4.3 after AIDS).

Table 17.15: Mortality rates/100 person years by AIDS classification for risk groups

Risk Group	Follow up (person years)	AIDS		Non AIDS		Total	
		No. deaths	Rate/100 person years	No. deaths	Rate/100 person years	No. deaths	Rate/100 person years
IDU	1798.7	62	**3.4**	45	**2.5**	107	**5.9**
Het	221.3	12	**5.4**	2	**0.9**	14	**6.3**
Ho/bi	203	54	**26.6**	2	**0.9**	56	**27.5**
Others	23.4	3	**12.8**	1	**4.3**	4	**17.1**
Total	2246.4	131	**5.8**	50	**2.2**	181	**8.1**

Table 17.16: Mortality rates (per 100 person years) by AIDS classification for Non homo/bisexual patients by gender

Risk Group	Follow up person years	AIDS		Non AIDS		Total	
		No.	Rate/100 person years	No.	Rate/100 person years	No.	Rate/100 person years
Male	1251.5	55	**4.4**	36	**2.9**	91	**7.3**
Female	791.9	22	**2.8**	12	**1.5**	34	**4.3**
Total	2043.4	77	**3.8**	48	**2.3**	125	**6.1**

Table 17.17: Mortality rates (per 100 person years) by AIDS classification for all patients by gender

Risk Group		AIDS		Non AIDS		Total	
	Follow up person years	No.	Rate/100 person years	No.	Rate/100 person years	No.	Rate/100 person years
Male	1454.5	109	**7.5**	38	**2.6**	147	**10.1**
Female	791.9	22	**2.8**	12	**1.5**	34	**4.3**
Total	2246.4	131	**5.8**	50	**2.2**	181	**8.1**

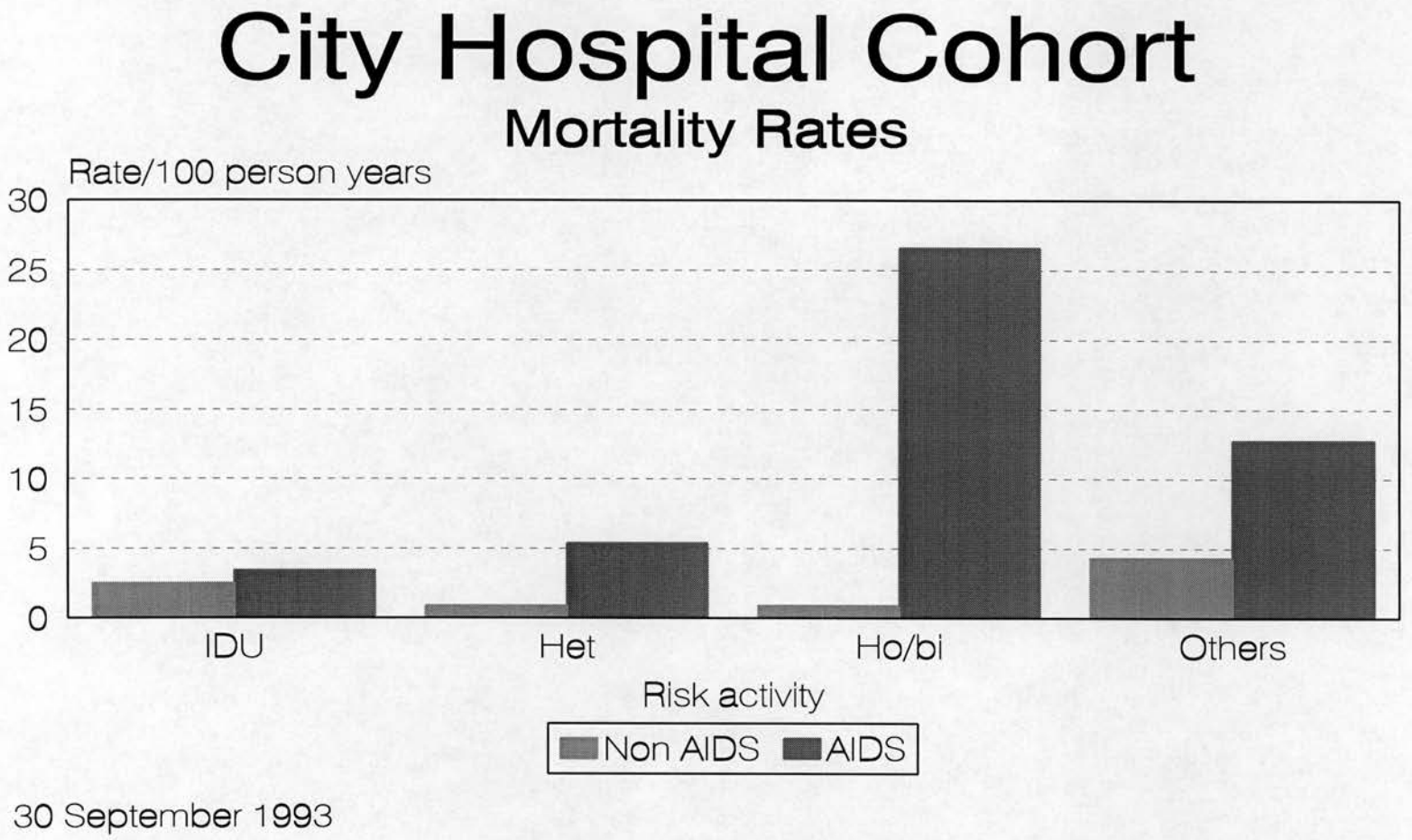

Figure 17.12: Mortality rates by risk activity and clinical stage

Discussion

Enrolment

The initial presentation of patients with HIV is very much affected by the health care system, the model of care adopted locally and whether patients enrol when well or when they develop symptoms. In Edinburgh 70% were regarded as clinically well on the WHO scale (acute seroconversion illness, asymptomatic or with only lymphadenopathy) at enrolment. Significant non AIDS symptomatic presentations at first visit were minor skin problems, HIV related thrombocytopaenia, weight loss, oral candida, oral hairy leucoplakia and severe bacterial sepsis.

The risk groups of those referred also reflected what is known about the Edinburgh epidemic. Early on the majority of those attending were injection drug users where as by the 1990's the pattern had changed such that many more heterosexuals were being seen and they accounted for 25% of new patients in 1992. [Interestingly the M/F ratios for heterosexuals was close to the reciprocal of the M/F ratio for drug users and this does not suggest that male to female transmission is much more effective than female to male transmission.] The clinical status of drug users and heterosexuals was more likely to be asymptomatic at their first visit (79% or 77%) compared to homosexuals (32%). As a consequence homo/bisexuals were more likely to present with significant clinical disease such as thrush or OHL by comparison to other risk groups but this is likely to be a related to local circumstances rather than intrinsic differences in risk group susceptibility.

An earlier enrolment into the clinic for women was noted in Chapter 14 and from the clinical data it appears that this enrolment was more likely to occur when the women were clinically well.

An initial presentation with AIDS was and is unusual for the majority of Edinburgh patients occurring in fact in only 11% of patients overall although it has become more common in later years with 25% appearing in 1993 with AIDS. This presumably reflects the effectiveness of the health care system in persuading patients with HIV to enter the system before the onset of ill health. The rise in the later years may in part be accounted for by referrals of patients with pre-existing AIDS (28%) from other centres for access to more difficult treatment schedules.

The commonest index diagnosis of AIDS for those patients presenting to the clinic at their first visit with AIDS was PCP (70%) followed by oesophageal candida (9%)

and then KS (7%). PCP as an index diagnosis in these patients peaked around 1991 (87.5%) and there after fell back to around 50% suggesting that perhaps prophylaxis is now in use even in those patients not attending the clinic.

Non AIDS clinical events

The majority (71%) of patients with HIV had developed some HIV related problem by 1993 and again the commonest problems were symptomatic thrombocytopaenia, minor skin problems, bacterial infections, oral thrush, OHL, and weight loss. Other than the fact that women presented earlier in an asymptomatic state there were no significant gender differences in clinical events other than for developing minor respiratory tract infections. There were however significant risk group differences; OHL was commoner in homo/bisexuals, weight loss of more than 10% was commoner in drug users whilst oral thrush was commoner in both drug users and homosexuals than heterosexuals.

The incidence rate of these important non AIDS clinical conditions were detailed in Table 17.8 and help quantify the risk group differences. The incidence of oral thrush was around 10/100 person years for both drug users and heterosexuals but was nearly 52.4/100 person years for homo/bisexuals. Similarly the incidence of OHL in drug users and heterosexuals was around 6/100 person years compared to over 39/100 person years for homo/bisexuals. In a report on the Bronx cohort of drug users the incidence of oral thrush was 11.2/100 person years compared to our 9.2/100 person years and the incidence of bacterial pneumonia was 5.8/100 person years compared to an incidence of severe bacterial infections in Edinburgh of 7/100 person years[4]. This is however much lower than the 19/100 person years quoted by the Amsterdam study[5]. This may reflect differences in drug use or chaotic behaviour between Amsterdam and either methadone maintenance programmes in the USA or combined medical and drug clinics in Edinburgh.

Encapsulated bacteria such as Streptococcus pneumonia and Haemophilus influenza are frequent respiratory pathogens and causes of bacteraemia in HIV seropositive individuals[6-9]. Our own experience of admissions was that the majority of admissions in both males and females were, for respiratory disorders especially recurrent bacterial infections[10]. Despite this only 6.5% of patients before AIDS were classified as having suffered severe bacterial infections. This suggests that perhaps these particular individuals have some additional susceptibility factor that might explain there problem with bacterial infections.

For females this susceptibility to bacterial infections may manifest itself as genital tract infections. One study reported a prevalence of 46% of lower genital tract infection for HIV positive female drug users compared to 20.5% for HIV negative drug users although the major infections were genital warts[11]. A higher prevalence of Human Papilloma Virus (HPV) infection has also been noted; 24% of 160 HIV negative drug users compared with 54% ($p<0.01$) of 224 HIV positive drug users[12]. Genital herpes, candidiasis and pelvic inflammatory disease were of particular concern in a study of 178 HIV seropositive women which commented that these infections were more prevalent, more aggressive and often recurrent in HIV positive females[13]. In a study of 40 HIV infected women, 75% in CDC stage 3, 80% had evidence of recurrent vaginal candidiasis[14]. The prevalence of reported genital infections in 465 HIV positive women, 23% with AIDS over a one year period was 31%[15]. This included vaginal yeast infections reported by 10% (4% with recurrent yeast infections as defined by more than 4 attacks per year), genital herpes infections by 5%, trichomonas infections by 4% and with pelvic inflammatory disease by 1% of women[15]. In a group of 117 women asymptomatic at the diagnosis of HIV the commonest first symptomatic problems were candida vaginitis in 37%, visible lymphadenopathy in 14.5% and bacterial pneumonia in 13%[16].

Thus women with HIV infection seem to be at higher risk of developing lower genital tract problems although well controlled studies with comparable HIV negative controls are relatively rare. Since individuals who acquire HIV may be more sexually active and therefore at more risk of becoming positive, simple comparisons of HIV positive with HIV negative groups may not be adequately controlled. In a study of HIV infected women who were clinically well 18 of 109 women had abnormalities of their lower genital tract[17]. Generally HIV positive women from a variety of sources have an incidence of cervical intraepithelial neoplasia (CIN) varying between 35 and 80%. In one study the incidence was 9% for HIV negative drug users but 36% ($p<0.01$) for HIV positive drug users[12]. The relative risk of CIN in HIV seropositives was 6.3[12]. Increasing immunosuppression as estimated by lower CD4 counts or poorer CDC clinical staging is significantly associated with worsening CIN[11,18-20]. For instance an incidence of CIN of 46.6% for CDC stage 3 or 4 compared to only 17.6% for CDC stage 2 ($p<0.026$)[19]. Studies from New York have confirmed previous suggestions of increasing cervical dysplasia and more severe dysplasia occurring with increasing immunosuppression although this increased cervical dysplasia was related to HPV since it did not occur if the patients were HPV negative[20,21].

A recent review of 21 published studies on the relationship between HIV and cervical dysplasia found that only 5 studies had comparative groups. However the summary odds ratio indicated that the odds of HIV infected women having cervical neoplasia was 4.9 times that of an HIV negative women[22]. The conclusion of the reviews was that whilst more work is needed in this area the available data suggests that regular screening of HIV positive women is necessary and that HIV counselling and testing should be considered in cases of women with cervical neoplasia at risk of HIV.

Caution is required however with this data since many of the infection problems of HIV relate to previous micro biological exposure. Individuals with previous pelvic infections before the advent of HIV related immunodeficiency will tend to present with pelvic infections. By comparison women with very little in the way of pelvic disease before HIV will probably not de novo develop these problems. Admissions to the City Hospital for urinary tract infections were increased for females (male to female ratio 4:11) whilst admissions for other infections showed no difference in the male to female ratio[10]. Only 4 of 168 female patients required admission with pelvic inflammatory disease. It is possible that female genital infections such as vaginal thrush may have been under reported in our clinic. However the recent establishment of a gyaenecological clinic for HIV infected women at the City Hospital should address this issue. The experience in Edinburgh is however that genital infections were relatively uncommon.

Non AIDS mortality

The increased susceptibility to bacterial infections in part explains the increased mortality of drug users from non AIDS events previously reported[23-25]. The overall mortality rate in Edinburgh was 8.1/100 person years compared to a rate of 6.0/100 person years reported from New York[4]. However only 28% of the 181 Edinburgh patients who had died did so before a diagnosis of AIDS. The 45 non AIDS deaths in IDUs out of 462 IDU patients gives a crude non AIDS mortality of 9.7% compared to 6.6% for HIV infected drug users in Amsterdam[5]. The Edinburgh non AIDS deaths represent a mortality rate of 2.5/100 person years of follow up which compares favourably with a non AIDS mortality rate in HIV infected drug users from Amsterdam of 3.8/100 person years and from New York of 2.6/100 person years.[4,5]. The non AIDS death rates for heterosexuals or homo/bisexuals were low at 0.9/100 person years.

As a consequence of the controversy over the relevance of AIDS definitions to women it is important to look at total survival for women rather than just survival after the development of AIDS. In Edinburgh we have not found any excess mortality for women compared to men, before or after the development of AIDS, suggesting that in Europe at least the definition of AIDS is not missing large numbers of deaths in HIV infected women and that overall, women are not disadvantaged in terms of their survival.

AIDS defining events

In the current analysis it has been possible to differentiate between those patients presenting with AIDS at their first clinical contact, the first diagnosis of AIDS irrespective of whether the patient was in follow up and the cumulative AIDS events that can occur in patients with AIDS. In Edinburgh AIDS at first clinical contact (excluding those referred from other centres with AIDS) is predominantly composed of PCP (69%), oesophageal candida (7%) and malignant disease (5.5%). At first diagnosis of AIDS it is composed of PCP (58%), oesophageal candida (15%), KS (6%), MAI (4%), toxoplasmosis (4%). The overall incidence of AIDS in the City Hospital Cohort was 8.8/100 person years, slightly higher than that quoted for the drug user cohorts from the Bronx (5.8/100 person years) and Amsterdam (4.5-5.8/100 person years)[4,5]. However the AIDS incidence rate for Edinburgh drug users alone was remarkably similar at 5.7/100 person years.

In comparing results from other cohorts it is important to differentiate between reports of index diagnoses of AIDS and cumulative totals of AIDS conditions. In the majority of reports, PCP is the commonest presentation of AIDS and usually occurs with a frequency varying from 30-60%; for instance 25-28% in French women and men[26], 37% in Haitian women[27], 43% in male homosexuals in San Francisco[28], 44% in New York[29], 46% in Denmark[30], 50-51% in UK studies of homosexuals and haemophiliacs[31,32] and 64% in US haemophiliacs[33]. In a group made up of predominantly drug users (47%) in the Bronx the reported rate of PCP was 59%[34].

The frequency of other conditions is variable; in the Bronx study the frequencies were; MAI 10%, cryptococcal meningitis 8%, KS 8% and oesophageal candidiasis 3.5%. A large study of all New York cases revealed that 17% presented with KS alone, 9% with KS and some other event, 12% with PCP and another event, 4% had two other events (not KS or PCP) as a presenting diagnosis[29]. In Denmark, KS occurred in 18% of presentations[30]. The St Mary's group (London) recently reported

a frequency of 24% for cutaneous KS, 10% for oesophageal candida and 4% for cerebral toxoplasmosis[35]. It is important to note that since KS is rare in non-homo/bisexuals the higher percentages for PCP in other risk groups may simply reflect the absence of KS rather than an increased susceptibility to PCP. Equally other major differences may simply reflect the number exposed to pathogens such as CMV or toxoplasmosis with an established latency.

Tuberculosis is the opportunistic infection usually associated with a particular risk group (drug users) and it is very common in Southern Europe where extra pulmonary TB made up 33% of the index diagnoses compared to less than 1% in San Francisco[36,28]. In New York a study looking at TB in patients undergoing investigations for PCP revealed that 2.4% had pulmonary TB[37]. In the UK it is relatively uncommon with a cumulative rate of only 7% and our experience was that it was a relatively uncommon infection (<2%) presumably because HIV is not common in the populations affected by tuberculosis[31].

Further geographical variations are noted in a study from Southern France were PCP accounted for only 27% of the initial and 35% of the cumulative events; the second commonest presentation was toxoplasmosis (14 and 22%) followed by KS (13 and 21%) and candida oesophagitis (12 and 19%)[26]. The cumulative frequency of the rarer events were; CMV 13%, extra pulmonary tuberculosis 8%, lymphoma 6%, MAI 6%, HSV 6%, HIV encephalitis 6%, cryptococcus 3% and cryptosporidiosis 3%[26].

By comparison the cumulative percentage of AIDS patients ever having particular conditions in Edinburgh were; PCP 91%, oesophageal candidiasis 28%, disseminated MAI 29%, CMV disease 21%, Kaposi's sarcoma 11%, lymphoma 12%, toxoplasmosis 11%, HIV dementia 10%, extra-pulmonary tuberculosis 2%. Risk group differences were noted in the cumulative AIDS events; KS, CMV and Toxoplasmosis were all commoner in homo/bisexuals; oesophageal candida was commoner in drug users and PCP in heterosexuals. No significant gender differences were however noted once homo/bisexuals were removed from the comparison.

Notable clinical events can also be expressed as a rate /100 person years of AIDS and this method provides a measure of morbidity or ill health. The overall morbidity rate was 176 clinical events/100 person years. Even this is an underestimate of the problem since conditions such as oral thrush are so frequent (and are often treated by general practitioners) that monitoring is too difficult in late stage disease. Thus each patient with AIDS can expect 1-2 clinical events per year of survival.

Analysis by risk activity clearly demonstrates the much higher morbidity associated with heterosexuals (227/100 person years) compared to drug users (179/100 person years) and homo/bisexuals (135/100 person years). Interestingly the other risk activities (IDU and homosexuals, blood products or unknown risk activity) have rather a high morbidity (245/100 person years) but this is probably related to the small numbers of patients and very short periods of follow up. It does however illustrate the problem of comparing morbidity from a variable starting point such as AIDS. Patients who avoid the diagnosis of AIDS for instance with the use of prophylactic agents such as co-trimoxazole may end up with shorter survival times from AIDS to death. These shorter survival periods then have high morbidity despite few clinical events.

It is also possible however to utilise these morbidity rates to provide better comparisons of the frequencies of these clinical events during AIDS. This reveals that PCP remains the commonest clinical event (69.4/100 person years) followed by MAI (22.4/100 person years), oesophageal candida (21.6/100 person years), malignant disease (17.4/100 person years, KS and lymphoma), CMV (15.8/100 person years) and toxoplasmosis (11.9/100 person years).

The commonest neoplasm associated with AIDS is Kaposi's sarcoma (KS) which occurs in 15% of the reported cases of AIDS (mainly associated with homosexuals) but in only around 3% of drug users[38]. The commonest malignancy associated with drug use appears to be malignant lymphoma which was reported in 8% of surgical specimens from drug users[39]. In a study of over 10,000 Italian cases of AIDS of which 720 or 6% were due to KS, women were less likely to present with KS than men. The odds ratios for KS amongst drug users (0.6), heterosexuals (0.4) or undetermined transmission category (0.4) were all more favourable for women[40].

Risk group differences have been reported by others. In the USA, figures available to the Centers for Disease Control show that conditions such as KS are unusual in the absence of homo/bisexuality. In drug users, KS, Cytomegalovirus and chronic Cryptosporidiosis are all significantly less common than for all other risk groups notified with AIDS; while PCP, Tuberculosis, oesophageal candidiasis and extra-pulmonary Cryptococcosis are more common[29]. However in France there was no risk group differences except for the increased frequency of KS in homo/bisexual men[26].

Other than genital tract infections and neoplasm's there have not so far been many reports to suggest that HIV infected women have a particular disease spectrum that differs from men. In a small series of 24 women with AIDS there was a lower incidence of Pneumocystis carinii pneumonia as the AIDS defining illness compared to men with AIDS in the same area. There was a large proportion of women with Candida albicans oesophagitis (38%) and HIV related wasting syndrome (25%)[41]. An updated report from the same authors on 44 women noted that oesophageal candidiasis was the commonest presentation (34%) closely followed by PCP (20%) and chronic mucocutaneous herpes simplex (18%)[16]. Similar finding were reported by a Danish study which included only 35 women among 618 AIDS patients[42]. A further study containing 7.7% of women noted more likely presentations for women than men of; oesophageal candidiasis (19% vs. 9.7%), atypical mycobacteria (16% vs. 8%) and the wasting syndrome (10% vs. 3%)[43]. The relative risk for candida oesophagitis in women was significantly different at 1.5 in another study[44]. which was our own experience.

Caution is required however in applying conclusions from such data to the UK. The majority of these reports come from the USA and from our own data it would appear that clinical presentations is affected by time of presentation and access to medical care. For instance a lack of access to care may mean that candidiasis is the first opportunistic event whereas regular attendance at clinics may provide access to appropriate prophylaxis resulting in delayed or prevented candida infections. Both candida oesophagitis and PCP are easily prevented by the application of prophylaxis and we see from the Edinburgh data that these presentations have no gender differences. As a result other OI's may increase in frequency as presenting features. Certainly in Edinburgh with homo/bisexuals excluded from the analysis there were no significant gender differences for either any of the possible AIDS manifestations (at first visit, presentation or cumulative). Data from France on a cohort of 114 women with AIDS also noted no differences in the first AIDS defining events other than KS which was more common in homo/bisexuals[26].

AIDS deaths

In the Bronx 15% of patients with AIDS died during their first admissions whilst in Edinburgh only 6% died during the first month and 11% during the first 2 months[34]. An earlier report from the Bronx Methadone Maintenance Programme (the HIV positivity rate in deaths was around 40%) suggested a crude AIDS death rate of 15%

and this compares to 13% in Edinburgh (an exact comparison with this report is not possible because the exact number of HIV positive patients were not known)[45]. Unfortunately it is not possible to calculate a mortality rate/100 person years from this particular paper. By 1992 the same unit reported an AIDS mortality rate amongst drug users with AIDS of 3.4/100 person years which is identical to our rate of 3.4/100 person years[4].

Despite the higher non AIDS mortality rate for drug users, after the development of AIDS homo/bisexuals had an 8 fold greater mortality rate than drug users (26.6 vs. 3.4/100 person years). This is in keeping with the poorer survival described in Chapter 14 and 15 for homo/bisexuals and the relatively short follow up period for this risk group.

Conclusions

Local factors perhaps dictated that differences over enrolment by risk group would emerge. The majority of drug users and heterosexuals enrolled when asymptomatic whilst the majority of homo/bisexuals enrolled with serious clinical disease. Changes were however observed over time in the distribution of risk groups enrolling with increased numbers of heterosexuals in later years. Enrolment with AIDS was unusual overall although by 1993 25% of patients were enrolling with AIDS.

Despite the fact that the majority of drug users and heterosexuals enrolled asymptomatic by 1993 70% of the patients had developed some HIV related clinical problem. Unlike previous reports, drug users were not more likely to develop severe bacterial disease. Interestingly OHL was more common in homo/bisexuals whilst oral thrush was commoner in drug users. Caution is however required since the different risk groups have very different follow times; short follow up times increases the event rate and may accentuate risk group differences. There were remarkable similarities between the City Hospital cohort and the Montefiore Medical Centre cohort in the Bronx; the incidence of oral thrush in the Bronx was 11.2/100 person years compared to 9.9/100 person years. In the Bronx the incidence of bacterial pneumonia was 5.8/100 person years compared to an incidence of severe bacterial infections in Edinburgh of 7/100 person years. This was however much lower than the 19/100 person years quoted for Amsterdam drug users. This difference may reflect differences in drug use or chaotic behaviour between Amsterdam and either methadone maintenance programmes in the USA or combined medical and drug clinics in Edinburgh.

The commonest clinical expression of AIDS was PCP followed by oesophageal candida, MAI, malignant disease and CMV disease. Whilst gender differences were not apparent differences were observed in risk groups as previously reported; KS, CMV and toxoplasmosis being commoner in homo/bisexuals whilst oesophageal candidiasis was commoner in drug users. Other conditions such as extra-pulmonary tuberculosis were uncommon unlike cohorts from the USA.

Considerable differences in mortality rates by risk group but not by gender were observed. The mortality rates for homo/bisexuals with AIDS were much higher than for drug users and reflects the survival differences noted in Chapters 14 and 15. The mortality rates for drug users were remarkably similar to published rates from Amsterdam and the Bronx, New York. This suggests that perhaps differences in drug use may not have a major effect on survival. Non AIDS mortality rates were significant for drug users but of a similar rate to that observed in Amsterdam and from the Bronx, New York.

Appendix

Table 17.18: Modified WHO classification system in use at RIDU, City Hospital, Edinburgh

Numerical computer code	Description
Asymptomatic disease - WHO Stage 1	
101	Asymptomatic HIV infection
102	Acute retroviral syndrome of initial infection
103	Persistent generalised lymphadenopathy
Symptomatic disease - WHO Stage 2	
201	Weight loss < 10% of body weight
202	Mucocutaneous manifestations (seborrhoeic dermatitis, prurigo, fungal nail infections, recurrent oral ulceration's, angular cheilitis).
203	Herpes zoster
204	Recurrent upper respiratory tract infections such as bacterial sinusitis
Symptomatic disease - WHO Stage 3	
301	Weight loss > 10% of body weight
302	Unexplained chronic diarrhoea > 1 month.
303	Unexplained prolonged fever (intermittent or constant > 1 month.
304	Candidiasis, oral.
305	Candidiasis, vulvovaginal for > 1 month
306	Oral hairy leukoplakia.
307	Pulmonary tuberculosis.
308	Severe bacterial infections (e.g. pneumonia)
309	Bed ridden for < 50% of the day during the last month.

Table 17.18 continued: Modified WHO classification system

Numerical computer code	Description
HIV related symptomatic disease (not classified by WHO) Stage 5	
501	Anaemia
502	Bronchitis
503	Lymphoid interstitial pneumonitis
504	Myositis or myopathy
505	Nephropathy
506	Neuropathy
507	Thrombocytopaenia
508	Tuberculous meningitis

Table 17.18 continued: Modified WHO classification system

Numerical computer code	Description
Symptomatic disease - WHO Stage 4	
401	Bed ridden for > 50% of the day during the last month.
402	Candidiasis of the oesophagus, trachea, bronchi or lungs.
403	Cryptococcus, extrapulmonary
404	Cryptosporidiosis with diarrhoea for > 1 month.
405	Cytomegalovirus disease of an organ other than the liver, spleen or lymph nodes.
406	Herpes simplex infection, mucocutaneous for > 1 month or visceral for any duration.
407	HIV dementia (encephalopathy).
408	Isosporiasis with diarrhoea for > 1 month.
409	Kaposi's sarcoma
410	Lymphoma
411	Mycobacterium tuberculosis - extra pulmonary
412	Mycobacteriosis- atypical and disseminated.
413	Mycosis - disseminated histoplasmosis or coccidioidomycosis.
414	Pneumocystis carinii pneumonia.
415	Progressive multifocal leuko-encephalopathy.
416	Salmonella septicaemia (non-typhoidal)
417	Toxoplasmosis of the brain.
418	Wasting syndrome due to HIV (code 301 plus 302 or 303).

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CHAPTER 18

Heterosexual Transmission of HIV in Edinburgh

Introduction

As a consequence of the services established for HIV at the City Hospital described in earlier chapters and the fact that the majority of patients enrolled were heterosexual the question of HIV transmission heterosexually was commonly raised by patients. In order to answer the questions being asked by the patients a research project was established in Edinburgh and this chapter details the results found to date.

It is estimated that world-wide, heterosexual transmission, is the commonest means of transmitting HIV yet relatively little is known of the underlying biological basis of transmission. Identifying behavioural and biological risk factors for heterosexual transmission of HIV is essential in understanding the heterosexual spread of HIV and providing relevant counselling for individuals at risk of HIV infection. Such knowledge would help the design of relevant health education and promotional campaigns to reduce the world wide spread of HIV. To date some of the answers to these questions have been provided by what are called "partner studies" mainly from the industrialised countries[1,2,3]. These "partner studies" are generally "small" cohorts of couples where retrospective data regarding sexual practices and contraceptive use are recorded to identify possible risk factors for HIV. The analyses resulting from these studies have generally been cross-sectional and limited by a number of factors; the type of behavioural and biological data collected; a lack of detailed knowledge of seroconversion times and relatively few prospective seroconversions.

This chapter provides an alternative method of analysis adopting a longitudinal approach which takes into account more fully the complex nature of the data and events which might effect the transmission of HIV. This new approach is compared with the more usual cross-sectional approach via an analysis of the MRC Edinburgh heterosexual partner study.

Patients and Methods

In 1983, large numbers of injecting drug users in Edinburgh became infected with HIV as a result of sharing needles[4-8](and Chapter 4). The majority of the individuals infected had not engaged in prostitution, were heterosexual and had long term sexual

relationships with partners who had not used drugs[9]. The MRC heterosexual partner study was established in Edinburgh in 1987 and patients were recruited from a General Practice, an Infectious Disease Clinic and a Counselling Clinic at the City Hospital[9]. Data were obtained using a structured questionnaire specifically designed for a similar study in London by Dr Ann Johnstone (AMJ) and administered by one of three trained nurses (SJD, RW,RW). Each member of the partnership were interviewed separately and information recorded on contraceptive methods, conceptions and sexual practices[9]. The biological data were collected prospectively on the patients recruited into the natural history studies on HIV at the City Hospital and the Muirhouse General Practice[10-14](and Chapters 14 and 15).

The index case or potentially infectious individual in each couple was defined as an HIV positive male or female with a known risk factor for HIV infection. The contact case in each couple was defined as a partner of the index case whose only risk of HIV infection was through heterosexual contact with the index case. At recruitment, the contact was offered an HIV test together with appropriate counselling, after ascertainment of past sexual contraceptive behaviour. Advice on the risk of HIV infection and on safer sex practices was also given.

If the couple were discordant for HIV, that is, the contact case was negative for HIV, and their sexual relationship was continuing then the contact attended for follow-up interviews where his/her HIV status and the couple's sexual behaviour and contraceptive use since the previous interview were re-assessed. If the relationship ended whilst the couple was discordant for HIV the contact was further encouraged to return for a final follow-up assessment, a few months after the end of the relationship, when his/her HIV status was determined.

Laboratory Methods

Sera from all index and contact cases were tested for HIV antibody with informed consent. Initial testing of specimens was by competitive or anti-globulin enzyme linked immunosorbent assay (ELISA). All reactive sera were considered positive if confirmed by methodologically distinct assays[15]. Index and contact cases were examined by a physician for symptoms and signs of HIV infection. Seronegative contacts were interviewed and re-tested when possible at six month intervals.

Lymphocyte surface markers including the CD4 count were performed throughout by flow cytometry on whole blood analysis as described in Chapter 13.

Data Construction

The data construction for the longitudinal approach is described in detail in the statistical appendix at the end of the chapter. A yearly profile of the couple over the period the contact was at risk of infection was constructed allowing sexual behaviour and infectivity of the index case to be time dependent.

Period of risk

The contact's period of risk of infection (ROI) started either with the year the relationship began or the year that the index seroconverted, whichever was the more recent. If the couple was concordant with respect to HIV then the ROI period ended when the contact seroconverted. If the couple were discordant with respect to HIV, then the last year of ROI was defined either by the year of the last negative test, the end of the relationship (if appropriate) or the most recent follow-up visit, whichever was the earliest. For the index cases there was not only detailed knowledge of the HIV infection curve but also a number of relatively short seroconversion intervals mainly due to retrospective testing of stored sera[6-8,16](and Chapter 15).

Demographic and Behavioural cofactors

The two demographic cofactors of major interest were gender and age of the contact. (Older age has been associated with increased transmission from male to female cases in two studies[1,17]). For the behavioural cofactor describing contraceptive behaviour, the analysis concentrated on condom use and abstinence from sexual intercourse. Other time dependent cofactors of interest were year of recruitment and knowledge of seropositivity of index. Data on "high risk" sexual practices (anal sex and/or post-coital bleeding for female contacts and sex during menstruation for male contacts) was also collected over time.

Measures of infectivity

Random effects models have been commonly used to describe square root CD4 decline after seroconversion. A multilevel approach was adopted by fitting quadratic growth curves[18] to estimate an expected CD4 value for each year post-seroconversion of the index case. The CDC classification was coded as a binary variable indicating an index satisfying stages 2 or 3 (asymptomatic disease or persistent generalised lymphadenopathy) or an index satisfying stage 4 (symptomatic disease).

A possible explanation for the associations of transmission with falling CD4 counts and advanced CDC disease is that both are acting simply as a surrogate for length of infection of the index. Variables were therefore constructed to indicate how long after seroconversion of the index the contact was exposed. To detect any possible early rise of infectivity and therefore transmission of HIV, if it exists, a binary time dependent variable was defined to indicate if the risk of transmission was the same in all years.

There is some evidence to suggest that infected individuals are either "transmitters" or "non-transmitters'" of the virus and this was examined by defining a binary time dependent cofactor which would indicate if the risk of transmission was the same in all years[21,22].

Statistical Analysis

The detailed methodology for the statistical analysis is presented in the appendix. In order to allow comparisons with other studies the results of a comparable cross-sectional analysis are also presented. The construction of the data was chosen to mimic that described in the European analysis[1]. Data on female to male transmission from the MRC Edinburgh heterosexual partner study were included in that analysis[1]. Covariates or cofactors of interest were similar to those used in the longitudinal analysis and were as follows; unprotected intercourse for HIV, square root CD4 count, "high-risk" sexual practices and age and gender of the contact. The cofactor describing the CD4 count is the estimated square root CD4 count in the year of last negative of the contact for discordant couples and the estimated square root CD4 count in the year of first positive of the contact for concordant couples.

In the European analysis the length of relationship was defined from the time of first sexual contact to the last negative HIV test for discordant couples and as the time from first sexual contact to the first positive HIV test for concordant couples controlled for in the multifactorial model. It was found that concordant couples had longer relationships than discordant couples ($p=0.01$) but when stage of disease was controlled for the association between duration of relationship and HIV transmission disappeared[1]. However, using this definition, for the Edinburgh cohort, it was found that concordant couples had shorter relationships than discordant couples ($p<0.10$). This is to be expected as the definition censors the length of the relationship for concordant couples at the date of first positive of the contact whereas follow-up information is used to define the length of relationship for discordant couples. This

highlights one of the problems with the cross sectional analysis method i.e. what is the most appropriate definition for some cofactors. Results presented in this paper define the length of relationship (in months) as the time of first sexual contact to the date of initial interview or end of relationship, whichever is earliest.

Results

Demographic data

From the start of the study in October 1987 to the beginning of April 1993 a total of 125 couples were recruited although 8 couples were not included in the analysis as the contact had never been tested for HIV. A further 8 discordant couples were also excluded as they reported consistent use of condoms and/or abstaining from sexual intercourse over the period of their relationship leaving 109 couples for the analysis.

These 109 couples or relationships were formed from 105 index cases of whom 82 (78%) were male and 23 (22%) were female. Two contact cases occurred with the same index and these were considered as belonging to two independent couples. Of the contacts, 86 (79%) were female and 23 (21%) were male. At recruitment 22% of the contacts (24) were HIV antibody positive; 21 (24%) of the female contacts and three (13%) of the male contacts. Two contacts (one male and one female) seroconverted after recruitment. The mean age at recruitment was 26.0 years (range 17 to 58 years) for female and 31.7 years (range 22 to 51 years) for male contacts. There was no significant difference in the length of the relationship at recruitment, between concordant couples and discordant couples although it was shorter ($p<0.10$) for male contacts compared with female contacts.

Of the 109 couples included in the analysis 34 (29%) started their relationship before the date of the index's last negative HIV test and so the start of the ROI period was defined by the simulated year in which the index seroconverted. Further, 6 (18%) of these index cases had a first positive date in the same year as their last negative date and so their year of seroconversion was known. Fifty-two couples (48%) started their relationship after the date of the index's first positive HIV test and so their ROI period was defined by the start of the relationship. The remaining 23 couples (21%) started their relationship during the seroconversion interval of the index case and so the their ROI period was defined either by the simulated year the index seroconverted or by the start of the relationship whichever was more recent. Two of these index

cases had their first positive date in the same year as their last negative date which also coincided with the year the relationship started.

The random effects model for square root CD4 decline estimated the "average" square root CD4 count at seroconversion as 26.2 (standard error 12.8), the linear coefficient as -0.15 (SE 0.38) and quadratic coefficient as 0.0002 (SE 0.002). Thus the "average" CD4 count at seroconversion was 690 cells/cumm and 2, 5 and 8 years after seroconversion it was 510, 300 and 240 cells/cumm, respectively. There were 9 (8%) couples where the index case had no CD4 measurements and therefore it was not possible to estimate the CD4 count in the years for which the contact case is at risk of HIV infection. These couples were omitted from the analysis which included the cofactor "square root CD4 count" in the model. Further, 2 of these couples were concordant with respect to HIV. The minimal information required to create the cofactor describing the CDC stage was the year CDC stage IV was reached. If the index case had CDC classifications unavailable for some years and was not known to have entered stage IV, then it was assumed that the index case was still occupying stage II or III. This seems reasonable since in order to satisfying CDC stage IV the index would need to be in poor health and therefore it was unlikely that he or she would not be in clinical care.

Data analysis

The results of the cross-sectional analysis of the data collected at recruitment is presented in Table 18.1. The only statistically significant predictor of increased transmission of HIV in either univariate or multivariate analysis was "high-risk" sexual practices (anal sex and/or post-coital bleeding for female contacts and sex during menstruation for male contacts, $p<0.01$). There was no evidence in this analysis that the length of pre-recruitment relationship, amount of unprotected intercourse, age of contact, gender of contact or low CD4 count increased the transmission of HIV.

Table 18.1: Cross-sectional analysis of transmission cofactors

Cofactor	log RR	RR	95% ci of RR ( ) or log(RR) [ ]	p-value
			Univariate Results	
unprotected intercourse for HIV	0.56		[-1.02,2.13]	NS
square root CD4 count	0.01		[-0.06,0.08]	NS
age of contact	-0.05		[-0.12,0.03]	NS
length of relationship (months)	-0.003		[-0.011,-0.006]	NS
sex of contact				
female contact	0.49	1.63	(0.50,5.32)	NS
male contact	0.0	1.0		
"high-risk" sexual practices				
yes	1.59	**4.92**	(1.93,12.57)	**p<0.01**
no	0.0	1.0		
			Multivariate Results	
unprotected intercourse for HIV	0.72		[-1.24,2.67]	NS
square root CD4 count	0.010		[-0.07,0.09]	NS
age of contact	-0.01		[-0.12,0.12]	NS
length of relationship	0.001		[-0.01,0.01]	NS
sex of contact				
female contact	0.76	2.70	(0.46,10.07)	NS
male contact	0.0	1.0		
"high-risk" sexual practices				
yes	1.76	**5.79**	(2.05,16.35)	**p<0.01**
no	0.0	1.0		

Table 18.2 presents the univariate analyses of the longitudinal data, based on 50 simulations. "High-risk" sexual practices (anal sex and/or post-coital bleeding for female contacts and sex during menstruation for male contacts) were again a statistically significant predictor of increased transmission ($p<0.01$) giving a relative risk (RR) of 3.8 (95% confidence interval (CI) 1.70-8.52). In contrast to the cross sectional analysis, high levels of unprotected intercourse (for HIV) were associated with increased transmission of HIV ($P<0.05$): for a couple having unprotected intercourse 0%, 25% and 50% of the time the RR's were 1.0, 1.3 and 1.7, respectively. Again unlike the cross sectional analysis, low levels of CD4 count were also associated with increased transmission of HIV ($P<0.05$). Contacts were at greater risk of HIV infection when the index case was in a more advanced stage of HIV infection, as characterised by a low CD4 count. On the other hand the CDC stage of the index showed the opposite effect, with late stage disease defined by CDC stage IV (symptomatic disease) indicating a protective effect on the transmission of HIV ($RR=0.30$, $p<0.20$). This was compatible with the result obtained for the cofactor "year after seroconversion of the index", with a cut-off point of 6 years (RR of 0.53, $p<0.25$). However, with a cut-off point of 4 years the univariate analysis indicated an increased risk for years four or more out from seroconversion of the index (RR of 1.85$p<0.20$). Recruitment into the study was also protective for transmission of HIV with a post-recruitment RR of 0.40 ($p<0.20$).

Table 18.2: Univariate analysis of longitudinal data: 50 simulations

Cofactor	log RR	RR	95% ci of RR ( ) or log(RR) [ ]	p-value
unprotected intercourse for HIV	1.04		[0.05,2.03]	**p<0.05**
square root CD4 count	-0.05		[-0.10, 0.00]	**p<0.05**
age of contact	-0.04		[-0.09,0.02]	p<0.25
sex of contact [baseline: male contact]				
female contact	0.47	1.60	(0.53,4.79) [-0.6, 1.95]	NS
year after seroconversion of index [baseline: > 1 year]				
≤1 years	-0.42	0.66	(0.21,2.08)	NS
year after seroconversion of index [baseline: ≤4 years]				
≥4 years	0.61	**1.85**	(0.79,4.32)	p<0.20
year after seroconversion of index [baseline: ≤6 years]				
≥6 years	-0.63	0.53	(0.19,1.49)	p<0.25
year after start of risk period [baseline: >1 year]				
≤1 year	0.56	1.75	(0.78,3.90)	NS
CDC stage of index [baseline: stage 2 or 3]				
stage IV	-1.20	0.30	(0.05,1.68)	p<0.20
knowledge of HIV in relationship [baseline: pre-knowledge]				
post-knowledge	0.39	1.48	(0.64,3.41)	NS
recruitment into the study [baseline: pre-recruitment]				
post-recruitment	-0.92	0.40	(0.12,1.33)	p<0.20
"high-risk" sexual practices [baseline: no]				
yes	1.34	**3.80**	(1.70,8.52)	**p<0.01**

Table 18.3 presents the multifactorial results for the longitudinal analysis. In this analysis the single cofactor "year after seroconversion of the index", with a cut-off point of 4 years, was used to model the suspected rise in infectiousness when the index case was in a late stage of disease, **rather than** the square root CD4 count or the CDC stage of disease. The results indicate increased transmission of HIV for four or more years from seroconversion of the index case (RR=3.21, $p<0.07$). The sexual behaviour cofactors "unprotected intercourse for HIV" ($p<0.06$) and "high-risk" sexual practices ($p<0.01$) were also significant predictors of HIV transmission. A second model was fitted (results not presented) to investigate, further, the effect of increased transmission of HIV for four or more years from seroconversion of the index case. The two cofactors of interest were: being 4 or 5 years out from seroconversion of the index case and being six or more years out from seroconversion of the index case. There was a significant increase in transmission ($p<0.04$) for being 4 or 5 years from seroconversion of the index case (RR of 3.78, 95% CI from 1.1 to 12.9) but the cofactor "6 or more years after seroconversion" was not statistically significant (RR=1.73, 95% CI from 0.35 to 8.53.

Table 18.3: Model based on duration of HIV infection: multifactorial analysis of longitudinal data with 50 simulations

Cofactor	logRR	RR	95% ci of RR ( ) or log(RR) [ ]	p-value
unprotected intercourse for HIV	1.10		[0.00,2.19]	**p<0.06**
age of contact	-0.03		[-0.12,0.06]	NS
sex of contact [baseline male contact]				
female contact	0.68	1.97	(0.55,7.01)	NS
year after seroconversion of index [baseline ≤ 4years]				
≥4 years	1.17	**3.21**	(0.94,10.97)	**p<0.07**
year after seroconversion of index [baseline later than 1 year]				
within 1 year	-0.09	0.91	(0.18,4.66)	NS
year after start of risk period [baseline later than 1 year]				
within 1 year	0.58	1.79	(0.63,5.08)	NS
knowledge of HIV status [baseline pre-knowledge]				
post-knowledge	0.46	1.59	(0.60,4.22)	NS
recruitment into the study [baselinepre-recruitment]				
post-recruitment	-0.68	0.51	(0.13,1.94)	NS
"high-risk" sexual practices [baseline no]				
yes	1.27	**3.58**	(1.43,8.91)	**p<0.01**

Table 18.4 presents multifactorial results of a second longitudinal analysis, based on 50 simulations, and summarises all variables included in the model, regardless of their statistical significance. In this model the square root CD4 count was used to model the decline in immunological status of the index. There was no indication of an early rise in infectiousness around seroconversion of the index (cofactor "within one year after seroconversion of index") but there was a strong effect ($p<0.01$) of increased transmission as the CD4 count drops with a log RR of -0.07. Thus it appears that even in the presence of cofactors "year after seroconversion of index ($\leq$1 year vs. > 1 year)" and "year after start of period of risk", increased transmission is attributable to low CD4 count. "High-risk" sexual practices ($p<0.02$) and "% unprotected intercourse for HIV" ($p<0.12$) were also significant predictors of increased transmission of HIV.

The cross-sectional and longitudinal analyses indicate that male to female transmission is approximately twice as efficient as female to male transmission, though with the relatively small number of couples and therefore low power, these results are not statistically significant. However, they are in agreement with the result of the European analysis[1].

Table 18.4: Model based on immunological decline: multifactorial analysis of longitudinal data with 50 simulations

Cofactor	log RR	RR	95% ci of RR ( ) or log(RR) [ ]	p-value
unprotected intercourse for HIV	0.92		[-0.23,2.08]	p<0.12
age of contact	-0.03		[-0.12,0.06]	NS
square root CD4 count	-0.07		[-0.13,-0.02]	**p<0.01**
sex of contact [baseline male contact]				
female contact	0.65	1.92	(0.52,7.11)	NS
year after seroconversion of index [baseline later than 1 year]				
within 1 year	-0.19	0.82	(0.18,3.69)	NS
year after start of risk period [baseline later than 1 year]				
within 1 year	0.31	1.36	(0.45,4.13)	NS
knowledge of HIV status [baseline pre-knowledge]				
post-knowledge	0.57	1.76	(0.67,4.63)	NS
recruitment into the study [baseline pre-recruitment]				
post-recruitment	-0.56	0.57	(0.15,2.24)	NS
"high-risk" sexual practices [baseline no]				
yes	1.24	**3.45**	(1.30,9.10)	**p<0.02**

Discussion

There are three main areas of interest in assessing the risks for HIV transmission: sexual behaviour, infectivity of the index case and susceptibility of the contact. All are involved in the risk of transmission of HIV within an individual couples relationship and to date studies including this one have not been designed to consider all of the facets of HIV transmission. In addition as this analysis demonstrates, when dealing with long term relationships it is important to consider the overall or total risk for the couple as well as the risk of individual sexual practices. Thus low risk sexual practices undertaken with a highly susceptible contact at a time of high index infectivity could result in HIV transmission.

The behavioural factors of interest in heterosexual HIV transmission are sexual practices and contraceptive methods. Their effect on HIV transmission have been most extensively reported via a number of partner studies. Different sexual practices have been found to be associated with male-to-female transmission compared with female-to-male transmission. Anal sex[1,2,3,28] painful vaginal contacts and post-coital bleeding are all factors associated with an increased risk of male to female transmission[1,2,3,28]. For female to male transmission of HIV the European study[1] found sexual intercourse during menstruation to significantly increase the risk of HIV transmission (couples from the MRC Edinburgh heterosexual partner study were included in this latter analysis)[1]. In contrast condom use has been found to be highly protective against HIV transmission[2,3,28].

There is some evidence to suggest that HIV infected cases might be more infectious later on in the course of their HIV disease. Since the infectivity of the index case is difficult to assess directly, in general, indirect measures or surrogate markers of infectivity have been used which have been equated with increased infectiousness, such as the CD4 count and the CDC stage of the index case[23]. Some studies have found an association between late disease stage in the index case, as measured by CD4 count and/or CDC stage, and increased transmission of HIV to the contact case[1,3,29-31]. In other words the index case appears to be more infectious as immunological competence declines. However not all studies have noted an association with CDC stage and it may be that the CDC stage alone is not sensitive enough to detect deterioration in all patients and thus a rise in infectivity)[3,9]. A combination of the CD4 count and clinical stage of disease as utilised in the new CDC/WHO classification may be a better method for future analysis[32].

There is also evidence to suggest a more infectious stage early on in the disease course of the index case, possibly just before seroconversion[5]. This increased infectivity around seroconversion has been one of the explanations put forward to explain the almost explosive spread of HIV amongst injecting drug users in Edinburgh[33]. Lastly it has been suggested that certain individuals may be "transmitters". It remains to be determined whether this is a stage all individual go through or is restricted to certain individuals.

The susceptibility of the contact is probably the facet of HIV transmission least well studied to date and has not therefore been considered in this particular analysis of the MRC Edinburgh heterosexual partner study. However preliminary data on susceptibility has been forthcoming from a number of studies and would suggest that it should be considered for future studies. A small study based on the Edinburgh Partner Study reported that secretors of blood group antigens into body fluids, are more susceptible than non-secretors for acquisition of HIV by sexual transmission[34]. Steel et al reported that a particular haplotype (A1,B8,DR3) seemed to increase the likelihood of parenteral HIV infection from infected blood products as a result of increased immunological activation[35]. The presence of genital warts in women, the use of an intrauterine device (IUD), the presence of vaginal bleeding during intercourse, older age in European women and younger age in African women and the uncircumcised penis in men have all been reported as susceptibility factors for the host[1,3,36-39]. In addition the presence of both ulcerative and non ulcerative sexually transmitted diseases have been reported to increase not only infectivity but also susceptibility[37-39]. The question of promoters of HIV transmission is not dealt with in this analysis because of the very low level of sexually transmitted diseases (STD's) and IUD's in this population.

One of the major problem in the cross-sectional analysis of partner studies is the limitation of the behavioural and biological data recorded. This might be for two reasons. Firstly the time periods of interest, such as, after the seroconversion of the index, before the seroconversion of the contact and before or after knowledge of HIV positivity in the relationship, may not be well defined due to a lack of information about the seroconversion intervals of the index and contact (if appropriate) and knowledge of the index case's seropositivity. Secondly limitations may arise because the data recorded does not necessarily reflect the time periods of interest, if indeed they are known, and may not reflect the time dependent nature of the cofactors. A further problem is how to summarise sexual behaviour for discordant couples over

time where there is information collected at the initial interview and further information recorded at follow-up visits This is not a simple problem. Partner studies assess retrospective sexual behaviour at the recruitment interview where questions are generally not designed to elicit behaviours occurring in specific calendar years. Follow up studies allow prospective data collection but are such data sets comparable?

Consequently cross-sectional analyses of partner studies have had to compromise on which are the most relevant behavioural and biological data to use in the analysis if such a choice of data is available. Since the majority of contact seroconversions are not observed during the follow-up period but occur before the couple is recruited into the study using the most relevant data, if they are available, is of great importance[1,2,3]. The Italian partner study was restricted to sexual behaviour data collected at the initial interview for the preceding year which may poorly reflect, for example, the behaviour of concordant couples around seroconversion of the contact case[3]. The European study collected sexual behaviour data before and after diagnosis of HIV in the index case and over the follow-up period for discordant couples[1]. Again these data might not necessarily reflect sexual behaviour at seroconversion of the contact case if only long seroconversion intervals are available.

There is also a problem in determining the HIV stage of the index cases at the time of transmission and many studies have recognised the difficulty in assessing the immunological or clinical status of the index case around the time of the seroconversion of the contact[24,40-42]. As an example the European study used the most recent CD4 count or CDC stage and noted that the duration of HIV infection and dates of appreciable immune deterioration were generally not available[1,41]. CD4 counts for the Italian cohort were only available for approximately 70% of the index cases and estimate imprecisely the disease stage of the index case at the time of the contact's seroconversion[3].

For all these reasons it seemed, that a more appropriate analysis for HIV transmission was a longitudinal approach where interest lies in modelling the risk of seroconversion over time for each couple. Data arising from the Edinburgh heterosexual study allowed this type of analysis to take place via a behavioural and biological profile of each couple, constructed, in yearly blocks, over the period during which the contact was at risk of infection. For the Edinburgh cohort there was not only detailed knowledge of seroconversion intervals for the index cases but also a

considerable amount of biological information such as CD4 counts and CDC staging information because the majority (92%) were in clinical care at an early stage. Further, the couple's contraceptive use was recorded on a yearly basis. These important data sets largely made the longitudinal analysis possible.

The European study analysis of the follow-up of couples discordant for HIV at recruitment, was based on 378 couples of whom 122 (32%) were non-condom users and of these 12 (10%) seroconverted during follow-up[1]. A survival analysis of these prospective data showed advanced stage of infection in the index case, as characterised by CDC stage IV (p=0.03), and genital infections in partner (p=0.05) were risk factors for transmission. For the Edinburgh study the current status of the 85 couples discordant for HIV at recruitment was as follows; 2 (2%) contacts had seroconverted, 41 couples' relationships (48%) had ended (includes 12 couples where the index has died and one couple where the contact has died), 9 couples (11%) who were either lost to follow-up, refused follow-up or had moved away from the area, and 33 couples (39%) who were in active follow-up. With so few couples in active follow-up combined with the intensive counselling for risk of HIV infection and safer-sex practices of contacts and index cases, the number of seroconversions observed during follow-up was likely to be low. However condom use was also relatively low (maximum of 43% of couples) despite this intense counselling and only two prospective seroconversions were observed[43] which is in keeping with the expected data from the European study[1].

The problem of low numbers of prospective seroconversions may be an inherent design problem of partner studies, since others have observed the same phenomena[1,2]. Equally it may be a particular factor associated with the time scale of the Edinburgh epidemic, since the study began only 2-3 years after the start of the HIV epidemic. Most other partner studies have occurred in areas where the epidemic was well established.

Despite these problems the analysis presented in this paper has demonstrated that when adopting a longitudinal approach it is not simply necessary to rely only on large numbers of seroconversions of contacts during follow-up. The majority of transmission events (92%) occurred before the couples were recruited into the study. Retrospective behavioural data collected at the initial interview and biological data on the index case enabled these couples to be entered into the longitudinal analysis. The results suggest that high levels of unprotected sex, engaging in "high-risk"

sexual practices and a low CD4 count for the index, all increase the risk of heterosexual transmission of HIV. The study has indicated a relationship with the number of exposures and the protective effect of condom use or abstinence in decreasing the risk for transmission of HIV. The protection afforded by condoms in this analysis would have been greater of course, if the data on couples who always used condoms or were abstinent had been included in the analysis. They were left out to make the data comparable with the European study[1].

These results are in keeping with what one would expect from such infectious agent. However not all studies have noted a connection with the number of exposures to the virus. The original London/Edinburgh study and the European study found no association with the number episodes of vaginal intercourse. This may be because the data was collected retrospectively over a long time period and may be inherently inaccurate especially when combined with an inaccurate period for ROI if the seroconversion date of the index is not known. The Italian study noted a relationship with number of exposures, as defined by sexual intercourse more or less than twice per week[3]. The Californian study also noted a relationship with exposure when analysed on a log scale[36]. Such a results would be in keeping with a virus of relatively low infectivity via the vaginal route in the absence of other promoters or factors such as STD's.

The present analysis also indicates for the first time the importance of the time period 4-6 years after seroconversion of the index. This peak of HIV transmission may be explained by rising biological infectivity and falling behavioural infectivity (possibly as a result of age or increasing ill health). The random effects model used to estimate CD4 counts would put this level of risk immunologically at around 300 CD4 cells/cumm. This is perhaps earlier than one would intuitively expect from knowledge of the disease process. A level of less than CD4 200 cells/cumm might be expected to be of importance for biological infectivity but it may well be that this increasing biological infectivity is tempered or reduced by falling behavioural infectivity. Thus whilst each episode of exposure may be at increased risk at this level of CD4 count the sum total of risk for a couple in a regular relationship may in fact be lower than earlier in the relationship when behavioural infectivity is much higher. However caution is required with any interpretation of this analysis since this study is not saying that sex with an individual with CDC stage IV or AIDS is safe. Essentially highly infectious individuals can only transmit if the opportunity occurs. Of course this interaction of biological and behavioural infectivity reaches its

ultimate in the protective effect of abstinence where behavioural infectivity is zero and over rides the effect of biological infectivity. This theory would explain why in the current longitudinal analysis CDC stage IV (observed propospectively) was not found to be associated with the risk of transmission. At a CD4 count of around 300 cells/cumm and 4-5 years out from seroconversion most of the index cases would have been asymptomatic.

The association with advanced disease in other studies may also be explained by recruitment bias from which all partner studies suffer. Partner studies tend to attract couples in long term stable relationships rather than casual short term relationships. This is mostly because of the difficulty and time required to recruit couples into a long term study. Recruitment, to be successful has to be handled in a sensitive manner and takes time. Consequently short term casual relationships of a few weeks are difficult to study. [The ultimate short term relationship is one sexual exposure and this has been best studied by looking at a group of prostitutes and a group of clients[37]]. In addition the majority of partner studies have recruited from a health service basis and as a result index cases with symptomatic disease are more likely to be recruited. If such long term relationships transmitted in the asymptomatic stage, but the relationships remain intact until recruitment via a health service facility a bias would be introduced towards advanced disease being associated with HIV transmission in stable couples. The very early establishment of services for HIV in Edinburgh at the stage of patients being asymptomatic may have reduced such a bias in this study.

The importance of the current study is to highlight the importance of HIV transmission at the asymptomatic rather than at an advanced stage of disease particularly for stable long term relationships in countries where promoters of transmission such as STD's are infrequent. Many couples rely on the idea of adopting protective measures such as condoms with the onset of ill health and this may well be too late for the contacts. The analysis also confirms the importance of the previously reported increased risk of transmission associated with "high risk" sexual practices such as anal sex for women and sex during menstruation for men.

Whilst all of the major studies have yielded important information with regard to heterosexual transmission they have all had difficulties in observing seroconversions prospectively. Perhaps what is required is a new type of heterosexual study based on retrospective behavioural data from concordant couples with prospectively collected

biological data on the index cases compared with discordant couples prospectively followed for biological and behavioural data. Unfortunately the lack of observed seroconversions in partner studies has meant that the majority of data analysis has been cross sectional with all its flaws or has had little power. The success of the studies in preventing seroconversions has also resulted in difficulty in attracting funds for continued studies and this has been the fate of the present study. The problem of funding in Edinburgh has occurred despite the fact that further seroconversions have come to light in Edinburgh out with the study, reinforcing the fact that heterosexual transmission is occurring in Edinburgh and can be studied successfully. The success of partner studies in preventing transmission in "high risk" couples should however be taken on board by health service as a useful model of how to deliver prevention to this important group. This current analysis indicates that longitudinal studies even with relatively small numbers of observed seroconversions can yield valuable information concerning heterosexual transmission of HIV.

Conclusions

A longitudinal analysis of biological and behavioural factors noted that "high risk " sexual practices, high levels of unprotected intercourse and a low CD4 count all increase the risk of heterosexual transmission of HIV. Unexpectedly, late stage of disease (as measured by CDC stage) was not associated with increased risk of transmission and the peak of transmission of HIV was in fact 4-6 years after seroconversion of the index. This initially unusual result seems best explained by the complex interaction of biological and behavioural infectivity within a long term relationship and this study has allowed us to throw some light on this complex relationship. The results have important implications for heterosexuals in countries where additional promoters of HIV transmission such as STD's are relatively infrequent.

Appendix

Data Construction

Essentially a yearly profile of the couple over the period for which the contact is at risk of infection was constructed, allowing sexual behaviour and infectivity of the index case to be time dependent.

Period of risk

The contact's period of risk of infection (ROI) started either with the year the relationship began or the year that the index seroconverted, whichever was the more recent. If the couple was concordant with respect to HIV then the ROI period ended when the contact seroconverted. Conversely, if the couple was discordant with respect to HIV, then the last year of ROI was defined either by the year of the last negative test, the end of the relationship (if appropriate) or the most recent follow-up visit, whichever was the earliest.

Thus in order to define the ROI period accurately, the time when the index (and contact if appropriate) seroconverted was required. However these dates were often not known exactly but were only known to lie within an interval from the last negative to the first positive test dates. Thus for some couples a profiled year cannot be determined with certainty as being pre- or post-seroconversion for either index or contact. This uncertainty over the seroconversion year of the index was overcome by generating a year of seroconversion for the index based on knowledge of the Edinburgh HIV infection curve for injecting drug users (see below). For the Edinburgh index cases there was not only detailed knowledge of the HIV infection curve but also a number of relatively short seroconversion intervals mainly due to retrospective testing of stored sera[6-8,16].

If the couple was concordant with respect to HIV then a year of seroconversion for the contact was also needed. The contact's seroconversion interval was not only defined by their own last negative and first positive test dates but also by the seroconversion date of the index, since the contacts only risk of HIV infection was sexual contact with the index case. It was necessary that the contact's year of seroconversion be later than the year of simulated seroconversion of the index. Thus the lower bound of the contact's seroconversion interval was the maximum of last negative date of contact (if available), the start of the relationship and the year the index seroconverted. The weighting used to determine the contact's seroconversion

interval was different to that used for the index due to less accurate knowledge of the HIV infection curve in non-injectors.

The year that the couple became aware of HIV in the relationship was taken as the year of the first positive test of the index case, ignoring dates of retrospective tests. This may not necessarily reflect when the contact was actually aware of the possibility of HIV in the relationship. In addition, many index cases may have assumed that they were HIV positive well before their HIV status was confirmed. This could occur because of previous "high-risk" behaviour to which the index attributed HIV infection and or knowledge of the HIV status of friends, with whom, injecting equipment had been shared for example. The year of first positive test, excluding retrospective tests, was not available for two index cases. These couples were omitted from the analysis which included the covariate "knowledge of HIV in relationship".

Demographic and behavioural covariates

The two demographic covariates of major interest were gender and age of the contact. Older age has been associated with increased transmission from male to female cases in two studies[1,17]. Two studies have also compared male to female transmission with female to male transmission and suggested that male to female transmission was the more efficient but with very different suggested rates between the studies[1,2]. The European study suggested that male to female transmission was twice as efficient whilst the Californian study found male to female transmission to be approximately twenty times more efficient[1,2].

For the behavioural covariate describing contraceptive use, the analysis concentrated on the two contraceptive methods known to be protective against HIV i.e. condom use and abstinence from sexual intercourse. Behavioural data were collected on a yearly basis for the 5 years preceding the initial interview or the length of the relationship, whichever was shorter and at the follow-up interviews. Abstinence was of particular importance in the Edinburgh study. It was not uncommon for some injecting drug user index cases to spend periods of time in prison which would be coded as periods of abstinence for the couple. It was also not uncommon for relationships to break-up for short periods of time and then to restart and in this situation these periods were also coded as abstinence. There is also evidence to suggest that couples abstain from sex when the index case becomes unwell with HIV[12]. A time dependent covariate for contraceptive use was constructed to

describe the proportion of time, in a particular calendar year, that the couple had unprotected sex (for HIV). This was defined as {1-(proportion of time in year using condoms and abstaining from sex)}. Unfortunately information on sexual practices, collected at the initial interview, was not coded on a yearly basis and therefore it was not possible to construct a yearly profile of sexual practices for the retrospective data. However, it was possible to construct a yearly profile of sexual practices for data collected prospectively at the follow-up interviews. This variable was therefore allowed where appropriate to be time dependent during the follow-up of the couple.

The sexual practices associated with increased transmission of HIV are different depending on the direction of transmission, male to female or vice versa. A single binary variable was constructed indicating whether couples with female contact cases had never/ever engaged in anal sex or recorded post-coital bleeding and whether couples with male contacts have never/ever had sexual intercourse when the female index was menstruating. Data collected for the Edinburgh study was limited with respect to this variable.

Other time dependent covariates of interest were year of recruitment and knowledge of seropositivity of index. These were defined as binary variables, being "switched on" in the year that the contact was recruited into the study or in the year when seropositivity of index case was known. However, since both these variables might have affected the levels of condom use/abstinence/ or "high-risk" sexual practices, an additional direct effect on transmission might not be detected.

Measures of infectivity

The most appropriate measure of infectivity for heterosexual transmission of HIV would be isolation or detection of virus at varying levels in body fluids such as semen or cervical secretions. However, this marker of infectivity is not available for most studies, including the Edinburgh Partner Study, and therefore some form of surrogate marker for infectivity such as immunological decline or clinical status has generally been used.

The two common immunological/clinical factors used to describe the anticipated later rise in infectivity of the index case have been the CD4 count and the CDC stage of HIV disease. In cross sectional studies, these data were usually collected at recruitment but the longitudinal approach to analysis requires a measure of the CD4 count in each year the contact was at risk of infection. The method used in most

studies has been to utilise the actual CD4 counts or some summary of the CD4 counts collected in each year such as the mean/median/minimum value. There is then the awkward problem of missing values in the earlier years when CD4 monitoring did not take place because the index case had not been diagnosed. To address this problem a method estimating for smooth individualised CD4 trajectories was adopted. Random effects models have been commonly used to describe square root CD4 decline after seroconversion as it had been recognised that there is a tremendous variation between individuals both in terms of CD4 count at seroconversion, and the loss of CD4 count per annum[18]. By fitting quadratic growth curves an expected CD4 value for each year post-seroconversion of the index case could be estimated.

An alternative surrogate marker of infectivity, assumed to act as a proxy for the suspected late rise in infectiousness, is the disease stage of the index case as given by the CDC classification of clinical disease[20]. The CDC classification was coded as a binary variable indicating an index satisfying stages 2 or 3 (asymptomatic disease or persistent generalised lymphadenopathy) or an index satisfying stage 4 (symptomatic disease). Unlike CD4 counts this CDC covariate only models the increase in infectivity when the index case is in an advanced stage of disease.

One possible explanation for previous reported associations of HIV transmission with falling CD4 counts or advanced CDC disease is that both are acting simply as surrogate for length of infection of the index. Thus instead of using only CD4 count or CDC stage to model the disease stage of the index case, time-dependent indicators were defined to distinguish if exposure was within 4 years of seroconversion of the index case; between 4 and 5 years after seroconversion of the index case; or was 6 or more years after the seroconversion.

Biological measurements of any possible rise in infectivity around the time index cases seroconverted are not generally available, unless the seroconversion is prospectively observed. To overcome this problem and in an attempt to detect any possible early rise of infectivity and therefore transmission of HIV, if it exists, a binary time dependent covariate was defined to indicate if the risk of transmission was different during the year after the simulated seroconversion year of the index compared to during the rest of the ROI period.

There is some evidence to suggest that infected individuals are either "transmitters" or "non-transmitters'" of the virus[21,22]. This implies that the sexual contact of a "transmitter" will become infected shortly after the start of the period of risk, if the

opportunity exits (that is condom use and abstinence are low). Conversely sexual contacts of "non-transmitters" will remain uninfected after prolonged periods of appearing to be at risk. This aspect of HIV transmission was investigated by defining a binary time dependent covariate which allowed an estimate to be made to indicate if the risk of transmission was different in the first year of the ROI period. However if only certain individuals are "transmitters" this analysis might fail to signal a differential first year average transmission risk and so will not detect this possibility.

Statistical Analysis

The uncertainty over the seroconversion year of the index was overcome by first generating a year of seroconversion for the index which conformed with prior knowledge about the HIV infection curve of the Edinburgh injecting drug users and fell within the index's seroconversion interval. There was not only detailed knowledge of the HIV infection curve but also a number of relatively short seroconversion intervals mainly due to retrospective testing of stored sera[6-8,16]. If an index has a seroconversion interval defined by [date of last negative, date of first positive] and year l, r represent the year of the last negative, and year of first positive, respectively then probability the index seroconverted in year i is given by

$$\frac{l_i w_i}{\sum_{j=l}^{r} l_j w_j}$$

where l_i is the length of the interval for year i, defined by the seroconversion interval, and w_i is the weight associated with year i, which indicates the HIV incidence associated with year i based on our knowledge of the likely number of HIV infections in that particular year. The year of seroconversion of the index case is simulated with respect to these probabilities which are functions of the weights w_i. The simulated year of seroconversion of the index case defines the start of the risk of infection if the relationship started before the first positive test date of the index.

For HIV infected contacts simulated seroconversion years were also generated but the prior information used was different, reflecting greater uncertainty in when non-IDU HIV infections occurred.

HIV infection in injecting drug users in Edinburgh was concentrated in 1983 and 1984 with very little infection in later years. This information was translated into 40% of HIV infections having occurred in 1983; 30% in 1984, 4% in each of the years 1985-1989, 3% in 1991 and 1992 [i.e. the weights used in the simulation of the

seroconversion year of the index case were as follows; w_{1983}=40, w_{1984}=30, w_{1985}=4, w_{1986}=4, w_{1987}=4, w_{1988}=4, w_{1989}=4, w_{1990}=4, w_{1991}=3 and w1992=3].

The method is illustrated for an index case with last negative in August 1993 and first positive in January 1986, so that seroconversion could have occurred during the last five months of 1983; in 1984 (12 months): in 1985 (12 months); or in January 1986.

Applying the information concerning weighting to our illustrated case whose seroconversion occurred in a 30 month interval, 5 months of it in 1983, the probability that the index seroconverted in 1983 is

$$\frac{5 \times 0.4}{5 \times 0.4 + 12 \times 0.3 + 12 \times 0.04 + 1 \times 0.04} = 0.33$$

In 1984 it is 0.59, in 1985 it is 0.08 and in 1986 it is 0.01. An "actual" seroconversion time is then randomly generated for our illustrated case in accordance with these calender year probabilities.

Each couple has repeated observations, in yearly blocks, over the period the contact is at risk of infection. The data were then analysed using a logistic model with random effects where interest lies in describing the outcome y_{it} for couple i in the year t, whether the contact from couple i seroconverted in year t as a function of covariates x_{it}, for example, the proportion of time in year t couple i has unprotected intercourse for HIV. The Generalised Estimating Equations (GEE) approach was used which provided population averaged estimates of the coefficients[23,24]. A "working" correlation matrix of the responses y_{it} was specified which took into account the correlation between repeated observations of a couple.

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CHAPTER 19

Outcome measures and quality of care for HIV and AIDS in Edinburgh

Introduction

There is much interest by the profession and others concerning medical audit, the quality of medical care and how the latter should be measured[1]. In order to begin the audit cycle however one needs to establish standards with which to compare subsequent activity. Not surprisingly in view of the interest in quality of medical care for other specialities there is also a growing need to develop National Benchmarks or Quality Measures for the care of HIV/AIDS patients since it is by such standards that carers will be judged[2,3]. A report on the quality of medical care commented that the quality of medical practice should be judged by its outcome[3].

Quality of care has been defined as the increase in health or at least the prevention in health deterioration that would have occurred[2]. Since the natural history of HIV/AIDS is not that well established this provides us with some problems in establishing quality of medical care for HIV/AIDS. However we do now have some ideas of what should occur with best medical practice. For instance we know that PCP prophylaxis can reduce the number of attacks of PCP and we may therefore assume that if applied effectively it should reduce the amount of time spent in hospital with attacks of PCP. However at present we do not know how effective PCP prophylaxis is in the day to day care of patients as opposed to the clinical trial situation i.e. efficacy versus effectiveness.

There is also a need to decide on what are preventable or avoidable early deaths with HIV. In this context the use of effective PCP prophylaxis could be considered as a way of reducing avoidable morbidity and the number of episodes of PCP after a defined point could be a method of measuring avoidable morbidity. Similarly the expectation of life or survival after certain clinical or immunological end points in HIV disease would be a reasonable measure of quality of care. Equally the number of days spent in hospital/year of HIV or AIDS life might also a reasonable initial measure of the quality of care for patients. It would however be important to take into account confounding factors in various outcome measures such as socio-economic status, risk activity, ethnic origin etc..

A practical approach to establishing a cycle of audit is to;

- identify what we should assess
- establish the criteria to be judged against, with other specialities these criteria have been established by the Royal Colleges or "other " interested groups
- identify and analyse the problems
- refine the criteria in the light of experience
- and formulate a set of recommendations

Quality measures for a population

Quality measures can be applied to both for the large scale public health management of HIV as well as to health teams caring for individual HIV/AIDS patients. As far as public health departments are concerned quality measures that might be considered would be to do with the reliability of the estimates of the size of the population or the effectiveness of reaching out and contacting particular groups.

As an example methods of determining the size of the HIV population in care and or at risk should be subject to quality control since they are used in the purchasers needs analysis of a population and will be used increasingly in the future to determine allocation of resources between Health Boards. Confidential registers have been established in some Health Boards in Scotland. Patients with a positive HIV test under the care of a clinician are reported to local AIDS control officers utilising a confidential identifier. The use of a confidential code or identifier such as a combination of the Soundex code together with initials, gender and date of birth allows the generation of a unique identifier. This confidential identifier can then be used in the construction of a confidential HIV register provided by individual clinicians for each region without impinging on the confidentiality of the patient. Whilst this method ensures total confidentiality for the patients it can lead to considerable errors in assessing the size of an affected population because of double counting of the infected population. This can occur because of patient movement between centres and or name changes. This is a particular problem with populations containing large numbers of women who may change their names depending upon current sexual partners. Further examples of population quality measures will not be discussed since they have not been dealt with in this thesis.

Quality measures for individual Units

For the HIV population in care the effectiveness of the health care system in contacting, retaining patients and delivering medical care could be assessed by some or all of the following indices.

It is possible to assess the success of any health care system in persuading individuals to come into the health care system. This overall assessment of the acceptability of a local health care system would essentially assess how user friendly were the services for different groups. It could be measured by various indices which act as surrogate markers of the use of health care for instance the percentage of AIDS cases presenting without prior HIV testing and or medical care.

The follow up rates for clinics can be used as a surrogate marker of the success of a health care system in delivering continuity of care. A target of 10% of patients lost to contact per year or a cumulative lost to follow up rate of 5% per year over 5 years seems initially acceptable. The loss to follow up rate would be a measure of the acceptability of the care to the user.

The extent of immunological monitoring of a population perhaps on a yearly basis would be another surrogate marker of the success of a health care system in engaging a population. Recently centres in the USA have reported levels of 60% under immunological monitoring each year. In the UK should we aim for a target of 90% of the population in care each year undergoing at least one assessment of immune status (CD4 counts). In addition perhaps the numbers declining such investigations should be recorded.

The mean CD4 count of a population at the time of the diagnosis of AIDS might be put forward as a surrogate marker for the success of delivering PCP prophylaxis and perhaps therefore health care in general. Does a lower level of CD4 count at AIDS diagnosis indicate better use of prophylaxis?. Perhaps a mean CD4 count at the diagnosis of AIDS of less than 100 cells/cu mm should be our target.

The number of episodes of PCP/patient lifetime and or the number of days in hospital per person year of life would be surrogate markers for the success of a health care system in providing secondary PCP prophylaxis. In this context we would be assessing the effectiveness of PCP prophylaxis in day to day care as opposed to clinical trials. The rates would vary with different populations under care and would

need to be judged with these problems in mind. They would however be measures of avoidable morbidity for AIDS.

The survival rates for common opportunistic conditions could be published as a measure of the appropriateness or effectiveness of a Unit in caring for patients. For instance the survival rate for first episode PCP should be greater than 95% and perhaps Units need to assess their own data against a generally accepted standard.

Some measure of length of survival from a clinical or immunological diagnosis such as AIDS, CD200 etc. to death would be useful in assessing the effectiveness of Units.. These measures would be another assessment of the appropriateness of care in increasing life expectancy. Since the mean for the UK is published and is currently around 16 months a target of getting within with in 2 standard deviations or greater than 12 months could be proposed. Similarly a first year survival of greater than 50% might be proposed for reasonable quality for a Unit.

Depending upon the population the number of patients suffering CMV or MAI infections in a population might be regarded as a surrogate marker of long term survival since they are both late diseases. This depends to a certain extent on the population under surveillance but with 80% seroprevalence for CMV for instance one might expect 15-20% of all AIDS patients to suffer this complication if long term survival is adequate.

The annual number of bed days spent in hospital post AIDS or CD4 200 as a marker of health care. Again this would depend upon risk group and survival but a figure of between 50-100 bed days per year might be agreed upon with some acceptable increase for particular problem areas such as drug users, low socio-economic status or ethnic origin.

The average length of stay (ALOS)per admission. In this situation in addition to quoting an ALOS it would also be possible to set a target of reducing the figure by a certain percentage each year and to demonstrate increasing use of day beds for the treatment of these disorders.

The number of admissions/year for patients with AIDS. This also would depend upon risk group and survival but one might overall expect between 2-3 admissions per year.

The extent of named patient drug use or participation in MRC trials. This would depend upon the units and their size but would be a measure of the availability of newer treatments. Of course for some patients not keen on experimental treatment a low figure would be desirable whilst for others a high level would indicate involvement in research and the availability of the latest treatment regimes. Perhaps a target of 5-10% of patients attending a centre would be an acceptable compromise.

Outcome measures for HIV and AIDS in Edinburgh

Outcome measures relating to the Edinburgh City Hospital were compiled from the data on the Edinburgh City Hospital Cohort presented in the previous chapters of this thesis and are summarised below.

Out patient medical care (Chapter 6)

Numbers attending

Coincident with the prescribing of oral methadone and a specific all day IDU related HIV medical clinic the total number of appointments increased from 28/month in May 1986 to 300/month by May 1989. The attendance rate continues to run at around 250-300/month.

Default or missed appointment rates

The number of defaulted appointments decreased from a maximum of 60% in 1985 to 16% in 1989. By 1990 the average default rate was 26%.

Laboratory monitoring

Laboratory monitoring of HIV, that is at least one sampling episode in a year, was achieved in 92-95% of the patients attending in 1989 and 1990.

Loss to follow up rates

The annual number of patients lost to follow up has varied between 7-11% per year but has not change significantly over time whilst the cumulative number of HIV infected individuals lost to follow up after 5 years was only 14%.

Harm reduction

Amongst HIV infected patients the percentage reporting injecting at more than 50% of the visits during a year fell from 42% in 1986 to 6.5% in 1990 and those reporting injecting at one visit during a year fell from 51% in 1986 to 23% in 1990.

Use of anti viral agents

The number of patients in the clinic offered zidovudine therapy was 68% and the number taking up this offer was 61%.

Morbidity (Chapter 17)

Pre-AIDS morbidity

In Edinburgh the commonest conditions which occurred before AIDS were oral thrush, OHL and severe bacterial infections. The rate of oral thrush varied from around 9-39 episodes/100 patient years depending upon risk activity. OHL, which is an indicator of impending illness but rarely causes symptoms, was found with an incidence of around 6-34 episodes/100 patient years. Perhaps the most life threatening event, that of severe bacterial infection occurred between 2.6-6.3 episodes/100 patient years.

Non AIDS mortality

The Edinburgh non AIDS mortality rate was 2.5/100 person years of follow up and not surprisingly this varied by risk activity. The non AIDS death rates for heterosexuals or homo/bisexuals were low at 0.9/100 person years.

AIDS Incidence

The overall incidence of AIDS was 8.8/100 person years and this varied from 5.7-33/100 person years depending on risk activity.

AIDS cases presenting without prior HIV

In Edinburgh only 11% had AIDS at their initial presentation to the RIDU, City Hospital, Edinburgh.

AIDS morbidity

The overall morbidity rate for patients with AIDS was 143 clinical events/100 person years. This is an underestimate of the problem since conditions such as oral thrush were not monitored effectively in late stage disease. Thus each patient with AIDS can expect 1-2 clinical events per year of survival.

Analysis by risk activity clearly demonstrates the much higher morbidity associated with heterosexuals (183/100 person AIDS years) compared to drug users (140/100 person AIDS years) and homo/bisexuals (137/100 person AIDS years). As far as particular conditions were concerned PCP was the commonest clinical event (52 episodes/100 person AIDS years or 0.7 episodes/patient) followed by oesophageal candida (19/100 person AIDS years or 0.3 episodes/patient), malignant disease (18/100 person AIDS years, KS and lymphoma), MAI (17/100 person AIDS years), CMV (14/100 person AIDS years) and toxoplasmosis (8.5/100 person AIDS years).

Inpatient medical care (Chapter 9)

Average length of stay (ALOS).

Each year the average length of stay in the Unit for HIV admissions has fallen from 16.9 before 1987 to 11.7 in 1992. The most dramatic fall in ALOS have been for patients with AIDS and those with severe immunodeficiency (a CD4 count of below 200). For instance the ALOS for AIDS and CD4 200 before 1987 were 36 and 31 days respectively and by 1992 these had fallen to 14 days and 13 days respectively.

Resource use does however vary with risk group. Whilst IDU related admissions are if anything shorter (13 days) than homosexual related admissions (15.5 days), drug users with AIDS utilise more bed days per year (65 days) than do homosexuals (54 days).

Number of admissions

In 1992 the number of admissions per patient per year was 2.6 for AIDS and 0.75 for non AIDS patients

First admissions.

Only 24% of men and 11% of women had their first admission with a diagnosis of AIDS.

Mean CD4 count at the time of diagnosis of AIDS.

The mean CD4 count at diagnosis of AIDS has been falling in Edinburgh from around 170 in 1987 to 50 cells/cu mm in 1992[4,5]. The falling level is as a consequence of the improved health care such as the use of zidovudine and prophylaxis for opportunistic infections. Comparisons show that the CD4 count in Edinburgh was the lowest of 5 cohorts including a haemophiliac cohort in London and a drug using cohort in Italy[5].

Survival (Chapter 14)

Survival at presentation

Only 6 (4.6%) patients died in the same month as the diagnosis of AIDS was made, whilst a total of 11 (8.5%) patients died in the two months after the diagnosis of AIDS was made.

Survival after AIDS

The current median survival for patients attending the RIDU after AIDS is 20 months with a one year survival rate is 66%, the two year survival rate is 44% and the three year survival rate is 25%.

The median survival of patients in the Lothian area is currently 3 times better than the worst Scottish Health Board. (Lothian median survival 21 months compared to 8 months for Tayside and 14 months for Glasgow) despite the fact that the majority of our patients are IDU related[6]. The median for Edinburgh is highly comparable with other centres. On an international basis a recent comparison of 5 cohorts with known dates of seroconversion Edinburgh had the longest survival and AIDS free time[5]. At 10 years the New York and Washington cohort had less than 40% free of AIDS compared to 50% for the London haemophiliac cohort and nearly 80% for the Edinburgh cohort. Similarly the survival of the American cohort was only 40% at 10 years compared to nearly 70% for Edinburgh (the extra deaths in Edinburgh occurred because of overdoses rather than HIV deaths)[5].

Table 19.1 Comparative Survival for Scotland and the UK of AIDS to death

	Edinburgh	Glasgow	Dundee	Other	UK
Survival at 1 year	66%	54%	37%	66%	60%
Survival at 2 years	44%	29%	-	-	30%
Median Survival	21 months	14 months	8 months	17 months	15.5 months

Survival of common conditions

The survival rate for first episode PCP was 96.6%

Survival after severe immunodeficiency (CD200 level)

The current median survival post CD4 200 (as defined by two consecutive values below 200) was 50 months with one year survival rate of 94%, two year rate of 80%, three year rate of 69% and a four year rate of 53%. If one count below CD200 is taken as the definitions then for Edinburgh the median survival was 40 months with a 1 year survival rate of 87%, a 2 year survival rate of 71% and a 3 year survival rate of 54%.

Conclusions

The RIDU model has reached over 600 patients infected with HIV (approximately 60% of the known HIV population in Edinburgh) and the majority of first admissions (76% of men and 89% of women) occurred before the diagnosis of AIDS. In addition the RIDU model of care for HIV has yielded acceptable outcome measures. For instance whilst the number of missed appointments remains relatively high at around 26%, laboratory monitoring of HIV was achieved in over 90% of the population under care. The annual loss to follow up was around 10% but the phenomena of re-attendance after considerable periods of absence results in a cumulative loss of follow up of less than 15%. Self reported improvement in high risk behaviour has also occurred; those reporting injecting at more than 50% of clinic visits during a year fell from 42% in 1986 to 6.5% in 1990.

The majority of patients presenting with AIDS survive the first admission, more than 95% surviving the first month of AIDS and more than 90% surviving the second month of AIDS. By comparison a large group of patients with AIDS from New York had an immediate mortality of 11.4% and a group of drug users from the Bronx had an immediate mortality of 15%[7,8]. The median survival for AIDS was 20 months; the 1 year survival was 66%, two year survival was 44% and the 3 year survival was 25%. Survival for the commonest presenting problem of AIDS, PCP, was high with a survival rate for a first episode of PCP at greater than 95%. Survival with severe immune deficiency other than AIDS can be assessed by survival from the immunological marker, CD200; the median survival was 40 months with a 1 year survival of 87%, a 2 year survival of 71% and a 3 year survival of 54%.

Whilst prophylaxis for the common opportunistic infections are more difficult in a drug using cohort, medical care in general has been successful since the mean CD4 count at which the diagnosis of AIDS was made has fallen over the years and is now around 50 cells/cumm. The effectiveness of medical care can also be measured by considering the number of episodes of preventable OI's for each patient; the average number of episodes of PCP per patient with AIDS was 0.7/patient or 52 episodes/100 person years of AIDS. The number of episodes of oesophageal candida for patients with AIDS was 0.3/patient or 19 episodes/100 person years of AIDS.

The number of patients developing CMV or MAI in an AIDS population is a surrogate marker of long term survival since they are only seen in patients with very depleted immunology. In Edinburgh the rate of atypical mycobacterial infections was 17/100 person years of AIDS and the rate of CMV infection was 14/100 person years of AIDS.

Whilst as yet we do not have assessments of quality of life as judged by the patient, reducing time in hospital could be taken as one measure of improving quality of life. The average length of stay (ALOS) for RIDU has consistently fallen from 17 in 1987 to 12 days in 1992 with the greatest fall occurring in the sickest patients; the ALOS for AIDS and CD4 200 before 1987 were 36 and 31 days respectively and by 1992 these had fallen to 14 days and 13 days respectively. At present however whilst IDU related admissions are not longer than other risk groups, drug users with AIDS do utilise more bed days per year suggesting that more work is required in this area to improve quality.

There is a need to establish generally accepted outcome measures for HIV and AIDS which can be applied not only to individual health care units but also to the effectiveness of the health care system in different geographical areas in delivering an acceptable level of care to the population. This chapter has detailed a number of possible outcome measures and summarised the results for the RIDU, City Hospital, Edinburgh.

The possible standard outcome measures that could be adopted are; lost to follow up rate, the level of CD4 monitoring per annum, pre aids mortality rate, pre aids morbidity levels, the incidence of AIDS, the percentage of patients with AIDS at first contact with a service, AIDS morbidity levels for WHO conditions, ALOS for admissions and the number of admissions per patient, survival at presentation of AIDS, survival of first episode PCP, mean CD4 count at AIDS and survival from AIDS and CD200 expressed as a median and percentages surviving each year. From this list a few key outcome measures could be selected which are available from national statistics such as the percentage of patients with AIDS at first contact with a service (via local HIV and AIDS registers), the ALOS for AIDS and non AIDS HIV admissions (via Information Services Division), deaths within 30 days of diagnosis of AIDS and deaths within 30 days of first episode of PCP (via Information Services Division). The others such as mean CD4 count at AIDS, survival from AIDS or CD200 or the number of episodes of PCP and oesophageal candida per person year of AIDS could be published via the AIDS Control Act annual reports.

Defining suitable outcome measures for HIV/AIDS is the beginning of efforts to improve the quality of care for individuals infected with HIV. The measures presented here would suggest that the quality of care for HIV/AIDS in Edinburgh is high despite the associated problem of drug use.

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CHAPTER 20

Summary

The original description of AIDS or the Acquired Immune Deficiency Syndrome only appeared in 1981 but it rapidly burst forth onto the world scene. By 1985 when a test for HIV, the cause of AIDS, appeared it was realised that a vast silent epidemic had occurred which is still not under control. The first specific treatment, zidovudine or AZT was licensed in 1987 and great improvements in survival followed its use in combination with prophylactic antibiotics for the commonest index diagnosis of AIDS, PCP or pneumocystis carinii pneumonia. Early hopes of a rapid cure were dashed when it was realised that whilst survival was prolonged the continual and inevitable immunological decline continued to reveal other even more complicated opportunisitic infections. It also became apparent that the natural history of HIV was slow by comparison to most infections with a median time from infection to AIDS of around 10 years. Consequently as a new infection to medicine, HIV and AIDS required further study. This thesis has detailed the establishment of an effective medical service for a population largely composed of injection drug users, the natural history of IDU related HIV, the clinical presentations to date, the effectiveness of the service and lastly the factors predicting heterosexual transmission.

Injection Drug Use

IDU is a small but important cause of serious problems in modern medical practice. The phenomenon of IDU related infection is now over a hundred years old but it continues to this day although the particular organisms associated with IDU have varied over time and with particular injection practices utilised by individuals. The use of unsterile equipment for instance increases an individuals susceptibility to bacterial and fungal infections (which is even further increased in the setting of HIV infection). The sharing of injection equipment has resulted in a number of problems over the years notably malaria (first described by an Edinburgh trained physician in 1929), various forms of hepatitis and latterly HIV. Prior to the advent of HIV the mortality rate in drug users was of the order of 1% per annum.

Injection Drug Use related HIV

IDU related HIV was first reported from New York in 1980 and seems to have spread via two basic patterns i.e. slow and gradual or rapid and explosive. Southern Europe was affected around 1981 and pockets of IDU related HIV were found to have

developed in Northern Europe as a result of the considerable mobility of drug users. One of these pockets of IDU related HIV occurred in Edinburgh. The considerable mobility of drug users is also the explanation for the similar explosive outbreak of IDU related HIV that has recently begun to spread through South East Asia.

Whilst there are a number of important medical problems, both non infective and infective in nature, associated with drug use the advent of HIV requires practitioners to have not only knowledge of these drug related medical conditions but also both the infection and non infection related HIV related medical conditions associated with IDU. A variety of micro-organisms may be associated with the non sterile nature of IDU and a number of blood borne viruses are easily transmitted to individuals involved in the sharing of injection equipment including retroviruses such as HIV.

As far as the clinical problems specific for HIV itself, there appears to be little variation between the risk activities with regard to presentation. In the USA conditions such as KS appear to be unusual in the absence of homo/bisexuality. In drug users PCP, tuberculosis, and oesophageal candidiasis seem to be more common. HIV has also been reported to cause some of the non infective problems previously associated with IDU particularly pulmonary hypertension, cardiomyopathy and emphysema. In addition the literature suggests that a number of conditions which occur commonly in drug users such as tuberculosis, pneumonia and endocarditis are increased by the presence of HIV in the host. The underlying mechanism behind the increased susceptibility to, and mortality of, bacterial infections is not as yet clear.

IDU related HIV in Edinburgh

The epidemic of IDU related HIV, which appears to have originated from Southern Europe, began abruptly in Edinburgh in 1983 and rapidly spread through known drug using cohorts. This explosive epidemic was the first of its type to be described in the world and unfortunately despite the relatively small number of drug users in Edinburgh it resulted in a large number of individuals infected with HIV. Per head of population the density of HIV infection in the 15-44 age group is certainly as great as any where else in the UK. However unlike other areas affected by IDU related HIV the epidemic in Edinburgh was detected within 2 years of its onset and as a consequence there was the opportunity to develop services before the onset of HIV related ill health or AIDS. These services were developed at the Regional Infectious Disease Unit (RIDU) located at the City Hospital, Edinburgh

Clinical services for IDU related HIV

Alternate site testing

The demand for an alternate site HIV counselling and testing facility at RIDU designed to attract in the first instance drug users was confirmed by the attendance of over 400 patients in its first year of operation, 64% being either injection drug users or their sexual contacts. It helped confirm the fact that HIV infection was commonplace amongst drug users but was less so initially amongst their sexual contacts. As a consequence of offering a test (in order to protect the Blood Transfusion Service) for a condition with no known treatment it was also necessary to develop accompanying medical services to cope with the condition. This was particularly important since the condition was infectious for other drug user or sexual contacts and initially those affected had little in the way of HIV related problems.

Models of care for IDU related HIV

The model of health care for HIV and AIDS utilised elsewhere had been developed from the experiences of San Francisco and London where the majority of patients have and still are homosexual or bisexual. This model of care did not apply to injecting drug users who have very different characteristics to other risk groups affected by HIV. The medical care of patients with AIDS and HIV is complicated by a number of medico-social problems which are further compounded by the problem of IDU.

A review of medical services revealed that in the USA continuity of care for HIV was not guaranteed unless the individual had private medical insurance and was almost non existent for IDU related HIV unless the patients were in a methadone programme. Although the San Francisco model for AIDS care, which is provided from a public hospital, does provide excellent out patient medical care even here continuity of care was not available for the numerous in-patient admissions unless the patient had private medical insurance. The New York health care system provides some continuity of care for the patient via the AIDS teams but the AIDS specialists rotate. Thus true continuity of care for inpatients was not available because subsequent admissions were under different Consultants. This was in contrast to the UK system where doctors were and are on service for the majority of the year and provide continuity of care via both inpatient and outpatient services.

The USA experience of HIV and AIDS did however emphasise the importance of a dedicated HIV service. The San Francisco experience suggested that specialisation was not only more efficient but improved the survival of patients. The management of HIV from a medical sense requires to be multi-specialist and infection, oncology and neurology problems are best considered in one department. The Amsterdam system whilst providing excellent continuity of care for drug use problems had not utilised its considerable experience for IDU related HIV problems. However the SFGH and Amsterdam experience of utilising specialised substance abuse counsellors or psycho-social nurses to help the patients and staff seems to be well worth considering for General Hospitals in the UK as the problem of IDU related HIV increases. Alternatively medical services are required experienced in the care of both HIV and IDU because the problems and solutions are so different from the services already established.

Whilst there are considerable problems for a health care service in engaging drug users the services developed at the City Hospital demonstrate that it is possible. In three areas an IDU related HIV medical service established at the RIDU, City Hospital, Edinburgh delivering substitute drugs and HIV medical services at the same site, was effective;

- in its ability to initiate contact,
- maintain that contact and
- help modify high risk (for HIV) IDU.

There were a large number of missed appointments but the majority of these were in fact related to less than 10% of the patient population. Although such a system is inefficient from the health services point of view, it appears necessary in order to maintain contact with the most difficult drug users and a medical care system which is experienced in the care of both HIV and injection drug use is able to deliver health care to injection drug users. Dedicated clinics offering both drug management and medical care are able to initiate and maintain contact with drug users as well as reduce their high risk IDU behaviour. Other proposed care systems which separate addiction from HIV medical care need to evaluate their results in order that medical care for HIV infected drug users can be based on facts rather than dogmas.

This work has shown that it is possible to adapt an **existing** health care system to be more "user friendly" for the lifestyle of injection drug users fulfilling the important

aims of initiating and maintaining contact with health care services. However this adaptation does have an effect on the established service in terms of default rate for existing patients and the referral of new patients.

Harm reduction

The strategy employed to contact drug users has come in for criticism since it is mistakenly thought to condone high risk behaviour. Harm reduction measures such as oral opiate substitution therapy and needle exchange when provided in the context of counselling and health education are able to initiate contact with drug users, to maintain that contact and to get across health education and prevention messages. There is now data demonstrating that such measures are safe in that they do not increase drug use or initiate drug use, are effective in changing high risk drug behaviour and that oral substitute prescribing such as methadone is protective against acquisition of HIV and may also be protective against progression to AIDS. It seems however that methadone or needles provided without counselling or health education are not effective. The evidence that needle exchanges are directly protective for acquisition of HIV is not yet available. However there is indirect evidence in the form of an improvement in high risk behaviour and highly suggestive evidence from those localities such as Edinburgh where needle availability was actively reduced. Not only has reduced needle availability failed to prevent an IDU epidemic it facilitated an IDU related Hepatitis B and HIV epidemic.

A harm reduction strategy for IDU related HIV should incorporate; outreach health education and counselling to initiate contact with and reduce high risk behaviour amongst drug users not in treatment, increased needle availability in the context of exchanges to reduce the sharing of equipment, increased availability of oral substitute prescribing to reduce IDU and increased availability of drug treatment to hopefully achieve eventual abstinence. There would appear at present to be no overwhelming reasons for society to avoid harm reduction for IDU and in view of the consequences of IDU related HIV for drug users as well as for vertical and heterosexual transmission of HIV every reason to increase such harm reduction programmes.

Inpatient resource utilisation

As a consequence of the HIV epidemic in Edinburgh a considerable number of young individuals came into the health care system. For instance by 1992 the RIDU HIV clinic population was utilising 1 admission per year and the average length of stay

(ALOS) for AIDS patients was not surprisingly significantly longer than a non AIDS admission. Similarly, those patients with a CD4 count below 200 cells per cumm had significantly longer ALOS. The number of admissions for patients with a CD4 count of less than 200 cells/cumm or without AIDS was low. Over the seven year period of the study the ALOS for each admission, when analysed by risk activity, revealed that homo/bisexual patients with AIDS had the longest ALOS whilst the number of bed days utilised per living patient per year was greatest for drug users. In Edinburgh, IDUs utilised inpatient care at an earlier stage in their illness than homosexual patients, with many IDU admissions occurring whilst being asymptomatic with regard to their HIV infection. The extra hospital resources for drug use related HIV during the initial phase of an HIV epidemic would appear to be in terms of more frequent admissions at an early stage of HIV disease rather than increased average lengths of stay per admission. The number of bed days per living patient per year was however greater for drug users. Thus the effect of risk activity on resource utilisation is complex.

The increased number of admissions and bed days compared with non HIV patients and the increased number of admissions and bed days for HIV patients with advancing immunodeficiency must be taken into account in health care planning terms. Whilst the increasing likelihood of admission with falling CD4 counts and clinical diagnoses of advancing disease was not unexpected, it underlined the fact that the allocation of resources needs to be based on the total population of HIV positives patients, since neither clinical diagnoses, laboratory measures of immunodeficiency, gender or risk activity alone were sufficient to predict health care needs.

HIV services for prisoners

In Edinburgh approximately 10% of the current HIV clinic population are in the local prison at any one time and their clinical stage of HIV reflects that of the HIV population as a whole. The service instituted from the RIDU at the City Hospital, has provided inmates with similar access to health care as patients in the community. Thus at present the system is achieving its aim of providing prisoners access to specialised HIV care although we are not as yet maintaining that contact after the inmate leaves prison. The system adopted in Edinburgh is without doubt expensive in terms of consultant time but it has ensured that patients in prison have the same availability of medical care as those in the community.

Problems for the health care service

The need to cope with large numbers of young current and former drug users within the health care system revealed a range of problems associated with IDU related HIV. These problems are not only extensive but also very different to those usually faced by the health service and include considerable self medication, verbal and physical assaults as well as other disruptive behaviour. The RIDU in Edinburgh has had to adapt in order to manage young drug users with a chronic illness. This adaptation has required new skills on the part of the staff and the gradual reduction in problems suggests that not only are the staff adapting but possibly the patients are also adapting to the our health care system.

Despite this improvement, the RIDU is still having to cope with a considerable amount of disturbed behaviour probably more so than other Units managing HIV in the UK. As IDU related HIV appears in other areas of the UK these Units will need to consider how best to cope with the associated disturbed behaviour. Hopefully the experience of the RIDU in Edinburgh in adapting and responding to the behavioural problems will be of some help.

One might question why should a health care system have to cope with this sort of behaviour and there seems no doubt that if the patients were not infectious and capable of infecting other individuals including health care staff it is unlikely that funds would continue to be made available for the current level of service. The service is extremely expensive (in the region of around £3-4 million per year) but the cost should be regarded as a necessary expense for society in the same was that society pays to ensure a clean blood supply. HIV/AIDS funds are now being reduced since it appears that the epidemic is about to plateau. However caution is required in the area of health care since any suggestion of lack of caring by society may result in a backlash with the possibility of increased levels of aggression towards the health service. Lower levels of staffing, the use of cheaper methods of staffing such as temporary ("bank") staff and a higher turnover of staff will all reduce continuity of care. If this is combined with a higher occupancy of difficult patients it may well lead to an increase of violent behaviour with increased risks for staff.

Initial use of anti-retroviral agents in IDU related HIV

The advent of HIV has resulted in a number of new anti-retroviral agents the majority of which initially are only researched on homosexuals. It was thought initially that a

large number of possible drug interactions could occur with the first agent, zidovudine, released onto the UK market. As a consequence it was felt important to investigate the safety and feasibility of treating drug users with this agent. As a result of the investigations it was found that the pharmacokinetics of zidovudine in patients taking opiates and benzodiazepines was very different from ex users not on opiates. The most striking differences were that users of large doses of opiates had approximately twice the are under the curve (AUC), twice the peak values and half the clearance of zidovudine but without alteration in the zidovudine half-life. In consequence opiate users in general would have an increased exposure to zidovudine compared to ex or non-drug users suggesting that for such patients smaller doses of zidovudine, possibly only half the regular dose, would be required.

Despite the practical problems of managing current or ex drug users on a potentially toxic drug it was possible to treat IDU related HIV with zidovudine. The experience of clinical monitoring of zidovudine treated IDU related HIV suggested that it was safe in a variety of drug use situations including recent injection drug use. The MCV change induced by zidovudine therapy is a convenient and cheap method of assessing compliance. The attendance of drug users on zidovudine was no different between those judged to be still using drugs and those thought to have discontinued IDU.

Natural History of HIV with particular reference to IDU related HIV

The establishment of the HIV and AIDS services at the RIDU in Edinburgh facilitated the initiation of a number of research projects investigating the natural history of HIV in drug users and possible differences with other risk groups. The key to the success of these projects was the clinical service. Without the service component the research detailed in this thesis would not have been possible.

Classification of HIV disease

In 1992 the CDC in Atlanta introduced a change in the definition of AIDS for the USA. This new definition did not seem to have biological plausibility in that clinical experience suggested that whilst falling below a CD 4 count of 200 cells/cumm put the individual at risk of AIDS it did not equate to AIDS. Survival analysis of the Edinburgh City Hospital Cohort indicated that the 1987 and 1992 definitions of AIDS were not identical, describing as they do patients at different stages of HIV infection. The CDC/WHO system of classifying HIV disease and the CD200 case definition that has been used in Edinburgh have merit as descriptions of imminent

immunodeficiency and therefore an increased risk of ill health i.e. all these are useful in clinical practice. However the current (1987) AIDS definition is essentially a functional assessment of the immune system, as described by a constellation of clinical problems. CD4 counts, by comparison, yield a numerical assessment of the immune system, which is of value in identifying those at risk of developing clinical illnesses, against which prophylaxis and anti-viral therapy have some success. The CD200 case definition employed in Edinburgh and Scotland has greater biological plausibility than immunological staging based on a single CD4 count of 200 or less, as proposed by the CDC/WHO classification.

Without a doubt there is a strong argument for a better classification of HIV disease which does not rely purely on clinical symptoms. Controversy over the proposed CDC reclassification of AIDS is essentially associated with the term AIDS rather than the condition of immunodeficiency itself. That this reclassification needs to involve the term AIDS is in doubt. A reclassification system such as CDC/WHO proposal which defines the various stages of severe HIV immunodeficiency (utilising lymphocyte counts or CD4 counts) is certainly required. From an analysis of the City Hospital Cohort the only major criticism of the CDC/WHO system is that the use of consecutive CD4 or lymphocyte counts provides a better definition of staging. HIV immunodeficiency described by **consecutive** CD4 counts of less than 200 cells/cumm could be called simply A3/B3, or perhaps severe HIV related immunodeficiency (SHRID).

Progression of HIV disease

Progression of HIV infection to AIDS or an immunological end point such as CD200 is affected by age but not apparently by having acquired the infection via drug use whether judged by local or international comparisons. Similar effects were noted for survival after the clinical or immunological end points. An analysis of the deaths to date confirms that as noted previously a significant number of HIV patients die before developing AIDS although the magnitude of the effect is not as great as that reported from the USA or Europe. The effect of zidovudine on survival appeared to be equally effective for drug users as for other risk groups.

The impression that Edinburgh drug users progressed at the same rate or slower than other risk groups was confirmed by studying a group with known length of infection of HIV(incident cohort). Unlike the data from the larger or prevalent cohort, there was no apparent age effect on progression but this was likely to be as a consequence

of the fact that the patients were very homogeneous with respect to age. Similarly there was no gender effect apparent. The clearest significant association for speed of progression was with the HLA haplotype A1-B8-DR3 whilst HLA B27 was associated with a relatively slow development of HIV immunodeficiency.

The incident cohort also allowed some estimates of the time to development of clinical and immunological end points for patients with ready access to a medical care system. Under the Weibull assumption the estimated shape parameter of the AIDS incubation distribution was 4.2 and the estimated mean and median AIDS incubation times were 11.0 and 11.1 years which is similar to a number of homosexual cohorts described in the USA. The estimated shape of the survival distribution was 4.5 and the estimated mean and median survival times were 10.7 and 10.8 years.

The use of the anti-retroviral, zidovudine at the RIDU for the majority of treated patients, was not in any way randomised. This can be seen by the fact that not surprisingly the decision to prescribe zidovudine was associated with an elevated risk of progression. However if this bias was controlled for in the analysis, it appeared that taking zidovudine before a CD4 count of 100 reduced the risk of progression to a clinical end point (CDC stage IV or AIDS) as well as reducing the risk of dying. By comparison taking zidovudine before a CD4 count of 200 only reduced the risk of dying and had no effect on the risk of progression to a clinical end point.

Clinical features of HIV with particular reference to IDU related HIV

Local factors perhaps dictated that differences over enrolment, by risk group, would emerge. The majority of drug users and heterosexuals enrolled when asymptomatic whilst the majority of homo/bisexuals enrolled with serious clinical disease. Changes were however observed over time in the distribution of risk groups enrolling with increased numbers of heterosexuals in later years. Enrolment with AIDS was unusual overall, although by 1993, 25% of patients were enrolling with AIDS presumably reflecting the growth of the Unit as a centre of excellence.

Despite the fact that the majority of drug users and heterosexuals enrolled well by 1993 70% of the patients had developed some HIV related clinical problem. Unlike previous reports, drug users were not more likely to develop severe bacterial disease. Interestingly OHL was more common in homo/bisexuals whilst oral thrush was commoner in drug users. Caution is however required since the different risk groups

have very different follow times; short follow times increases the event rate and may accentuate risk group differences. There were remarkable similarities between the City Hospital cohort and the Montefiore Medical Centre cohort in the Bronx; the incidence of oral thrush in the Bronx was 11.2/100 person years compared to 9.9/100 person years. In the Bronx whilst the incidence of bacterial pneumonia was 5.8/100 person years compared to an incidence of severe bacterial infections in Edinburgh of 7/100 person years. This was however much lower than the 19/100 person years quoted for Amsterdam drug users. This difference may reflect differences in drug use or chaotic behaviour between Amsterdam and either methadone maintenance programmes in the USA or combined medical and drug clinics in Edinburgh.

The commonest clinical expression of AIDS was PCP followed by oesophageal candida MAI, malignant disease and CMV disease. Whilst gender differences were not apparent differences were observed in risk groups as previously reported; KS, CMV and toxoplasmosis being commoner in homo/bisexuals whilst oesophageal candidiasis was commoner in drug users. Other conditions such as extra-pulmonary tuberculosis were uncommon unlike cohorts from the USA.

Considerable differences in mortality rates by risk group but not by gender were observed. The mortality rates for homo/bisexuals with AIDS were much higher than for drug users and were remarkably similar to published rates from Amsterdam and the Bronx, New York. This suggests that perhaps differences in drug use may not have a major effect on survival. Non AIDS mortality rates were significant for drug users but of a similar rate to that observed in Amsterdam and from the Bronx, New York.

Outcome measures or quality of care for HIV/AIDS

The RIDU model has reached over 600 patients infected with HIV (approximately 60% of the known HIV population in Edinburgh) and the majority of first admissions (76% of men and 89% of women) occurred before the diagnosis of AIDS. In addition the RIDU model of care for HIV has yielded acceptable outcome measures in initiating and maintaining contact with patients, in survival as judged nationally or internationally, and in morbidity levels.

A number of possible standard outcome measures could be adopted such as; lost to follow up rates, the level of CD4 monitoring per annum, pre aids mortality rates, pre aids morbidity levels, the incidence of AIDS, the percentage of patients with AIDS at first contact with a service, AIDS morbidity levels for WHO conditions, ALOS for

admissions and the number of admissions per patient, survival at presentation of AIDS, survival of first episode PCP, mean CD4 count at AIDS and survival from AIDS and CD200 expressed as a median and percentages surviving each year. From this more extensive list a few key outcome measures available from national statistics such as the percentage of patients with AIDS at first contact with a service (via local HIV and AIDS registers), the ALOS for AIDS and non AIDS HIV admissions (via Information Services Division), deaths within 30 days of diagnosis of AIDS and deaths within 30 days of first episode of PCP (via Information Services Division) should be adopted. Others such as mean CD4 count at AIDS, survival from AIDS or CD200 or the number of episodes of PCP and oesophageal candida per person year of AIDS could be published via the AIDS Control Act annual reports.

Defining suitable outcome measures for HIV/AIDS is the beginning of efforts to improve the quality of care for individuals infected with HIV. The measures presented here would suggest that the quality of care for HIV/AIDS in Edinburgh is high despite the associated problem of drug use.

Heterosexual Transmission of HIV

Perhaps one of the most important areas of HIV research for both individual and society at large is the question of heterosexual transmission of HIV. A longitudinal analysis of prospectively collected data on biological and behavioural factors noted that "high risk " sexual practices, high levels of unprotected intercourse and a low CD4 count all increase the risk of heterosexual transmission of HIV. Unexpectedly, late stage of disease (as measured by CDC stage) was not associated with increased risk of transmission and the peak of transmission of HIV was in fact 4-6 years after seroconversion of the index. This initially unusual result seems best explained by the complex interaction of biological and behavioural infectivity within a long term relationship and this study has allowed us to throw some light on this complex relationship. The results have important implications for heterosexuals in countries where additional promoters of HIV transmission such as STD's are relatively infrequent.

Postscript

The services established at the City Hospital for HIV are of high quality and have facilitated equally high quality research into the important questions surrounding HIV. It appears that progression of patients with HIV to immunodeficiency is not particularly accelerated by cofactors such drug use or gender. The genetic features of the individual, at present described simply by HLA typing, seems to be a far more influential factor in predicting the onset of immunodeficiency. Transmission via heterosexual intercourse is dependent upon a complex interaction of behavioural and biological factors which seem to maximise transmission 4-6 years after infection. Despite the extensive time course associated with HIV infection by 10 years over two thirds of patients had become symptomatic and considerable morbidity has been documented in association with the condition. A few unexplained differences in clinical features do exist between risk activities associated with HIV infection but in general the clinical course was remarkably similar between not only risk groups but also different geographical areas.

This description of HIV can only be part of the story. It is after all only 10 years since HIV arrived with such explosive force in Edinburgh and it is likely that the full natural history of the illness will probable take at least 20 years to document. Despite the relatively short time span, a considerable number of health care services have been developed and have managed to adapt to large numbers of injection drug users with a chronic terminal disease. These services have managed to deliver care and achieve considerable behaviour modification not only with respect to HIV transmission but also with respect to the interaction between the service and the patient.

I hope that this thesis is a fitting tribute to the memory of so many lives lost prematurely to this modern plague.

Collegiate Members' Symposium

THE CROOM LECTURE 1986

HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION IN EDINBURGH

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The original description of AIDS or the Acquired Immune Deficiency Syndrome appeared in 1981 in a report from New York and California.[1] This describes patients with firstly Kaposi's sarcoma, a skin tumour until then seen only in elderly men, in African races and in those with considerable iatrogenic immunosuppression, and secondly men with oral thrush and *pneumocystis* pneumonia, usually associated with iatrogenic immunosuppression. The connection between the two groups was that the men were all young male homosexuals with a mean age of 32 years.

AIDS is a remarkable disease not only for its effect on patients but also for its dramatic effects on society. Since its first description there has been widespread lay and medical publicity about AIDS, much of it inaccurate. The title of a *Readers Digest* article 'AIDS—The Plague of Fear' succinctly summarises the problem. This fear persists despite the reassuring evidence, now widely publicised, that this is not a highly contagious condition.

The Centers for Disease Control (CDC) definition of AIDS, compiled to ensure statistical accuracy, requires only a clinical diagnosis of conditions that are moderately predictive of cellular immunodeficiency without an underlying cause. By August 1986 there were more than 30,000 cases of AIDS known in the world, 24,000 of them in the USA,[2] more than 2,000 in Europe[3] and more than 450 in UK.[4] Patients may present with infections or with tumours or with both (68, 24 and 10 per cent respectively).[4] Common presentations are *pneumocystis carinii* pneumonia, invasive candidiasis, disseminated mycobacterial infections, severe herpes simplex and cytomegalovirus infections and lastly, Kaposi's sarcoma skin lesions.

LIMITATIONS OF ANTIBODY TESTING

Between 1983 and 1984 the virus of AIDS was isolated and characterised.[5, 6, 7] There have been a profusion of names used for this virus but Human Immunodeficiency Virus or HIV has been adopted as a neutral name covering its clinical effects.[8]

Isolation of the virus led to the development of a variety of antibody tests to detect those that had been exposed to it. Antibody demonstration indicates presence of the virus in 95 per cent of patients, but lack of antibody does not necessarily indicate absence of infection. Reports in the literature illustrate the deficiencies of available tests which may lack both sensitivity but also specificity.

A recent case report illustrates the dangers of high risk individuals donating blood. An individual who was negative on the screening tests unfortunately was infectious to the recipients.[9] In addition, studies on asymptomatic homosexuals have found that in 6 per cent virus could be demonstrated in their lymphocytes, although the screening tests had all been negative.[10]

There is, at least, a three month incubation period for seroconversion using currently available tests and therefore, a clinical history of exposure is more important than a negative screening test in the decision to employ infection control measures.

Some legislators in California are suggesting draconian measures to notify, limit and identify AIDS patients. Similar measures have been suggested in this country but these efforts are doomed to failure because of the limitations of the available tests for the virus.

As a consequence of the availability of antibody tests, we now have a better idea of the spectrum of HIV infection. To date, the full blown syndrome or AIDS has received most attention and the CDC initially introduced a definition to help collate information. It is now known that there are a number of other conditions which are related to HIV. The exact relationship is not known and a number of interconnection diagrams have been produced. In an attempt to ease the problem the CDC recently came up with a classification system which is purely descriptive and does not, at present, attempt to map the interconnections.[11] It essentially details four categories of HIV infection as shown in Table 1.

TABLE 1

Classification of effects of HIV infection

I	acute infection with seroconversion		
II	asymptomatic infection		
III	persistent generalised lymphadenopathy		
IV	A	constitutional disease	
	B	neurological disease	
	C	immunodeficiency	
		C1	CDC definition of AIDS
		C2	outwith definition
	D	tumours in CDC definition of AIDS	
	E	Other, eg, Hodgkins, carcinoma, lymphoid interstitial pneumonia	

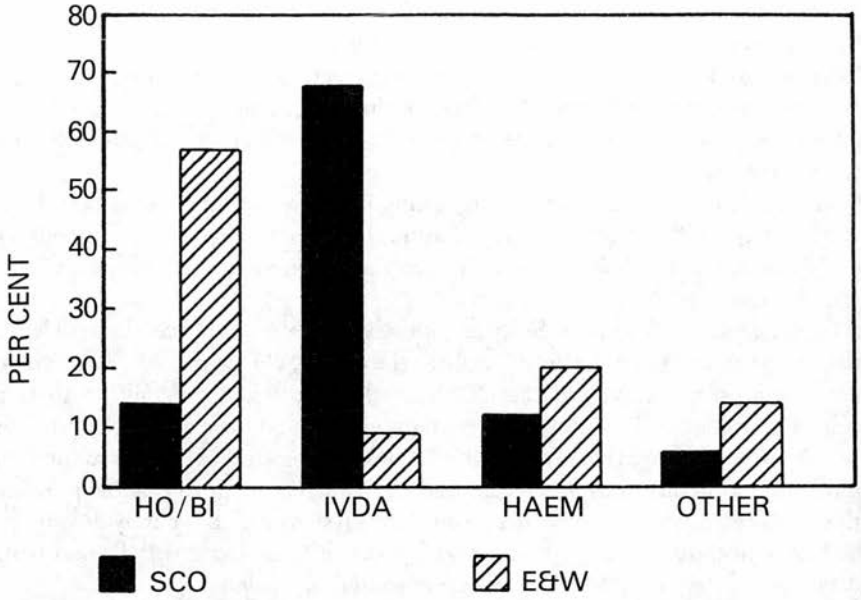
MMWR 1986 35(20) 334–339.

THE PROBLEM FOR SCOTLAND

To date, 89 per cent of patients with AIDS notified in the United Kingdom have been involved in homosexual or bisexual activity, but of these only 2.5 per cent came from Scotland.[4] Whereas in England and Wales only 54 out of 2,081 patients positive for HIV antibody were intravenous drug misusers (IDMs).[12] In Scotland 503 out of 795 patients were IDMs[13] (Figure 1). Of these 482 have come from Edinburgh.

FIGURE 1

Relative proportions of HIV seropositivity in risk groups for the first three months of 1986



Risk Groups	
HO/BI	Homosexual or bisexual
IVDA	Intravenous drug abuser
HAEM	Haemophiliacs
SCO	Scotland
E&W	England and Wales

The first indications that Edinburgh had a particular problem came with the finding that 14 out of 44 haemophiliacs had acquired HIV antibody between 1983 and 1984 after treatment with locally produced Factor VIII.[14] An epidemic started in 1983 amongst heterosexual drug abusers.[15, 16] In 1985 Peutherer found that 40 of 106 sera sent for hepatitis tests from suspected IDMs were also positive for HIV.[15] Further studies in Edinburgh have confirmed this startling work.[16, 17] The consequences for Edinburgh have been grave with spread of infection through the IDM community, as well as spread to new born children of affected individuals and sexual partners. This has resulted in the contamination of the blood pool, and necessitated the development of counselling and screening services.

THE NEED FOR SCREENING AND COUNSELLING OF HIV INFECTED PATIENTS

The most immediate consequence of this epidemic was the threat to the blood bank. The response, when antibody testing became generally available in October 1985, was to introduce screening of all donated blood. The need to screen

individuals extends into other areas such as organ donation, bone banks and semen banks. In the South East of Scotland the positivity rate amongst voluntary blood donors is 1/13,074 and this compares with 1/41,598 in the West of Scotland and 1/50,000 for the UK as a whole.[18] With screening of blood donations came the necessity to prevent individuals in high risk groups from donating blood since such individuals may be infectious but not have HIV antibody.[9] It was, therefore, necessary to provide voluntary confidential screening and counselling at alternative testing centres to prevent the Blood Transfusion Services being used as a diagnostic facility.

Experienced counselling is important to avoid the fear and ignorance surrounding this condition. Headlines such as 'Dying mum's baby has AIDS' are a direct result of bad counselling and inexperience on the part of the legal and medical professions. In the extreme, bad counselling may result in suicide. Poor pre-test counselling or non-voluntary testing may lead to legal claims for damages following inability to obtain life assurance or a mortgage. In the USA seven states have made non-voluntary HIV antibody testing illegal and punishable by fines of up to $10,000.

CITY COUNSELLING AND SCREENING CLINIC

As in England and Wales 60 per cent of patients reported positive for HIV were homosexuals, screening and counselling occurred mainly in Genito-Urinary Medicine (GUM) clinics.[12] In Scotland, where 60 per cent of the patients were drug misusers, it was apparent that a screening clinic additional to GUM was necessary.[13] A voluntary self-referral clinic, the City Screening Clinic (CSC), was established in the Edinburgh Regional Infectious Diseases Unit on 16th October 1985. This provided open access counselling and HIV antibody testing. It also set out to determine the extent of HIV infection among individuals who chose to attend a self-referral clinic for testing in preference to a GUM clinic or their general practitioner. Apart from self-referrals, patients may also be referred by social workers, drug self-help groups, general practitioners and other hospitals.

The clinic is supervised by a consultant in Infectious Diseases (R. P. Brettle) and is held in the Infectious Diseases Unit of the City Hospital, Edinburgh. It operates for a four-hour session, five times a week. Each session is staffed by a doctor and a nurse counsellor. The clinic has its own telephone line with an answering machine which informs out of hours callers of clinic hours. This telephone number was carried in press announcements and is available from the Blood Transfusion Service, the Scottish AIDS Monitor Group and the Gay Switchboard and was circulated to all general practitioners and Drug Abuse Agencies.

Most patients are offered an appointment within two days. The clinic presents a non-medical image since it does not set out to conduct a full clinical examination and assessment. Each patient is given a half-hour first appointment so there is time for pre-test counselling and history taking. On arrival, all patients receive a simple

sheet which explains the advantages and disadvantages of being tested. These are discussed at the counselling session and additional information obtained from each patient using a confidential questionnaire. If the patient then decides to proceed, blood is taken and a further appointment is given for one week later when a confirmed result will be available.

The patients with a positive test are counselled, provided with written advice and then offered a further appointment, if necessary, plus a medical appointment for a full clinical assessment. The written advice given depends on the relevant risk group.

Patients with a negative test are also given advice depending upon their risk factors. If there has been a high risk activity within the past twelve months, the patient is advised to attend the clinic again for further testing and counselling to aid compliance with previous advice. At first attendance, patients are asked to give written consent to the test result being given to their general practitioner. If a patient refuses, the test is done but the result is given only to the patient, in person. Leaflets provide the written advice for clients to take away after counselling, whether or not the result is positive.

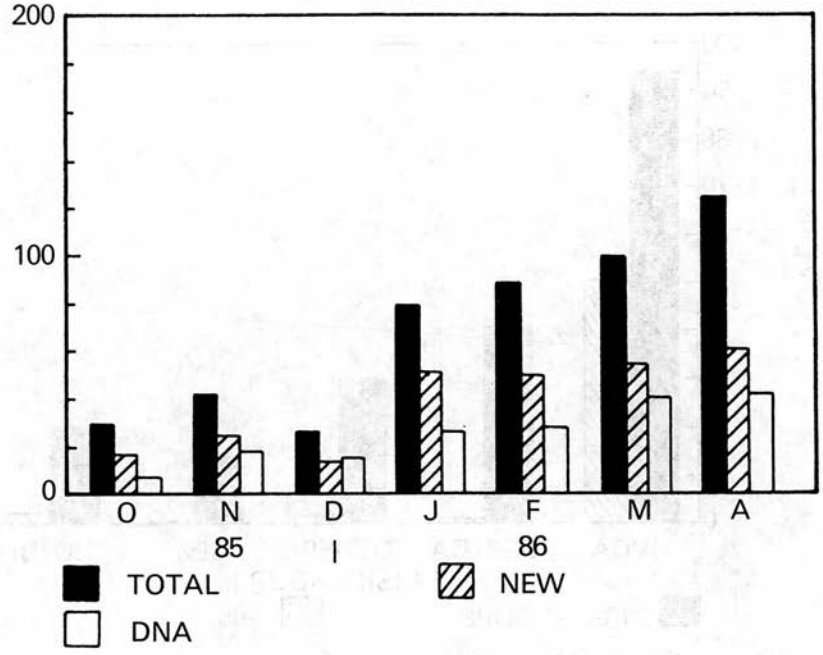
Confidentiality. From the outset, the aim of the clinic was to offer a confidential service and to this end all records are kept within the clinic and there is no other record of attendance unless the client takes up the offer of medical screening. However, in dealing with the IDMs it is important, where possible, to have good lines of communication with the general practitioner because this is one way a patient may obtain drugs. Our aim has been always to persuade the client of the advantages of their general practitioner being informed. Because of their irregular life-style we were often left with results and not knowing whether we could inform any other doctor. We now obtain at the first visit written permission to inform the general practitioner and or to send follow up appointments. Results are otherwise only given out in person at a clinic attendance. We have also had numerous enquiries from such groups as doctors, nurses, pharmacists, the police and the fire brigade as to whether a particular individual is seropositive. Such requests are met by a statement of our policy of confidentiality followed by a discussion of what relevance the result would be to the enquirer and how to cope without the result.

Contact Tracing. Contact tracing is not undertaken but the patients are encouraged to bring their sexual or needle sharing partners to the clinic.

Attendance. There is certainly a demand for such a facility as can be seen from the attendance figures (Figure 2). To date over 400 patients have been counselled and screened: over 60 per cent of them involved in the drug scene either directly or via a sexual partner (Figure 3).

FIGURE 2

Monthly attendances at the City Screening Clinic, October 1985-March 1986



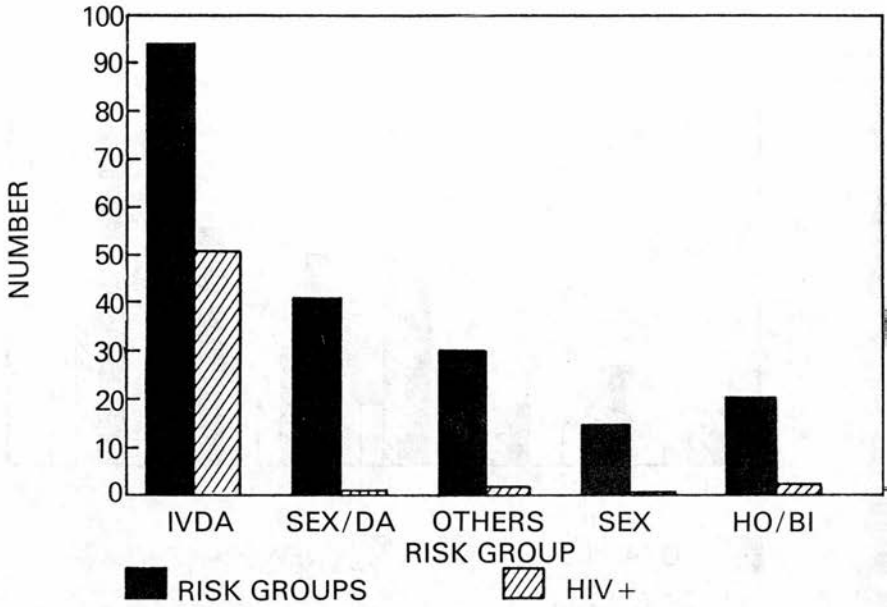
DNA Did not attend

The default rate of 33 per cent is a matter of concern, since this means that the counsellors are underutilised. Cost was initially thought to be a deterrent since the clinic is located six miles from the City Centre but the majority are, in fact, eligible for a refund of bus fares. To evaluate the possibility that distance was important one session of the clinic was moved to Leith Hospital, which is in an area of high drug misuse, but the default rate has remained unchanged. The post-testing default rate is 21 per cent which compares favourably with 30 per cent from 'alternative testing sites' in the USA.[19] It appears that irregular attendance is a part of lifestyle and has been noted in a general practice within Edinburgh.[20]

Pre-Test Counselling. A comparison of risk groups attending the CSC shows that when IDMs attend they rarely refuse the test whereas those with few risk activities have a refusal rate of 20 per cent. The overall refusal rate is 6 per cent and this compares with 16 per cent in the USA.[19] However, the overall positivity rate in the USA was 17 per cent compared to our 28 per cent. The major aim is to ensure that the patients realise that ongoing medical care is available from the clinic staff should they prove to be positive.

FIGURE 3

Proportions in each risk group attending the City Screening Clinic, October 1985-March 1986



IVDA	Intravenous drug abusers
SEX/DA	Sexual contacts of IVDAs
SEX	Sexual contacts of non-IVDAs

CHARACTERISTICS OF THE EDINBURGH EPIDEMIC

The overall infection rate in those attending the clinic was 28 per cent during the first six months. Two patients infected by blood products were counselled. The 'worried well', homosexuals and sexual contacts had an infection rate below 10 per cent. In contrast, 51 out of 94 IDMs were positive for HIV antibodies, and none admitted to homosexuality. The male/female ratio was 2.13/1 and the mean age 25.5 years, 24 years for those found to be seropositive and 28 years for those found to be seronegative ($p < 0.001$). The mean age of onset of intravenous drug misuse was 19.5 years, 17.5 for those found to be seropositive and 21.5 years for those found to be seronegative ($p < 0.0001$).

By comparison, the percentage HIV positivity in Dundee is 39[21] in Glasgow only 4.5 and in England and Wales only 10[22, 23] This geographical variation for IDMs has also been noted in Europe[24] and in the USA where 17 per cent of AIDS patients are IDMs but it is 72 per cent in New York compared to 2 per cent in California.[25, 26] Despite the Press reports, Edinburgh is by no means the AIDS capital of Europe since IDM HIV positivity in Europe varies from 20–76 per cent.[27–32].

To understand some of the reasons for these differences in IDM HIV positivity, it

is important to appreciate that drug misuse in Scotland, and in Edinburgh in particular, is different from in England. Intravenous drug misuse appears to predominate in Edinburgh, and important differences in the habit of sharing of needles seems to exist.

Historically, IDMs report that needles and syringes became unavailable in Edinburgh after 1981 to 1982 when a surgical supplies shop ceased trading. They also report that their equipment was commonly removed by the police during searches and then destroyed. Pharmacists were then unwilling to supply IDMs. Possession of equipment contaminated with heroin may be used as evidence of illicit use and IDMs might then be asked to give evidence against a supplier. Some suppliers forced IDMs to use their drugs on site, thus leaving no incriminating evidence. A limited supply of needles and syringes led to considerable sharing; one or two sets of equipment might be used by all a supplier's clients who could number up to 40 in a day. At this time, there were large gatherings of IDMs, anything from 5 to 20, in the style of shooting galleries, where one set of equipment was passed around. In January of 1986 in response to the AIDS problem, the Pharmaceutical Society in Scotland recommended to its members that needles and syringes should be sold to IDMs.

Comparisons of self-reported habits between Edinburgh and Glasgow or Edinburgh and South London show much more sharing of needles and syringes in Edinburgh.[33, 34] For instance, the mean number of times equipment was shared in Edinburgh was 46 times per month compared to only 15 times per month in Glasgow. In addition, sharing occurred with twice as many individuals, 14 versus 7 per month.[33] Of 78 Edinburgh IDMs 42 per cent shared daily and 63 per cent weekly by comparison to only 14 or 31 per cent of 45 South London IDMs who admitted to sharing within the last three months.[34] There is supportive medical evidence of this intense sharing of equipment in Edinburgh IDMs from the high rate of hepatitis B markers currently between 60–80 per cent[15, 16, 17] and an increase in the rate of skin sepsis and endocarditis.[35]

With this background, it is not surprising that when in 1983 HIV was introduced into Edinburgh it spread rapidly.[16, 17] There was an association between the frequency of needle sharing and HIV seropositivity ($p < 0.05$). In addition, 59 out of 79 IDMs had markers of past or present infection with hepatitis B virus and there was an association with HIV infection.

Over 700 HIV infected individuals have been identified in Scotland and over 500 in Edinburgh.[13] Estimates of the number of IDMs in Edinburgh are poor but there are probably at least 2,000–2,500.[21] The three series from Edinburgh would suggest a seropositive rate for HIV infection of 50 per cent in the IDM community and there are, therefore, probably at least 1,000 infected individuals in Edinburgh. Likely spread from the IDM pool is as follows:

.. The current pool of IDMs. The rapid rise of HIV infection seen between 1983–1985 will continue over the next two years if nothing is done, until HIV positivity rates approach those of hepatitis B, now about 85 per cent.

2. New IDMs entering the community. Unlike the IDM habit itself or hepatitis B infection, HIV infection lasts for life; therefore the size of the pool of infection continues to grow. Estimates of this 'new blood' group is scarce and the best that can be made is around 10 per cent per year.
3. Spread to other cities. Out of 23 Edinburgh-based IDMs who had shared needles in other cities, 14 were positive for HIV antibody. The cities in which these IDMs shared are shown in Table 2.
4. Sexual spread. Unlike in the USA, very few of the drug misusers are homosexual. About 10 per cent of homosexuals in the USA are also IDMs. Ten per cent of Edinburgh homosexuals tested have been positive for HIV.

TABLE 2

CSC—Needle sharing by Edinburgh IDMs

Location	Number of patients
London	7
Glasgow	4
Aberdeen	1
Stirling Prison	1
Wick	1
Elgin	1
Oxford	1
Liverpool	1
Northampton	1
Stonehenge	2
Rotterdam	1
Amsterdam	1
Paris	1
Total	23
Number HIV positive	14 (61%)

Because most IDMs in Edinburgh seem to be heterosexual, we are faced with the fact that heterosexual spread will occur, but at what rate? The number of AIDS cases involving heterosexual contact is currently small, only 39 men and 185 women in the USA, but a study from the Walter Reed Institute of cases in the US Army suggested that 37 per cent were heterosexually acquired and that there was no association with anal intercourse.[2, 36] However, this study has been criticised because both homosexuality and drug addiction are, of course, court maritial offences. Vaginal intercourse is a risk as demonstrated by the fact that artificial insemination with infected semen resulted in infection in 50 per cent of the recipients.[37] The data from the sexual partners of asymptomatic HIV positive haemophiliacs suggests that 6–10 per cent of the partners are affected at present.[38, 39] A recent study of five regular heterosexual partners of HIV positive individuals put the risk at 20 per cent.[40] We have currently screened 112 individuals with a claimed risk of only heterosexual activity and 6 of these are

positive. All the positives were, however, within the group claiming to have a drug abusing partner giving a rate of just over 10 per cent. For those in whom we could confirm the status of both partners the rate was 15 per cent giving an approximate risk per year of 5 per cent. The risks appear to increase up to 50 per cent if the affected partner has AIDS.[41] This may simply reflect length of exposure or be related to increased virus excretion.

Whilst the heterosexual population cannot, at present, be at great risk, they cannot remain so for long. Human immunodeficiency virus must sooner or later become a general sexually transmitted disease here, as it already appears to be in the USA. The US military introduced HIV screening of recruits in October 1985 and the prevelance was found to be 1.6/1000.[42] Perhaps of more importance was the fact that the male/female ratio was 3/1, whereas in AIDS patients at present, it is around 13/1. This suggests either that HIV is already a heterosexual disease or drug misuse is more prevelant than hitherto suspected.

5. Vertical spread. Spread of the virus to new born children occurs and this is occurring in Edinburgh because ⅓ of the affected population are female. The data on vertical transmission is also scant. Seventy-five per cent of paediatric cases in the USA have a mother in a high risk group, mostly drug misuse.[41] There is evidence that the virus can infect a child during pregnancy because two children had no postpartum contact with the mothers.[41] Infection can also occur after birth via breast milk.[41] The rate of infection is less well documented and varies from 0–65 per cent. In well mothers who acquired the virus by artificial insemination, no transfer of virus occurred.[41] In children less than five years of age with a mother dying of AIDS, the positivity rate was 22 per cent but it rose to 65 per cent where the mother had given birth previously to a child who developed AIDS.[41] In Edinburgh Dr Jacqueline Mok[43] is following 22 children born from seropositive mothers. Definite infection cannot be ascertained for up to 12 months because of the problem of passive transfer of maternal antibodies and exposure to blood at birth. However, preliminary data indicate that half of them may be infected.

6. Horizontal transmission. The remaining method of spread out of high risk groups is horizontally to non-sexual and non-drug misusing individuals. Whilst the risks are small they are certainly not perceived as so by the medical and general public. A household survey of contacts of AIDS patients revealed no non-sexual spread[44] whereas with hepatitis B infection, spread to family members is around 37 per cent.[45] Similarly the risks for health workers involved in the direct care of AIDS patients is only 1 per cent compared to 30 per cent for hepatitis B.[46] That is not to say that precautions are unnecessary since two cases of HIV transmission have been reported in non-professional careers who took no precautions when caring for infected individuals.[47] However, the commonest mode of transmission to health workers is by needle stick injury.[46] It is instructive to review where IDMs end up within the

medical care system. A study of those attending a casualty department revealed that only 4 per cent were referred to the Infectious Diseases Unit and the rest the general medical and surgical wards.[48]

MANAGEMENT OF HIV INFECTION

Effective chemotherapy is not yet available for AIDS, let alone for asymptomatic HIV infection, and the current management of HIV infection can only aim at prevention of progression to AIDS and the prevention of its spread. Measures such as prevention of pregnancy and barrier contraception are effective for both aims and are particularly important for a heterosexual population. There is also a suggestion that normal semen can be immunosuppressive for females and therefore barrier contraception is recommended for seropositive females not only to protect the male partner but also to prevent progression to AIDS. A more complete list of measures is shown in Tables 3 and 4. As a consequence of this and other data, it has been necessary to modify our approach to patients with HIV infection.

TABLE 3

HIV—Management

prevent progression to AIDS
- —avoid pregnancy
- —use barrier contraception
- —avoid anal intercourse
- —avoid needle drug abuse
- —avoid infections, ie, VD, etc
- —avoid immunosuppressive drugs, eg, steroids
- —prevent recurrent infections
  - ketoconazole
  - acyclovir
  - IV gammaglobulin

TABLE 4

HIV—Management

prevent spread of HIV
- —avoid pregnancy
- —use barrier contraception
- —use spermicides, eg, nonoxynol-9
  - 1–12.5% effective 60s
  - 5% destroys lymphocytes
- —avoid needle sharing
- —avoid anal intercourse
- —reduce number of sexual partners

DENTAL TREATMENT

The dental health of IDMs is generally poor and their attendance at dentists is as irregular as at all other medical services. However, periodontal disease is probably the commonest recurrent infection experienced in this group and it is important to deal with this. In Edinburgh there was already a mechanism for dealing with patients with hepatitis B and with the help of Mr Gordon Bolas, Assistant Area Dental Officer, we have been able to offer a service for these patients.

CONTRACEPTION

One third of the patients with HIV in Edinburgh are female and the prevention of pregnancy is important on the grounds of progression to AIDS in the mother as well as the prevention of transmission to the child.[41, 49] In the USA only 25 per cent of seropositive mothers were well 2.5 years after delivery. However, these mothers were selected by the fact that they had already produced one child with AIDS and this data may not apply to Edinburgh.[49] Despite what seemed to be adequate counselling unwanted pregnancies have occurred and as with other IDM problems it was necessary to do more than just offer the advice 'avoid pregnancy' or 'use barrier contraceptives'. With the help of Dr Nancy Loudon of the Family Planning Service in Edinburgh the CSC is now acting as an outpost of that service offers on site-advice and supplies.

OBSTETRIC AND PAEDIATRIC SERVICES

With the number of affected female patients it is to be expected that Edinburgh will continue, for some time, to be faced with HIV affected pregnancies and children. The aim has been to offer medical services for both mother and child at one clinic in an attempt to overcome the problems of a haphazard life-style. Two sessions are now devoted to the follow up of those children identified as at risk of HIV infection and utilises the services of a nurse counsellor from the CSC, a Consultant Community Paediatrician, Dr Jacqueline Mok, and a liaison Health Visitor to help co-ordinate follow up. The mothers are encouraged to attend routine baby clinics but the CSC co-ordinates their immunisations and medical care. Eventually it is hoped, with the help of our obstetric colleagues, to develop a system to ensure that none of these families are unintentionally lost to the medical services.

ADDICTION

Obviously the major problem in dealing with these patients is how to cope with their addiction. In Edinburgh there is a lack of a co-ordinated policy towards the management of drug misuse. There is no Drug Dependency Unit and inpatient facilities for voluntary detoxification are restricted to one bed in each of the seven general psychiatric wards. Abstinence has, until now, been the major goal of dealing with IDMs but with the appearance of HIV these goals need to be adjusted to one of 'risk or harm reduction'. Conversion from homosexuality to heterosexuality is not proposed as a means of dealing with HIV and in a similar

way a message based on abstinence is unrealistic. The eventual goal is still one of abstinence but initially it is important to start with a more realistic goal identified for each patient. Depending upon the individual, this may encompass substitution therapy on a long or short term basis in order to avoid needle drug misuse, or the provision of needles and syringes to reduce sharing. All this, of course, needs to be accompanied by considerable education and general supportive measures.

The CSC results confirm previous work in Edinburgh which has reported HIV antibody rates in IDMs of between 38 and 51 per cent.[15, 16] Those affected in Edinburgh are characteristically younger, have markers of current or past infection with hepatitis B virus and are more likely to share needles/syringes frequently. In areas with a large IDM problem there is a place for self-referral clinics for counselling and HIV antibody testing in an attempt to educate and prevent further spread.

THE FUTURE

AIDS is an expensive illness to treat and current costs vary from around £6,000 to £40,000 per year per patient.[50] The variations depend upon what actually is included in the costing. Variations occur even in the USA and it appears cheaper to have a designated Unit as well as being better for the patients because they spend less time in hospital. New treatments such as interferon are expensive at around £65,000 per treatment course but since it is only effective in 25 per cent of patients this raises the costs to over £100,000 for each successful treatment course. Any treatment for the HIV infection itself will be lifelong and the ultimate costs are not yet calculable. Any treatment that does become available will prolong life and therefore the costs per AIDS patient can only go up. These sorts of costs are equivalent to transplantation but these procedures are rationed and AIDS and HIV will be demand led. These costs also do not take into account other less direct costs such as counselling, blood product screening, etc, (Table 5). It makes economic sense, therefore, to spend money now on prevention.

TABLE 5

HIV—Implications

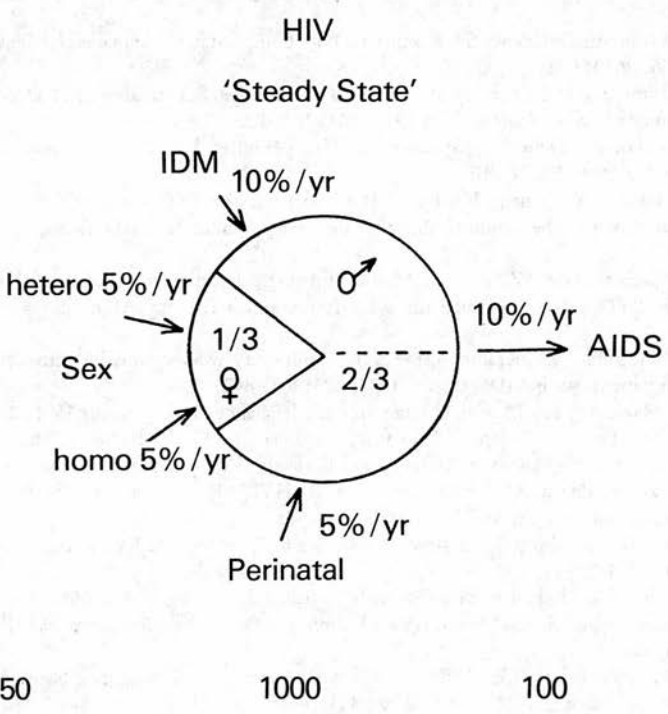
Costs

inpatient care
outpatient care
HIV ab screening
  BTS
  organ donation, etc
  voluntary screening and counselling
heat treatment of blood products
deterrent advertising
infection control measures
dental services
staff training

Many individuals think this is a problem that will go away in time because the patients are all going to die. This assumes total control of spread, something we have only once managed with an infection, ie, smallpox. There are two reasons why this problem will remain with us for the rest of our working lives.

1. Although the mean incubation period for AIDS is four years the maximum yet recorded is 14 years. This means that the patients currently infected will not all present with AIDS until the year 2000.
2. A critical mass has now been achieved in terms of infected individuals and this means that we can expect by 1987 onwards 10 per cent or 1–200 AIDS patients per year in Edinburgh. If spread is not prevented, then a steady state will be achieved because it will only require 10 per cent spread per year for all methods, ie, old IDMs, new IDMs, heterosexual, homosexual and vertical spread (Figure 4).

FIGURE 4



It, therefore, behoves us all in the medical community to grapple with the problem of HIV infection in its many forms because it will be with us into the next century.

ACKNOWLEDGEMENTS

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Epidemic of AIDS related virus (HTLV-III/LAV) infection among intravenous drug abusers

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Abstract

Stored blood samples from 164 intravenous drug abusers who attended a Scottish general practice were tested for HTLV-III/LAV (human T cell lymphotropic virus type III/lymphadenopathy associated virus) infection. Of those tested, 83 (51%) were seropositive, which is well above the prevalence reported elsewhere in Britain and Europe and approaches that observed in New York City. The timing of taking samples of negative sera and continued drug use suggest that as many as 85% of this population might now be infected. The infection became epidemic in late 1983 and early 1984, thereafter becoming endemic. The practice of sharing needles and syringes correlated with seropositivity, which, combined with the almost exclusive intravenous use of heroin and other behavioural patterns, may explain the high prevalence of HTLV-III/LAV infection in the area. Rapid and aggressive intervention is needed to control the spread of infection.

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Introduction

HTLV-III/LAV (human T cell lymphotropic virus type III/lymphadenopathy associated virus) seropositivity has been described among groups of intravenous drug abusers in the United States and lately in Europe.[1,2] Recently, in a laboratory study of drug users, in which blood samples from patients who had attended various departments of the Royal Infirmary, Edinburgh were used, 38% of heroin users were infected with the virus.[3] It has not yet been explained why there is such a high incidence of infection in heroin users from this city. Previous research has correlated seropositivity with the number of injections but not with sharing needles and syringes, and it is assumed that sexual transmission of the infection may also be important.[4] A combination of these factors, along with local practices and regional variations in the availability of sterile equipment, may explain the wide variation in seropositivity among different groups of heroin users, which is already known to exist in the United States and Europe.[3,5]

The West Granton Medical Group serves a population of about 18 000 patients in a deprived area of Edinburgh that is known to have many intravenous drug abusers.[6] The policy has always been to manage drug users who are known to the practice before the onset of drug misuse but to resist taking heroin users for treatment who approach the practice from outside a specific geographical area of the city. In 1982 an outbreak of hepatitis B infection in the heroin users who attended the practice led to routine blood testing for hepatitis B markers, the epidemic being attributed to an increase in sharing needles and syringes owing to an acute shortage after the local, legal retail supplier was closed and a subsequent unofficial prohibition by pharmacists. More recently, increasing anxiety about the risk of the acquired immune deficiency syndrome (AIDS) to intravenous drug abusers and their spouses and sexual contacts and to the children of infected women led to our decision to test retrospectively stored serum samples for the HTLV-III/LAV antibody to obtain information to manage these patients. This study

therefore examines the behaviour, injection practices, and seropositivity of a geographically selected population of known heroin users.

Method

The study group comprised 164 patients of the practice who were known to be or to have been heroin users. There were long term users, casual users, and those who had experimented with heroin but never developed an addiction, making the population representative of heroin users as a whole. Sera that had been taken from each heroin user most recently and stored in one of the region's two virus laboratories were tested for HTLV-III/LAV antibody using commercially available ELISA, and if positive this was confirmed by immunofluorescence or Western blotting techniques, or both. If the most recent serum was positive, previous samples (when available) were successively tested until a negative result was obtained, thereby identifying the period during which seroconversion occurred. Hepatitis B marker state was also ascertained. Detailed information about the patient's drug practices, lifestyle, and behaviour was recorded on standardised case summaries, having been extracted from the practice case notes and interviews. Most of these patients attended the practice regularly (often weekly over several years), which allowed insights to be made into their lifestyle and behaviour that is rarely possible in hospital studies.

Results

Serum from 164 heroin users was tested. Of these, 83 (51%) patients were HTLV-III/LAV positive, 60 men and 23 women, mean (SD) age 24·1 (4·70) years. Eighty one (49%) patients were seronegative, 55 men and 26 women, mean (SD) age 26·9 (5·66) years. There were no sex differences between the seropositive and seronegative groups, but the seronegative patients were significantly older ($t=3·44$, $p<0·01$). The mean age of onset of intravenous drug abuse in 77 seropositive patients was 19·1 years, and in 60 seronegative patients for whom this information was available it was 19·9 years. The mean duration of heroin use could therefore be estimated as 4·6 years for seropositive patients and 6·1 years for seronegative patients.

Figure 1 shows the cumulative numbers of first recorded seropositive sera, the first positive serum being taken in September 1983. Similarly, the period

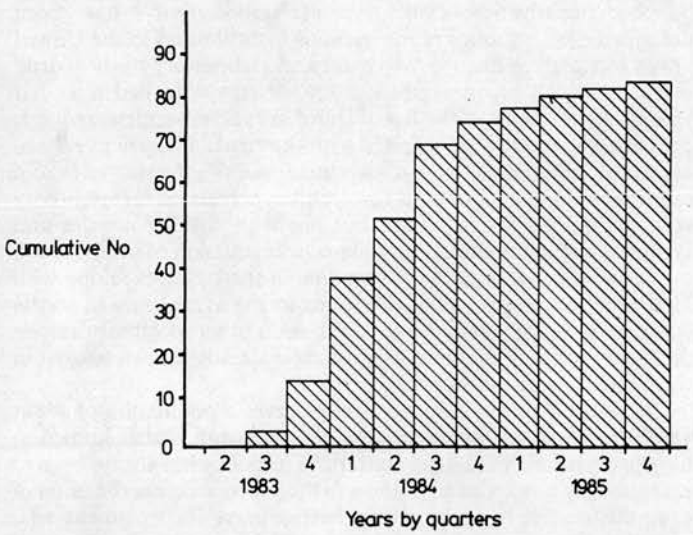

FIG 1—Cumulative number of first positive HTLV-III/LAV antibody test results among 83 intravenous drug abusers by quarters.

of time during which seroconversion occurred was known for 33 patients (fig 2). Twenty five (32%) of the seropositive patients and 21 (35%) of the seronegative patients for whom information was available were known to have begun injecting heroin after the infection is thought to have entered this population. There is no indication therefore that seropositivity is related to the duration of drug misuse. The interpretation of seronegative state is complex, however. Twenty antibody negative patients had had no serum taken since the onset of the epidemic, and of those who had, 11 were known to have injected drugs within three months and 26 to have continued to inject drugs after their final serum sample was taken. Thus any of these 57 patients may have seroconverted after the final serum sample was taken. If all of these were now infected there would be an overall prevalence of HTLV-III/LAV of 85%. Interestingly, the prevalence of hepatitis B marker was 84%, 27 patients being negative for both hepatitis B markers and HTLV-III/LAV antibody.

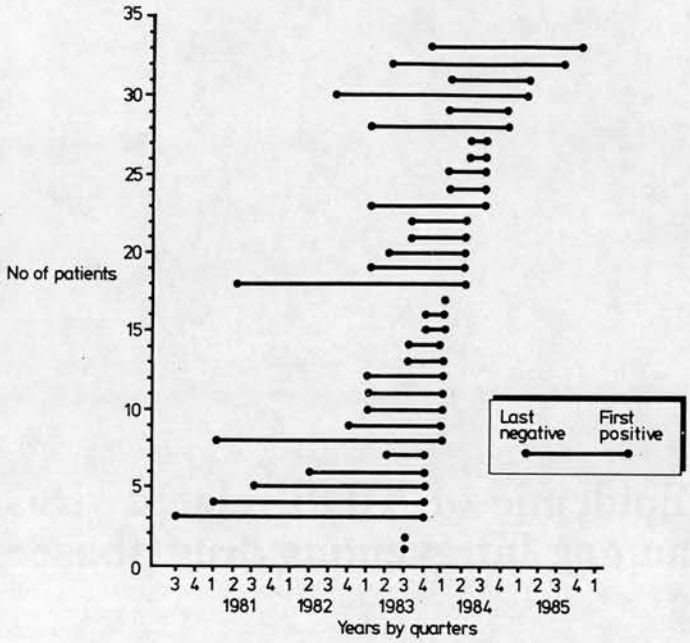

FIG 2—Last negative and first positive HTLV-III/LAV antibody tests for 33 intravenous heroin users against time.

Clinical and epidemiological information drawn from the patients' case summaries indicated consistent and repeated patterns and practices of drug misuse. The primary route of heroin administration was almost exclusively intravenous (98%), and 83% of 116 users for whom information was available reported sharing equipment (table I). The serological differences between those who reported sharing needles "usually," "sometimes," or "never" were statistically significant ($\chi^2=12·2$; df 2; $p<0·01$), indicating a correlation between the frequency of sharing equipment and seropositivity.

TABLE I—*Self reported sharing of needles and syringes in 164 heroin users with and without antibodies to the HTLV-III/LAV virus*

Sharing needles and syringes	No (%) who were HTLV-III/LAV antibody positive	No (%) who were HTLV-III/LAV antibody negative	Total No (%)
Usually	36 (52)	12 (26)	48 (41)
Sometimes	27 (39)	21 (45)	48 (41)
Never	6 (9)	14 (30)	20 (17)
Unknown	14	34	48
Total	83 (100)	81 (101)	164 (99)

In an attempt to find the causes of the outbreak and rapidity of onset of the epidemic a group of about 40 early seroconverters were identified who had been interviewed before January 1984. The group formed an intimate equipment sharing community between 1980 and 1983. Initially using personal equipment only, the sharing of needles and syringes became routine as the supply of clean equipment failed. Particularly important were consistent reports of gatherings of 10 to 20 drug users sharing a single needle and syringe during 1983—not unlike the "shooting galleries" described in the United States.[7] Because the equipment often belonged to the heroin supplier the people who attended such gatherings each day would vary, increasing the possibility of infection. The equipment was reported at best to be rinsed with tap water between injections, but there was no serious attempt at sterilisation despite the routine practice of "washout" (drawing blood back into the syringe after injection to flush out any remaining heroin). Drawing heroin solution through cigarette or cotton wool filters to absorb

impurities provided a source of further injectable heroin when these could be soaked in water. These practices appear to have continued throughout 1984 and have been moderated only recently owing to anxiety about the risk of AIDS.

From National Health Service identification numbers it could be shown that 88% (144) of the study group were born in Edinburgh and only 2% outside Scotland. Specific questioning about travel within the United Kingdom and abroad up to January 1984 showed only a limited use of heroin outside of Edinburgh (table II). Two patients were known to have travelled internationally, one to the United States and North Africa but denying drug use in either place, the other to Germany in 1976. The group as a whole rarely travelled outside Edinburgh.

TABLE II—*Reported locations of heroin use of 70 heroin users up to January 1984*

Location	No (%) of heroin users
Edinburgh (practice area)	70 (100)
Edinburgh (other areas)	38 (54)
London	5 (7)
Oxford	2 (3)
Grangemouth	1 (1)
Kendal	1 (1)
Newcastle upon Tyne	1 (1)
Germany (Berlin)	1 (1)

Despite recent reports of a brief influenza like illness shortly after initial viral exposure a study of case notes indicated no such phenomenon among these patients.[8] At the time of writing no patient from the study group had been diagnosed as having AIDS, although a small but growing number are showing AIDS related illnesses such as persistent generalised lymphadenopathy and candidiasis.

Discussion

HTLV-III/LAV infection was observed in half of the intravenous drug abusers studied; this is well above the prevalence observed in previous European studies and approaching that reported in New York City.[1,3] Although it is not clear how the virus was introduced into this population, the rapid spread of infection (see fig 2) appears to have resulted from a combination of the almost exclusive intravenous use of heroin, the frequency of sharing equipment owing to difficulties in obtaining sterile needles and syringes locally, and injection practices that increase the risk of exposure to the virus. Indeed, the frequency of needle and syringe sharing has been positively correlated with seropositivity and seems to be the most likely cause of the high incidence of infection. Preventing the sharing of equipment may therefore be the quickest and most efficient means of containing the spread of HTLV-III/LAV in drug users. The rapidity with which the epidemic spread in this study population, in addition to the presumed risk of infection from drug users to the non-drug using heterosexual population, shows the need for aggressive intervention by all agencies in the community.

Managing HTLV-III/LAV infection in general practice necessarily includes both preventing the spread of the virus and dealing with the medical, social, and psychological problems of those already infected. The general practice in this study has a policy of advising intravenous drug abusers who attend the practice of the risk of infection to themselves, their sexual contacts, and children. Appropriate counselling is offered that deals with reducing the risk through altered drug use and sexual behaviour, the importance and desirability of antibody testing, and the specific consequences of infection. In attempting to further prevent the spread of the AIDS related virus it has been the policy of two clinical authors to supply clean equipment to selected drug users on an exchange basis—a clean set being given only on the return of the old one. Local education campaigns, including providing literature with guidelines for safer sex and safer drug use, have been initiated by general practitioners through local self help groups. An alternative means of reducing equipment sharing, prescribing non-injectable methadone as a heroin substitute, has not yet been introduced because it is opposed to movements away from prescribing opiate drugs to drug users. This and other interventions, however, must be considered soon and introduced where appropriate to contain the spread of infection.

Many AIDS related medical and social problems are being dealt with, especially with reference to women of child bearing age and those who are pregnant, who on the whole remain reasonably healthy. At the time of writing two women had been recommended terminations, and two had given birth to infants found to be seronegative. An uncertain proportion of infected heroin users will develop AIDS, and a few more will develop AIDS related illnesses which do not fulfill the criteria of AIDS itself. Links with local clinics that specialise in such problems have been established. Recent evidence suggests that heroin users are more at risk of developing AIDS once infected than male homosexuals.[9] In a city such as Edinburgh, with large numbers of heroin users and a high prevalence of HTLV-III/LAV, but with a prevalence of infection among male homosexuals undoubtedly of less than 5% (A McMillan, personal communication, 1985), heroin users may represent most clinical AIDS cases seen. AIDS is likely to become the leading cause of death among the patients examined in this study.[10]

Our results indicate that geographical variations are likely in the prevalence of HTLV-III/LAV infection among intravenous drug users owing to differing equipment sharing practices and differing times of arrival of the virus into populations of drug users. Areas where the seropositivity is known to be low but where needle and syringe sharing is routine among heroin users must expect the virus to spread rapidly in the absence of immediate intervention.

We thank the doctors and staff of the West Granton Medical Group for their help in collecting samples and information, Dr E Edmond and J D Dickson, University of Edinburgh Bacteriology Department, and I Collacott from the Regional Virus Laboratory, City Hospital, Edinburgh.

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and to restrain a patient effectively and minimize the risk of injury to all concerned.

Management by staff

Staff who have been properly trained will be fully aware that the spectrum of AIDS-related psychiatric disorder comprises conditions with which they are thoroughly familiar in other clinical contexts, i.e. acute anxiety reaction with prominent somatic features and hypochondriacal self-concern, obsessive-compulsive disorder, reactive and psychotic depression, schizophreniform psychosis associated with organic brain disease, delirious reactions and presenile dementia. Where the clinical indications make it appropriate to do so, they will apply the provisions of the Mental Health Act 1983 confidently and competently to secure the compulsory detention and, if need be, the compulsory treatment of patients suffering from these psychiatric disorders when they are associated with AIDS, just as they would do so with patients suffering from such psychiatric disorders in other clinical contexts. They will be aware that, depending on the character and the course of the particular psychiatric problem, the treatments with which they are familiar in other settings can be employed as appropriate with an expectation of therapeutic benefit. These include counselling, psychotherapy, behaviour modification techniques, family and marital therapies, electroconvulsive therapy and the exhibition of anxiolytic and antidepressant drugs and the major tranquillizers. In other words, they will have no expectation of AIDS-related psychiatric disorder being manifested as bizarre syndromes for which they have no training or knowledge, and requiring novel and esoteric therapeutic interventions which are quite outside the range of their experience.

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Drug abuse and human immunodeficiency virus infection in Scotland

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Keywords: AIDS, human immunodeficiency virus, drug abuse, counselling, screening, Scotland

Introduction

To date, 89% of the patients with the acquired immune deficiency syndrome (AIDS) notified in the United Kingdom have involved homosexuality or bisexuality and only 12 or 2.5% have been diagnosed in Scotland[1]. In addition, only 1% of such reports have implicated intravenous drug misuse (IDM) alone as a high-risk activity[1]. In England and Wales, IDM represents only 54 (2.6%) out of 2081 reports of human immunodeficiency virus (HIV) antibody positivity[2]. This contrasts markedly with the position in Scotland, where 503 (63%) of 795 reports of HIV antibody positivity have implicated IDM[3], and of these 482 (60%) have come from Edinburgh.

The first indications that Edinburgh had a particular problem came with the finding that 15 of 34 haemophiliacs (44%) had acquired HIV antibody between 1983 and 1984 after being treated solely with locally produced Factor VIII[4]. The epidemic started in 1983 amongst heterosexual drug abusers[5,6]. In 1985 Peutherer *et al.*[5] found that 38% of 106 sera sent for hepatitis tests from suspected IDMs were also positive for HIV. Further studies by Robertson *et al.* and ourselves have confirmed this startling finding[6,7].

The need for screening and counselling of HIV-infected patients

The most immediate consequence of the HIV epidemic was the threat to the blood bank. The Government's response when antibody testing became available was to introduce screening of all donated blood in October 1985. According to Dr B L McClelland, Director of the South East Regional Blood Transfusion Service, Edinburgh, the HIV seropositivity rate amongst voluntary blood donors in the south east of Scotland is 1/13 074, and this compares with 1/41 598 in the west of Scotland and 1/50 000 for the UK as a whole (personal communication). With the screening of blood donations came the necessity to prevent individuals in high-risk groups from donating blood, since such individuals may be infectious but not have HIV antibody. It was therefore considered necessary to provide voluntary confidential screening and counselling at alternative testing centres to prevent the Blood Transfusion Service being used as a diagnostic facility.

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City Counselling and Screening Clinic

In England and Wales 60% of the HIV reports are from homosexuals, and this screening and counselling exercise has occurred largely in genitourinary medicine clinics[2]. However in Scotland, where 60% of the HIV reports are from drug abusers, it was apparent that an additional screening clinic was necessary. A voluntary self-referral clinic, the City Screening Clinic (CSC), was therefore established in the Edinburgh Regional Infectious Disease Unit on 16 October 1985 to provide open-access counselling and HIV antibody testing. It also set out to determine the extent of HIV infection amongst individuals who chose to attend a self-referral clinic for testing in preference to attending a genitourinary medicine clinic or their general practitioner.

There is certainly a demand for such a facility and to date over 400 patients have been counselled and screened, over 60% of them involved in the drug scene either directly or via a sexual partner. The default rate of 33% is a matter of concern, since this means that the counsellors are under-utilized. Cost was initially thought to be a deterrent since the clinic is located 6 miles from the city centre, but the majority are in fact eligible for a refund of bus fares. To evaluate the possibility that distance was important, one session of the clinic was moved to Leith Hospital, which is located in an area of high drug abuse, but the default rate has remained unchanged. It appears that irregular attendance is a part of the lifestyle and has been noted in a general practice within Edinburgh (J R Robertson, personal communication). The post-testing default rate of 21% compares favourably with 30% from alternative USA testing sites[9].

A comparison of risk groups attending the CSC shows that when IDMs attend they rarely refuse the test, whereas those with few risk activities have a refusal rate of 20%. The overall refusal rate is 6% and this compares with 16% from the USA[9]. However, the overall positivity rate in the USA was 17% compared to our 28%.

From the outset, the aim of the clinic was to offer a confidential service. To this end, all records are kept within the clinic and there is no other record of attendance unless the offer of medical screening is taken up. However, in dealing with IDMs it is important, where possible, to have good lines of communication with the general practitioner, because this is one way that drugs are obtained from more than one source. Our aim has always been to persuade clients of the advantages of their general practitioner being informed. Because of their irregular lifestyle, we were often left with results and no knowledge of whether any other doctor could be informed. We have now moved to the situation of obtaining at the first visit written permission to inform the general practitioner and/or to send follow up appointments. The results are otherwise only given out in person at a clinic attendance. We have also had numerous enquiries from such groups as doctors, nurses, pharmacists, the police, the fire brigade, etc., as to whether a particular individual is seropositive. Such requests generate a standard statement of our policy of confidentiality, followed by a discussion of what relevance the result would have and how to cope without it.

Contact tracing is not undertaken, but clients are encouraged to inform or bring their sexual or needle-sharing partners to the clinic.

Characteristics of the Edinburgh epidemic

The overall infection rate in the first 200 patients attending the clinic was 28%. Of 94 IDMs, 51 (54%) were positive for antibodies to HIV virus; none admitted to homosexuality. The male/female ratio was 2.13/1 and the mean age 25.5 years, 24 years for those found to be seropositive and 28 years for those found to be seronegative ($P<0.001$). The mean age of onset of intravenous drug abuse was 19.5 years, 17.5 for those found to be seropositive and 21.5 years for those found to be seronegative ($P<0.0001$).

By comparison HIV positivity in Dundee is 39%[10], in Glasgow only 4.5% and in England and Wales only 10%[11,12]. This geographical variation for IDMs has also been noted in Europe[13] and the USA, where the overall incidence of IDM AIDS is 17% but it is 72% in New York compared to 2% in California[14,15]. IDM HIV seropositivity in Europe varies from 20% to 76%[16–21].

In order to attempt to understand some of the reasons for these differences in IDM HIV positivity, it is important to appreciate that drug misuse in Scotland in general and in Edinburgh in particular is different from England. IDM appears to predominate in Edinburgh, and important differences in the habit of sharing needles seem to exist.

Comparisons of self-reported habits between Edinburgh and Glasgow or Edinburgh and South London reveal considerably more sharing of needles and syringes in Edinburgh[22,23]. For instance, the sharing of equipment occurred 46 times per month in Edinburgh compared to only 15 times per month in Glasgow. In addition, sharing occurred with twice as many individuals, 14 versus 7 per month[22]. Of 78 Edinburgh IDMs, 42% shared daily and 63% weekly compared to only 14 (31%) of 45 South London IDMs who admitted to sharing within the previous 3 months[23]. There is supportive medical evidence of this intense sharing of equipment in Edinburgh IDMs from the high rate of hepatitis B markers – currently between 60% and 80%[5–7] – and an increase in the rate of skin sepsis and endocarditis (J Webb, personal communication).

With this background, therefore, it is perhaps not entirely surprising that when in 1983 HIV was introduced into Edinburgh, it spread rapidly as a consequence of the habit of equipment sharing[6,7]. There was an association between the frequency of needle sharing and HIV seropositivity ($\chi^2=4.24$, $P<0.05$). In addition, 59 of 79 (75%) had markers of past or present infection with hepatitis B virus and there was an association with HIV infection ($\chi^2=4.81$, $P<0.05$).

Over 700 HIV-infected individuals have been identified in Scotland and over 500 in Edinburgh[3]. Estimates of the size of the drug abuse community in Edinburgh are poor, but it is thought that there are probably at least 2000–2500[10]. The three series from Edinburgh on HIV infection in IDMs would suggest a level of 50% infection in the community and there are therefore probably at least 1000 HIV-infected IDMs in Edinburgh. Consequently spread will occur from this pool to a number of areas:

(1) The current pool of IDMs: The rapid rise of HIV infection seen between 1983 and 1985 will continue over the next 2 years if nothing is done until HIV positivity rates approach those of hepatitis B, currently approaching 80–90% infection.

Table 1. Needle sharing in other cities by Edinburgh intravenous drug abusers attending the City Screening Clinic

Location	*No. of patients*
London	7
Glasgow	4
Aberdeen	1
Stirling Prison	1
Wick	1
Elgin	1
Oxford	1
Liverpool	1
Northampton	1
Stonehenge	2
Rotterdam	1
Amsterdam	1
Paris	1
Total	23
No. with HIV antibody	14 (61%)

(2) New IDMs entering the community: Unlike IDM itself or hepatitis B, HIV individuals are infected for life and therefore the size of the infected group continues to grow. Estimates of this 'new blood' group is scarce and the best that can be made is around 10% per year.

(3) Geographical spread to other IDMs in other cities: Out of 23 Edinburgh-based IDMs who had shared needles in other cities, 14 (61%) were positive for HIV antibody. The cities in which these IDMs shared are shown in Table 1.

(4) Sexual spread: Because the majority of drug abusers in Edinburgh seem to be heterosexual, we are faced with the fact that heterosexual spread will occur – but at what rate?

The number of AIDS cases involving heterosexual contact is currently small, only 39 men and 185 women in the USA, but a study from the Walter Reed Institute of cases in the US Army suggested 37% were heterosexually acquired and that there was no association with anal intercourse[24,25]. However, this study has been criticized because in the US Army both homosexuality and drug addiction are a court martial offence and may not, therefore, be admitted. Vaginal intercourse is a risk, as demonstrated by the fact that artificial insemination with infected semen resulted in infection in 50% of recipients[26]. Data from the sexual partners of asymptomatic HIV-positive haemophiliacs suggest that 6–10% of partners are currently affected[27,28]. A recent study of 5 regular heterosexual partners of HIV-positive individuals put the risk at 20%[29]. Our own experience with sexual contacts of drug misusers would suggest that around 15% have acquired the virus sexually, and this would put the risk in regular sexual relationships at approximately 5% per year. The risks appear to increase to 47% if the affected partner has AIDS or AIDS-related complex[30]. This may simply reflect length of exposure or be related to increased virus excretion.

Whilst AIDS is not at present a heterosexual disease in the UK and the USA, this cannot remain so for long and it appears that it is beginning to occur in the USA. The US military introduced HIV screening of recruits in October 1985 and the prevalence was found to be 1.6/1000[31]. Perhaps of more importance, the male:female ratio was 3:1 whereas in AIDS patients at present it is around 13:1. This suggests either that HIV is already a heterosexual disease or drug abuse is more prevalent than hitherto suspected.

(5) Vertical spread: Spread of the virus to newborn children does occur, and is occurring in Edinburgh because one-third of the affected population are female. The data on vertical transmission are also scant. In the USA, 75% of paediatric cases have a mother in a high-risk group, mostly drug abuse[30]. There is evidence that the virus can infect the child during the pregnancy, because 2 children had no post partum contact with their mothers[30]. Infection can also occur after birth via breast milk[30]. The rate of infection is less well documented and varies from 0% to 65%. In well mothers who acquired the virus by artificial insemination, no transfer of virus occurred[30]. In children less than 5 years of age with a mother dying of AIDS the positivity rate was 22%, but it rose to 65% where the mother had given birth previously to a child who developed AIDS[30]. In Edinburgh, Dr Jacqueline Mok is currently following 22 children who have been born from seropositive mothers. Definite infection cannot be ascertained for up to 12 months because of the problem of passive transfer of maternal antibodies and exposure to blood at birth. However, Dr Mok's preliminary data support a rate of 50% (personal communication).

(6) Horizontal transmission: The remaining method of spread out of high-risk groups is horizontally to non-sexual and non-drug-abusing individuals. Whilst the risks are small they are certainly not perceived as so by the medical and general public. A household survey of contacts of AIDS patients revealed no spread to non-sexual or drug-abusing partners[32], whereas by comparison in hepatitis B it is around 37%[33]. Similarly, the risk for health-care workers involved in the direct care of AIDS patients is only 1% compared to 30% for hepatitis B[34]. That is not to say that precautions are unnecessary, since 2 cases of HIV transmission have been reported in non-professional carers who took no precautions when caring for infected individuals[35]. However, the commonest mode of transmission to health-care workers is by needle-stick injury[34]. It is instructive to review where such patients are located within the medical care system. A study of IDMs attending a casualty department revealed that only 4% were referred to the infectious disease unit and the majority were located within the general medical and surgical wards[36].

Management of HIV infection

Effective chemotherapy is not yet available for AIDS, let alone asymptomatic HIV infection, and therefore the current management of HIV is based on the prevention of progression to AIDS and the prevention of spread of HIV infection. Many of the measures, such as prevention of pregnancy and barrier contraception, are effective for both aims and are particularly important for a heterosexual population. A more complete list of the measures is shown in Table 2. As a

Table 2. Current management of HIV infection

Prevent spread of HIV	*Prevent progression to AIDS*
Avoid pregnancy	Avoid pregnancy
Use barrier contraception	Use barrier contraception
Use spermicides, e.g. nonoxynol-9 (1–12.5% effective 60s, 5% destroys lymphocytes)	Avoid anal intercourse
Avoid needle sharing	Avoid needle drug abuse
Avoid anal intercourse	Avoid infections, i.e. venereal disease, etc
Reduce number of sexual partners	Avoid immunosuppressive drugs, e.g. steroids
	Prevent recurrent infections (ketoconazole, acyclovir, i.v. gamma-globulin)

consequence of this and other data, it has been necessary to modify our approach to patients with HIV infection.

One-third of the patients with HIV in Edinburgh are female and the prevention of pregnancy is important on the grounds of progression to AIDS in the mother as well the prevention of transmission to the child[30,37]. In the USA, only 25% of seropositive mothers were well 2.5 years after delivery. However, these mothers were selected by the fact that they had already produced one child with AIDS and the data may not apply exactly to Edinburgh[37]. Despite what seemed to be adequate counselling, unwanted pregnancies have occurred and as with other IDM problems it has been necessary to do more than just offer the advice 'avoid pregnancy' or 'use barrier contraceptives'. With the help of Dr Nancy Loudon of the Family Planning Service in Edinburgh, the CSC is now acting as an oupost of the Family Planning Service to offer on-site advice and supplies.

It is to be expected that Edinburgh will continue for some time to be faced with HIV-affected pregnancies and children. The aim has been to offer medical services for both mother and child at one clinic in an attempt to overcome the problems of a haphazard lifestyle. Two sessions are now devoted to the follow up of those children identified as at risk of HIV infection, and utilize the services of a nurse counsellor from the CSC, a Consultant Community Paediatrician, Dr Jacqueline Mok, and a liaison health visitor to help coordinate follow up. The mothers are encouraged to attend routine baby clinics, but the CSC clinic coordinates their immunizations and medical care. Eventually it is hoped that with the help of our obstetric colleagues, a system will be developed to ensure that none of these families is unintentionally lost to the medical services.

Obviously the major problem in dealing with these patients is how to cope with their addiction. Abstinence has until now been the major goal of dealing with IDMs, but with the appearance of HIV these goals need to be adjusted to one of 'risk or harm reduction'. Conversion from homosexuality to heterosexuality is not proposed as means of dealing with HIV, and in a similar way a message based on abstinence is unrealistic. The eventual goal is still one of abstinence but initially it is important to start with a more realistic goal identified for each patient. Depending upon the individual, this may encompass substitution therapy on a long- or short-term basis in order to avoid needle drug abuse, or the provision of needles and syringes to reduce sharing. All this, of course, needs to be accompanied by considerable education and general supportive measures.

The CSC results confirm previous work in Edinburgh which has reported HIV antibody rates in IDMs of between 38% and 51%[5,6]. Those affected in Edinburgh are characteristically younger, have markers of current or past infection with hepatitis B virus and are more likely to share needles/syringes frequently. In areas with a large IDM problem, there is a place for self-referral clinics outwith genitourinary medicine for counselling and HIV antibody testing in an attempt to educate and prevent further spread.

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HIV counselling: some practical problems and issues

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Keywords: AIDS, human immunodeficiency virus, counselling, public education

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Counselling means facilitating understanding: (1) by individual support, discussion and health education of patients, lovers, families and carers; (2) by health education for society as a whole and all its subgroups, on routes of human immunodeficiency virus (HIV) transmission, methods of risk-reduction and infection control; and (3) by the training and support of staff working with HIV-infected patients. The work of those providing HIV counselling involves supporting and informing the vulnerable, whether or not they recognize their vulnerability. A consistent theme in all three emphases of the counsellor's work is the need to motivate people to change the ways in which they relate to each other, often when they do not appear to desire such motivation, or when they have been motivated by competing ideas and influences (frequently inspired by media misreporting).

Individual support

Clinical reports highlighted the need for counselling intervention following AIDS-related diagnoses long before HIV antibody testing was available[1,2], or indeed before the virus was first reliably characterized[3]. With the widespread patient and carer recognition of the high fatality rates associated with AIDS[4], reactions to diagnosis have included those familiar to oncologists and oncology counsellors[5–7]. Many writers have identified consistent themes in post-diagnostic reactions[8], together with consistent psychiatric and psychological concerns that invariably arise to complicate further management (Table 1). The wide range of neurological syndromes

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Contemporary Themes

Human immunodeficiency virus and drug misuse: the Edinburgh experience

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Abstract

During 1985 many drug abusers who lived in Edinburgh were found to be infected with the human immunodeficiency virus (HIV). As a result an alternative counselling and screening clinic for testing for antibodies to HIV was established for use by drug abusers. Four hundred and forty one patients were counselled in the first year, and over 60% were either drug abusers or their sexual contacts. One hundred and fourteen (26%) patients were positive for HIV antibody, and 100 (88%) of these were current or former drug abusers. The HIV seropositivity rate in drug abusers was 52% but was only 7% in their sexual contacts. Services were provided for these people as well as counselling before and after the test. The cost of this counselling service for the first year was £27 000 or £61.22 per patient.

The unexpected mobility of 23% of the Edinburgh drug abusers, particularly to other areas of Britain, suggests that similar services need to be set up elsewhere.

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Introduction

In the United Kingdom 88% of the notified cases of the acquired immune deficiency syndrome (AIDS) have implicated homosexuality or bisexuality, but only 1% of notifications have implicated intravenous drug abuse alone as a high risk activity. In the United States, however, at least 17% of reports have implicated intravenous drug abuse.[1,2] Only 14 (2%) cases of AIDS have been reported in Scotland, and one was in a drug abuser.[3] In England and Wales drug abuse alone has been implicated in only 232 (5·7%) of 4001 reports of human immunodeficiency virus (HIV) antibody positivity.[4] But in Scotland 618 (61·3%) of 1008 reports of HIV antibody positivity have implicated drug abuse[5]: 607 (60%) have come from Edinburgh, and this is second only to the North West Thames region in England. Seropositive rates of between 38% and 65% in drug abusers have been reported in three studies.[5-7]

Intravenous drug abuse with opiates predominates in Edinburgh,[6,7] and comparisons of self reported habits between drug abusers in Edinburgh and Glasgow or Edinburgh and south London show much more sharing of needles in Edinburgh.[8,9] Thus when HIV was introduced into Edinburgh in 1983 it spread rapidly. When national screening of all blood donations was introduced in October 1985 it was obvious that an alternative testing site was required for this population.

City counselling and screening clinic

A self referral clinic was established in the Edinburgh regional infectious diseases unit to provide open access for counselling and HIV antibody testing. The clinic started on 16 October 1985 to coincide with the start of testing of all blood donations by the National Blood Transfusion Service.

Apart from self referrals, patients may also be referred by social workers, drug self help groups, general practitioners, and other hospitals. The HIV antibodies are detected by a competitive enzyme linked immunosorbent assay (ELISA) and confirmed by a conventional ELISA. Doubtful positive

tests are confirmed by immunofluorescence or Western blotting. So far there have been none in these patients.

The clinic is supervised by a consultant in infectious diseases (RPB) and is held in the outpatient department of the infectious diseases unit of this hospital. There are four hour sessions five times a week, and each session is staffed by a medical officer, nurse counsellor, and receptionist-secretary. Although the cost of staffing covers one part time medical officer and one part time nurse-counsellor, the sessions are shared by three medical officers and two nurses.

The clinic has its own telephone line with an answering machine which informs out of hours callers of clinic hours. Most patients are offered an appointment within one or two days of telephoning. The clinic presents a fairly non-medical image as it does not conduct a full clinical examination and assessment. Because it was expected that most of the patients would be drug abusers, a medical officer is present at all times. Phlebotomy is often difficult in drug abusers, and they tend to use services such as ours as a primary care system. Although this is generally discouraged, a medical officer needs to evaluate the problems.

The aim of the clinic was to offer a confidential service. Thus all records are kept in the clinic, and there is no other record of attendance unless patients take up the offer of medical screening. Our aim has always been to persuade our patients of the advantages of informing their general practitioner of their HIV antibody state. We were often left not knowing whether to inform other doctors of the results. We then decided to obtain written permission at the first visit to inform the patient's general practitioner of the test result. The results are otherwise given out only to the patient at a clinic attendance. Contact tracing is not undertaken, but the patients are encouraged to bring their sexual or needle sharing partners to the clinic. When the clinic opened there was no written material specifically for drug abusers, and leaflets were produced for these patients.

Pretest counselling

Each patient is allocated at least 30 minutes for the initial appointment, although in practice this is not strictly adhered to. The patients receive a printed sheet which explains simply the advantages and disadvantages of HIV antibody testing, and this is discussed at the counselling session. The main objectives of the pretest counselling are general education regarding HIV, including how it is transmitted, risk activities, and how to reduce the risk. Specific risk activities are assessed for each person and advice given. In view of the high default rate and the almost invariable lack of comprehension when the result is positive as much information as possible is provided at the first visit.

Because of the prolonged incubation period for seroconversion our policy is to offer repeat testing for up to one year after a person's last risk activity, and during that time the person is advised to assume that he or she is seropositive in terms of risk reduction measures. Advice on contraception and supplies are also provided.

The implications of the test are then discussed, and if the patient decides to proceed blood is taken for HIV antibody and hepatitis B marker tests. A further appointment is given for one week later, when a confirmed result is available. No other specific screening is undertaken—for instance, to exclude sexually transmitted diseases—but if the medical officer considers it necessary referrals are arranged to departments of genitourinary medicine, dermatology, psychiatry, etc.

One important function of the clinic is to be a point of contact for providing advice and information to health care workers, social workers, occupational nurses, and foster mothers, as well as to people who are worried, whether or not they are in identified high risk groups. The clinic staff are therefore an important resource for disseminating information to many people apart from those directly concerned with this infection.

Post-test counselling

At the return visit patients whose antibody test result is negative are given advice which depends on their suspected exposure time and risk factors. If there has been a high risk activity within the past 12 months the patient is advised to attend the clinic again for further testing in six to 12 months.

Patients whose test is positive are counselled about reducing the relevant risk, with the initial emphasis on reducing the progression of the disease in the patient and spread of the virus in the community. Depending on the circumstances this includes advice on safe sex and safe drug use, advice with regard to sexual and needle sharing partners, advice on diet and physical activity, and reassurance about lack of transmission to non-sexual non-needle sharing partners. For women it also must encompass the risk of pregnancy.

Obviously a big problem with current drug abusers is how to cope with their drug addiction. In Edinburgh there is no coordinated policy for managing drug abuse. There is no drug dependency unit, and inpatient facilities for voluntary detoxification are restricted to one bed in each of the seven general psychiatric wards. Abstinence has until now been the major goal in dealing with drug abusers, but with the appearance of HIV these goals need to be adjusted to one of "risk or harm reduction." The long term goal is still abstinence from all drugs, but it is important to start with a more realistic goal for each patient such as substitution therapy in the long term or short term to avoid drug abuse with needles or providing needles and syringes to reduce sharing. Exhorting abusers to use clean equipment is pointless, however, unless it is available, though widespread availability of equipment, as in Italy, does not ensure a lack of sharing. Education is needed to emphasise the dangers of needle sharing and the importance of cleanliness and sterility in the use of equipment. Celibacy is not considered a realistic means of dealing with sexually transmitted HIV infection. The message is education with regard to "safe sex." Similarly, a message based solely on abstinence is unrealistic for drug misusers.

One third of our patients with HIV are women, and the prevention of pregnancy is important on the grounds of progression to AIDS in the mother as well as preventing transmission to the child. The rate of infection for babies who are born to seropositive mothers is not well documented and varies from 0% to 65%. At present we can advise only that the chance of becoming infected appears to be roughly 50%.[10] In the USA only one quarter of seropositive mothers were well two and a half years after delivery.[11] These mothers, however, were selected by having already given birth to a child with AIDS, and these data may not apply to Edinburgh. As with other drug abuse problems it is necessary to do more than offer advice such as "avoid pregnancy" or "use barrier contraceptives." With the help of the family planning service in Edinburgh the clinic is now acting as an outpost of the service to offer on site advice on contraception and supplies. Occasionally, urgent referrals for termination of pregnancy are necessary.

Further management

Patients with a positive HIV antibody result are offered appointments for further counselling as well as an appointment for a medical examination. Because one third of the affected patients are women Edinburgh will probably continue for some time to be faced with pregnancies and children affected by HIV. Our aim was to offer medical services for both mother and child at one clinic to try to overcome the problems of a haphazard lifestyle. One session is devoted to the follow up of children who are at risk of HIV infection, and the services of a nurse counsellor from the screening clinic, a consultant in community child health, an infectious diseases physician, and a liaison health visitor to help coordinate follow up are used. The mothers are encouraged to attend routine baby clinics but our clinic coordinates their immunisations and medical care. With the help of our obstetric colleagues we hope to develop a system to ensure that none of these families is unintentionally lost to the medical services.

The dental health of drug misusers is generally poor, and their attendance at dentists is as irregular as for all other medical services. In Edinburgh there was already a procedure for dealing with patients with hepatitis B, and with the help of the Lothian area dental service we can offer treatment for these patients. In the near future a dental surgery on site should reduce the poor dental attendance.

Results

A total of 441 new patients had been counselled at 980 clinic attendances by 30 September 1986, and there were 402 (41%) non-attendances. Three hundred and forty five (78%) of the patients were from the city of Edinburgh, 55 (12·5%) were from the rest of the Lothian region, 27 (6%) were from other parts of Scotland, three (0·5%) were from England, and 11 (3%) gave no address.

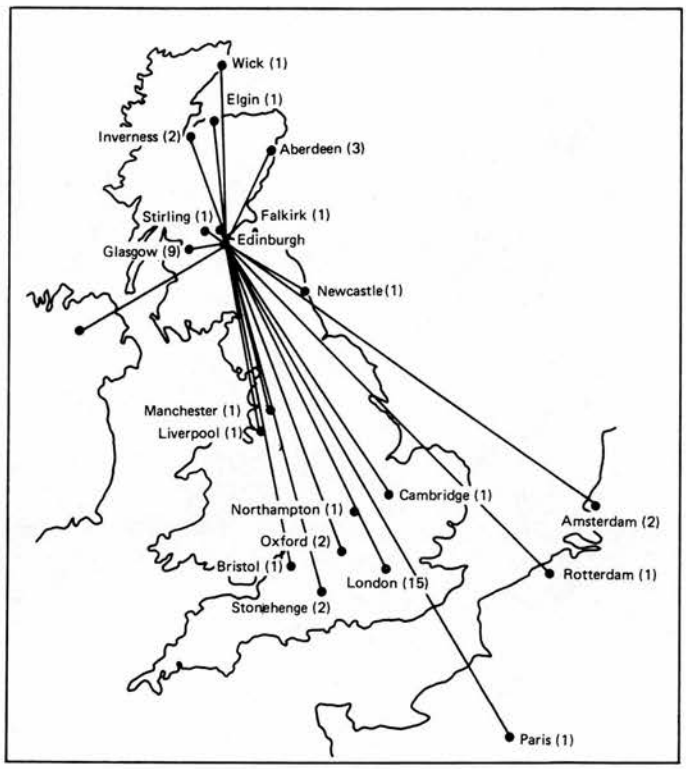
A total of 30 (6·8%) people declined HIV testing after pretest counselling, and, not surprisingly, those with the least risk were more likely to decline testing (table). One hundred and fourteen (26%) HIV positive patients were counselled, 100 (88%) of whom were current or former drug abusers. A total of 191 patients admitted to intravenous drug misuse (119 (62%) men and 72 (38%) women) and the seropositivity rate was 52%. None of the drug abusers admitted to practising homosexuality. The mean age of drug abusers was 26 years (25 years for those who were seropositive and 27·5 years for those who were seronegative ($p<0·01$)). The mean age of onset of intravenous drug abuse was 20 years (18 years for those who were seropositive and 22 years for those who were seronegative ($p<0·0001$)). The male to female ratio was 1·6:1 (1·3:1 for those who were seropositive and 2·1:1 for those who were seronegative). Forty three (60·5%) of the women were HIV antibody positive compared with 57 (49·5%) of the men, but this difference was not

significant. Forty four (23%) Edinburgh based drug abusers had shared needles in 48 other locations, and of these, 52% were positive for HIV antibody (figure). On 1 January 1986 the family clinic for seropositive mothers and their newborn children was established and by 30 September 1986, 23 babies at risk and their mothers had been counselled and examined.

City screening clinic: October 1985 to September 1986

Risk group	No attending (% of total)	No HIV antibody positive (% of risk group)	No declined test (% of risk group)
Intravenous drug abuser	191 (44)	100 (52)	5 (3)
Sex with intravenous drug abuser	88 (20)	6 (7)	3 (3)
Homosexual or bisexual	40 (9)	4 (10)	3 (8)
Sex with someone who is not a drug abuser	53 (12)	0	5 (9)
Other	69 (16)	4 (6)*	14 (20)
Total	441 (100)	114 (26)	30 (7)

* All related to iatrogenic contamination of blood products.



Locations where 44 Edinburgh drug abusers who attended the city screening clinic shared needles.

The total cost of this counselling and screening service in the first year was £27 000: £18 500 in salaries, £3000 in initial equipment, £2500 in consumables, and £3000 for HIV and hepatitis B testing. The cost per patient in the first year was therefore £61.22 or £27.55 per attendance. A total of 2080 hours were available for counselling per year. Allowing about one hour for counselling each patient and a 15% time loss for holidays and 40% for default appointments, roughly 1000 patients could have attended. This number of patients in subsequent years would cost £21 000 for counselling and £7300 for HIV and hepatitis B testing, or £28.30 per patient. A more compliant population would reduce costs even further to roughly £20 per patient, made up of £12 for counselling and £8 for HIV and hepatitis B testing.

Discussion

The demand for the facility that we offer has been confirmed with 441 new patients attending in the first year, 63·5% being either drug abusers or their sexual contacts. In Edinburgh five of seven HIV positive blood donors who were identified by the blood transfusion service were former intravenous drug abusers, and this further emphasises the importance of offering alternative testing sites.[7] The clinic has counselled a total of 114 (26%) HIV positive people, 88% of whom were intravenous drug abusers. The fact that HIV infection is common (52%) among drug abusers but is less so among their sexual contacts (7%) has been confirmed. This supports the results of previous work suggesting that HIV infection in drug abusers is spread by needle sharing rather than by sexual activity.[7]

Those in Edinburgh who are affected are characteristically young, have markers of current or past infection with hepatitis B virus, and are more likely to share needles and syringes frequently.[8,9] By comparison HIV positivity in Glasgow is only 4·5% and in England only 10%.[12,13] This geographical variation for drug abusers has also been noted elsewhere. In New York the HIV positivity among drug abusers who entered detoxification programmes was reported to be 87% compared with only 1·7% among Californian drug misusers, and in Italy the difference between two adjacent provinces was 90% compared with 10%.[14-16] These differences presumably reflect local variations in drug abuse, drug administration, date of arrival of virus, etc.

Not surprisingly, people with the least risk were most likely to decline the test after counselling, 20% *v* 2·6% of drug abusers. Overall 7% declined testing compared with 16% in the USA, where the positivity rate was 17% compared with our rate of 26%.[17] Our default rate after testing is 21%, which compares favourably with 30% in the USA.[17] An overall default rate of 42% is of concern as this means that counsellors are underused. Cost and distance do not seem to be factors in the default rate, and it may be a feature of either lifestyle or the anxiety associated with screening for this particular virus.

Most HIV counselling and screening in the UK has been undertaken by genitourinary medicine clinics, and as this has been an additional workload separate costing has not been readily available. Our HIV counselling and screening clinic was set up de novo for a particularly difficult risk group. For many reasons it was thought necessary to have a medical officer on site at all times, and this obviously adds to the expense. We can, however, provide a realistic estimate of the cost of providing a counselling and screening service. In the first year the cost was £61.22 per patient without taking into account the cost of premises, which were available at no extra cost to the health board. With increased numbers of patients and a lower default rate this cost could fall to about £20 per patient. At present there are calls for widespread voluntary screening in, for instance, antenatal clinics, and £20 per patient is a realistic cost of providing such a service.

The mobility of drug abusers has not been well appreciated, and we have shown, as others have, that abusers who are based in Edinburgh share needles in many locations (figure).[6] Presumably this mobility also applies to other abusers who are not based in Edinburgh. Recent reports suggest that the HIV seropositivity rate is rising in England and Wales,[13] and it will not be long, therefore, before other cities in the UK have a problem with HIV similar to Edinburgh's. This, and the fact that the spread of HIV by needles occurs at five to seven times the rate by sexual intercourse, should re-emphasise the fact that if this disease becomes disseminated into the general population it will do so from heterosexual parenteral drug abusers.

More generalised screening and counselling facilities are needed, especially for drug abusers, to delineate the problem further and prevent the transmission of HIV to other drug abusers, their sexual contacts, and children.

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City and Leith Hospitals; and Dr Martin Bland of St George's Medical School for donating the statistical computer program.

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Effect of zidovudine on platelet count

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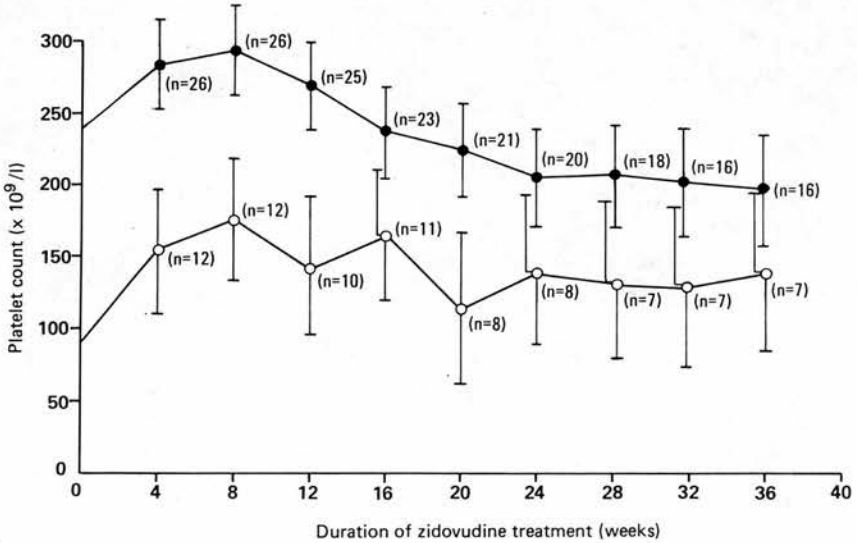
One of the short term effects of zidovudine (3'-azido-3'-deoxythymidine, AZT) is a rise in the platelet count in thrombocytopenia related to HIV infection.[1,2] The long term effects on platelets have not been reported, and doctors have been reluctant to use zidovudine in the presence of severe thrombocytopenia because of its association with myelosuppression. We report our experience of up to 36 weeks of treatment with zidovudine in both patients with thrombocytopenia and those with normal platelet counts.

Patients, methods, and results

Thirty eight patients, 14 with AIDS and 24 with symptomatic HIV infection, were treated with zidovudine for over 12 weeks. Platelet counts were estimated with a Coulter counter (S PLUS IV), the normal reference range being 150-450$\times10^9$/l, and results were available up to 36 weeks for 23 patients. Before treatment 12 patients (10 intravenous drug misusers, one homosexual, and one recipient of blood products) had platelet counts that were persistently below normal (mean count 91·5$\times10^9$/l, 95% confidence interval 49 to 134$\times10^9$/l). In two patients with symptoms of spontaneous bruising the initial counts were less than 15$\times10^9$/l. Twenty six patients had normal counts before treatment (mean 241$\times10^9$/l, 211 to 271$\times10^9$/l).

Platelet counts rose in both groups over the first eight weeks (mean rise from value before treatment 64$\times10^9$/l). Among the group with a normal platelet count before treatment, however, the count fell gradually after eight weeks to a value below that recorded initially. Counts were better maintained among the patients with thrombocytopenia (figure), and there was a significant association between an eventual rise in platelet count and an initial count below normal (nine out of 12 patients, $p<0·05$, χ^2 test with Yates's correction). The two patients with severe thrombocytopenia had platelet counts of 119$\times10^9$/l and 102$\times10^9$/l after 32 and 16 weeks' treatment respectively.

To assess which factors determined whether the platelet count fell eventually variables were studied before and during treatment. An eventual fall in platelet count was associated with the development of severe anaemia (haemoglobin concentration <80 g/l) that necessitated blood transfusion (five patients, $p<0·05$) but not with other markers of possible myelosuppression such as neutropenia and lymphopenia, or with risk group, clinical state, and occurrence or treatment of opportunistic infections. Severe anaemia developed only in patients who had normal platelet counts initially.



Mean platelet counts and 95% confidence intervals in patients with (○) and without (●) thrombocytopenia taking zidovudine

Comment

An immune thrombocytopenia related to HIV infection results from the reticuloendothelial removal from the circulation of platelets coated with immunoglobulin, but other causes of a fall in platelet count in HIV infection include clinical progression to AIDS, recovery from *Pneumocystis carinii* pneumonia,[3] and myelosuppression from drugs, or antibodies to glyco-

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protein (gp120) in the viral envelope.[4] During the first few weeks of treatment with zidovudine platelet counts rose in both patients with thrombocytopenia and those with normal counts. This suggests that reticuloendothelial inhibition may not be the only mechanism.

The eventual fall in platelet count with longer treatment probably had several causes, but the only significant association in our patients was with the development of probable myelotoxicity due to zidovudine, suggesting that this was the cause. We found no easily identifiable variables before treatment, other than a low platelet count, that predicted a good eventual response.

Current treatments for thrombocytopenia related to HIV infection have potential disadvantages—namely, immunosuppression from steroids and splenectomy with consequent risk of progression of the disease, problems of availability of high dose immunoglobulins, and lack of access to veins, especially in intravenous drug users. Zidovudine may be a useful alternative for symptomatic thrombocytopenia. The good response among those with even severe thrombocytopenia shows that this should not be considered a contraindication to treatment.

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Use of zidovudine for drug misusers infected with human immunodeficiency virus

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Summary

The use of zidovudine in drug misusers, especially current drug misusers, has not been extensively studied. Since periods of abstinence may be interspersed with drug misuse, it is necessary to establish the safety of zidovudine in injection drug misuse-related human immunodeficiency virus (HIV) infection under a variety of conditions. HIV serology became available in October 1985 and we have now examined medically 289 HIV seropositive patients, 85% of whom acquired their infection via injection drug misuse. Since March 1987 we have treated 40 individuals with zidovudine, 25 of whom were former or current injection drug misusers and one who was a heterosexual contact of a drug misuser.

Eighteen patients were taking various types of opiates. Six of this latter group injected either occasionally or regularly whilst taking zidovudine. There were no adverse clinical events associated with zidovudine treatment and continued opiate drug misuse whether by mouth or by injection. Although defaults from clinic visits were a problem, these defaults were not associated with any particular form of drug misuse. Compliance with zidovudine therapy as judged by change in the mean corpuscular volume was no different for the various risk groups. In our experience it is possible to treat safely current and former drug misusers with zidovudine.

Introduction

Zidovudine has been shown to increase survival and lessen the morbidity of patients with acquired immunodeficiency syndrome (AIDS) and acquired immune deficiency syndrome-related complex (ARC). As 60 to 70% of zidovudine is metabolised via liver glucuronidation the potential for a number of drug interactions is considerable. The early toxicity studies noted an association between neutropenia and concurrent paracetamol ingestion, utilised a four-hourly dosage regime, close monitoring for toxicity and a highly motivated patient group.[1,2] Although injection drug misuse (IDM) is the fastest-growing risk group for HIV infection in Europe and the second commonest risk group in both the U.S.A. and Europe little has been reported with regard to zidovudine treatment.[3]

Current drug misusers are involved in an illegal activity, and often tend to manipulate those with whom they are in contact; they distrust official organisations such as social work and health care. This is often matched by a distrust of drug misusers by those same organisations and professions. Injection drug misusers often have a high default rate for appointments and

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consequently tend to utilise existing services at times of crisis. For these reasons, the use of zidovudine in IDM-related HIV has not been extensively studied. Not surprisingly there is concern whether the pharmacokinetics of zidovudine are altered in the presence of prescribed and non-prescribed drugs, whether the drug misusers will be motivated to follow a complicated treatment regime, with reliability and compliance.

Drug misuse may be interspersed with quite long periods of abstinence. The outcome of zidovudine treatment may differ between chaotic injection misusers and those who have discontinued IDM some years before. Analysis of results for IDM-related human immunodeficiency virus (HIV) must therefore, wherever possible, take into account these differing subgroups even if the groups are largely based on self-reported data backed up by clinical impressions.

The extensive HIV epidemic in Edinburgh amongst heterosexual current and former drug misusers with evidence of clinical HIV disease has allowed an assessment of some of these questions.[4,5]

Methods

We began to treat patients with zidovudine in March 1987 and patients with IDM-related HIV infection in August 1987. The patients were initially selected on clinical grounds alone when progression to Centers for Disease Control (CDC) stage IV seemed to have occurred but latterly various prognostic factors such as absolute T4 count, IgA and IgM levels, the presence of anaemia, HIV antigenaemia or loss of core antibodies were also used. Patients started on doses of 20 mg/kg/day in divided doses four or five times per day.

The first 13 patients were admitted to hospital to start their treatment because of concern over possible drug interactions but thereafter patients commenced taking zidovudine as outpatients and were reviewed, usually at monthly intervals.

They were monitored by attendance, weight, clinical examination, haematology, biochemistry, immunoglobulin levels and lymphocyte subset analysis. Later when available, HIV antigen and antibodies were added to the investigations. The initial 13 patients also underwent a pharmaco-kinetic trial to study the effect of prescribed and non-prescribed drugs on the levels of zidovudine.

Results

Since October 1985, 289 patients known to be HIV seropositive have been medically examined and of these 245 (85%) acquired their infection as a consequence of IDM. To date eight (3·2%) have died from either violence or apparent drug overdoses. The Infectious Disease Unit of the City Hospital has cared for a total of 25 patients with a diagnosis of AIDS and eight have died. Five of these 25 patients with AIDS acquired their infection via IDM; one of these has died. One patient with AIDS acquired her HIV infection from her IDM sexual partner.

Zidovudine therapy was first used in March 1987 and to date 40 (14%) patients have been treated with zidovudine, 30 males and ten females. Thirteen patients acquired the virus homo/bi-sexually, while 26 patients became infected secondary to IDM-related HIV and one patient from a blood transfusion. The average age of the homo/bisexual patients is 38 years (range 29–58 years), while those with intravenous drug-related infection had an average age of 28·8 years (range 22–39 years). The patient who became infected following a blood transfusion is 47 years old.

Patients were given zidovudine when they developed AIDS or other CDC HIV classification category IV problems. Table I shows the CDC category of the patients when they started taking zidovudine. The mean absolute T4 counts of patients starting treatment with zidovudine were as follows: IDM-related HIV with AIDS (four patients) $0{\cdot}15 \times 10^9$/l (range 0·06–0·26), others with AIDS (11 patients) $0{\cdot}11 \times 10^9$/l (range 0·05–0·2), IDM-related HIV without AIDS (22 patients) $0{\cdot}28 \times 10^9$/l (range 0·1–0·46), others without AIDS (three patients) $0{\cdot}12 \times 10^9$/l (range 0·09–0·16). Thirty-four of the 40 patients have had HIV antigen tests performed to date and 24 (70·5%) were found to be positive. There was no significant difference between the risk groups or CDC status as far as HIV antigenaemia was concerned.

To date three (7·5%) patients who received zidovudine have died. One homosexual patient was unable to tolerate zidovudine because of marrow toxicity and died 16 months after commencement of zidovudine therapy for AIDS; one bisexual died of recurrent cerebral toxoplasmosis 7 months after commencement of zidovudine and one IDM-related HIV with concomitant cirrhosis secondary to type B chronic active hepatitis died of a massive variceal haemorrhage after 6 months of zidovudine therapy. His HIV related problems did not progress while he was taking zidovudine.

The drugs most commonly misused in Edinburgh include heroin, methadone, dihydrocodiene (DF118), buprenorphine (Temgesic), dipipanone (Diconal), temezepam, triazolam, diazepam, cannabis and alcohol. As far as we are able to establish, of the 26 IDM-related HIV patients, one (4%) patient denies ever misusing intravenous drugs and seems to have acquired her infection heterosexually from her drug-misusing partner, seven (28%) no longer misuse oral or intravenous drugs, (although four continue to smoke cannabis), 18 (72%) patients are on oral substitution therapy (12 are prescribed oral methadone by the City Hospital HIV Clinic and six receive oral replacement therapy from their General Practitioners). In total six (24%) patients admit to having injected drugs while taking zidovudine (this includes five patients who receive oral methadone from the City Hospital). The average length of follow-up for the 26 IDM-related HIV patients is 8·2 months (range 2–14 months) compared with 8·76 months (range 3–18 months) for the 13 homo/bisexual patients.

Of the 40 patients started on zidovudine, 14 (35%) developed side-effects severe enough to necessitate a reduction in the dose of zidovudine. Table II demonstrates the CDC category and risk factors of these patients. Two patients suffered more than one side-effect; three patients had gastro-intestinal symptoms on starting therapy which resolved when treatment was withdrawn and then slowly reintroduced; 11 (27·5%) patients became

Table I *CDC category of patients when commenced on zidovudine*

CDC category	IDM-related HIV infection	Homosexual	Blood transfusion
4A	7	1	—
4B	2	—	—
4C1	4	7	—
4C2	12	1	—
4D	—	2	—
4E*	1	—	1
Dual†	—	2	—
Total	26	13	1

* Thrombocytopenia.
† 4C1 and 4D occurring in the same patient.

Table II *CDC category and risk factor of patients who developed side effects with zidovudine*

	IDM-related HIV infection	Homosexual	Blood transfusion
4A	—	—	—
4B	2 (1, 0, 1)	—	—
4C1	3 (3, 1, 0)	2 (2, 0, 1)	—
4C2	4 (2, 1, 1)	—	—
4D	—	1 (1, 0, 0)	—
4E	—	—	—
Dual†	—	2 (2, 1, 0)	—
Total	9	5	—

(Side-effects denoted by (anaemia, neutropenia, gastro-intestinal) in table.)
* CDC 3 with immunological impairement.
† 4C1 and 4D occurring in the same patient.

anaemic, ten (25%) severely enough to require transfusion and one who was stabilised on a reduced dose of zidovudine. Transfusion requirements for those patients who became anaemic on zidovudine are shown in Table III. As has been shown previously, the patients with AIDS were more likely to become transfusion-dependent than those with ARC ($\chi^2 = 10{\cdot}98$ with Yate's correction, $P < 0{\cdot}001$). We are assuming here that CDC IV other than AIDS is equivalent to ARC. We were unable to predict the likelihood of patients becoming transfusion-dependent by the presence or absence of HIV antigen or the level of the absolute T4 count at the start of treatment. Continuing to use drugs orally or via injection did not have an adverse effect on the T4 count or make transfusion more likely.

Three (7·5%) patients became neutropenic on zidovudine (two with AIDS). In one this was recurrent despite decreasing doses. In this patient the zidovudine was eventually discontinued. The other two patients (both IDM-related HIV and one with AIDS) were stabilised on a lower dose of

Table III *Transfusion requirements of anaemic patients on zidovudine according to CDC category and risk factor*

	4C1 or 4D		Others	
	Homo/ bisexual	IDM-related HIV infection	Homo/ bisexual	IDM-related HIV infection
$x^* > 4$	1	—	—	—
$3 < x < 4$	—	—	—	2
$2 < x < 3$	2	1	—	—
$1 < x < 2$	—	2	—	—
$1 < x$	2	—	—	—

* x, Number of units of blood transfused per month since becoming transfusion-dependent.

Table IV *Defaults from HIV medical clinic according to risk group and CDC category*

Defaults	Ex/Non	Oral	Injection + oral	Total (%)
0	2	6	3	11 (42)
1–3	5	4	3	12 (46)
4–5	1	2	0	3 (12)
Total (%)	8 (31)	12 (40)	6 (23)	26 (100)

zidovudine. The non-AIDS IDM-related HIV patient had previously been stable on treatment for 1 year.

Injection drug misusers are notorious for defaulting from out-patient appointments and for non-compliance with treatment due to their chaotic lifestyle. The defaulters from the City Hospital HIV Clinic were analysed and are shown in Table IV.

None of the homo/bisexual group missed any clinic appointments. Of the 26 IDM-related HIV patients on zidovudine, 11 (42%) patients had no defaults, 12 (46%) missed one to three clinic visits and three (12%) missed four to five clinic visits. When the attendance of drug misusers was further assessed it was apparent that missed appointments were not related to continued IDM, current *vs.* ex IDM, AIDS *vs.* non-AIDS or gender. The most reliable attenders were those receiving oral methadone from our clinic ($\chi^2 = 3{\cdot}72$ with Yate's correction, $P = 0{\cdot}05$).

If a rise in red blood cell mean corpuscular volume (mcv) is taken as an indication of zidovudine compliance, our data suggest that compliance in the IDM-related patients is comparable with those in other groups (mean rise in mcv in IDM-related HIV patients on zidovudine is +21·2 fl, in the other groups it is +18·0 fl (the data from those patients who have received transfusions has not been included in this analysis).

In 12 (30%) patients the course of zidovudine was interrupted and in five (12·5%) patients this was for medical reasons (anaemia, neutropenia, or gastro-intestinal upset). One of these patients as already mentioned had to discontinue zidovudine permanently. Six patients, all IDM-related HIV, discontinued the drug without consulting the clinic. In one patient whose lifestyle was particularly chaotic it was felt unsafe to continue with zidovudine as its effects were being inadequately monitored. None of these patients suffered ill-effects as a result of these stoppages. Two patients, one who had not used drugs for 4 years and one on oral methadone have defaulted for long periods (mean 5·5 months) and then returned to the clinic. None of the homo/bisexual patients have stopped zidovudine without medical indication.

Eight out of 40 (20%) patients developed infections and/or malignancy after having been on zidovudine for 6 weeks or longer. One homosexual man in category 4C1 developed lymphoma, one homosexual man who had candidal oesophagitis prior to starting zidovudine developed a cotrimoxazole-sensitive pneumonia which was assumed to be due to *Pneumocystis carinii*, one homosexual man had a probable recurrence of his *Pneumocystis carinii* pneumonia, (PCP) and one bisexual man had a recurrence of his cerebral toxoplasmosis. One IDM-related HIV patient moved from category 4A to 4C2, another had a proven recurrence of her PCP and two IDM-related HIV patients had attacks of herpes zoster.

Discussion

The medical care of individuals engaged in drug misuse is difficult and is complicated by a lack of support in the community and often differing goals for doctors and misusers. Periods of misuse are interspersed with variable periods of abstinence such that therapy which demands abstinence would be fraught with dangers. Consequently it is necessary to establish the safety of zidovudine in misusers under a variety of conditions. Abstinence from a particular form of drug misuse (e.g. oral *vs.* inhalation *vs.* injection) would not be a safe criterion on which to initiate treatment since the drug use state might alter during treatment.

Perhaps it is not surprising that IDM-related HIV as a group had a worse attendance record than homo/bisexual patients and this is probably more related to differing life style and background. A study of general practice in Muirhouse, Edinburgh revealed a uniform default rate of two visits per patient per year irrespective of drug misuse.[6]

Overall 58% of IDM-related HIV patients missed one appointment but 75% of the ex- or non-IDM patients also missed at least one appointment. By comparison only 50% of those judged to be still injecting whilst on oral substitute theapy missed at least one appointment.

There is little as yet reported in the literature with regard to zidovudine use in IDM-related HIV. However at the Fourth International Conference on AIDS in Stockholm there was a preliminary report from New York of IDM-related HIV and zidovudine.[7] The population studied was not exactly the same as our own since 14/60 or 23% of the IDM-related HIV patients from New York were heterosexual contacts compared to our 4% (one patient) and only

30% admitted to concurrent medication whereas at least 88% of our patients were using concurrent drugs and 24% admitted to current IDM. Superficially, however, the results were surprisingly similar in that 81% from New York missed from zero to three appointments compared to our 86%. However only 1% of the patients in New York had no defaults compared to our 42% and New York had 12/60 or 20% lost to follow-up compared to our two (8%). Even these latter two patients are still in contact with their General Practitioners or our counselling clinic. Similarly the New York group reported no excess toxicity.

To date we have not been able to study the safety and efficacy of zidovudine with continued heroin injection drug misuse since at present the majority of our injection misusers are injecting black market pharmaceutical preparations. The use of illicit pharmaceutical opiates by injection did not appear to interact with zidovudine. The pharmacokinetic data of zidovudine levels in combination with a variety of opiates, benzodiazepines, cannabis and alcohol will be published separately.

Since our patients are issued with a supply of zidovudine sufficient for 1 month at each visit intermittent treatment has occurred because of missed appointments but this has not resulted in any harm to the patients. In addition several treatment courses were interrupted on medical grounds and no deterioration was observed. This differs from recent reports.[8]

A commonly expressed fear is that IDM-related HIV patients will sell their supply of zidovudine on the black market. Although this may have happened, the rise in mcv suggests it has not. It would also appear to be uncommon when a reasonable supply of an oral substitute is given even if injecting does continue. The mcv change is, therefore, a convenient and cheap method of assessing compliance and only those patients who did not experience an mcv rise need be further investigated for malabsorption or lack of compliance. Interestingly the mcv change also occurred with a far less rigorous regimen, usually four or five times per day organised around meal times. The more widely spaced regimens do not so far appear to be detrimental but continued monitoring is required.

There are a number of practical issues which are more specific to this group. Because of the unknown effect of zidovudine upon the fetus, currently we recommend termination in the case of pregnancy although we would continue treatment if requested. One of our patients became pregnant while receiving treatment.

Venous access is a considerable problem in a few patients, because of the need for repeated venepuncture over many months or years, currently we favour sampling from the external jugular in the head down tilt rather than the femoral vein.

As a consequence of limited resources, large numbers of patients, the problem of compliance with clinic appointments, a relatively well population and small numbers of patients with AIDS at present we adopted monthly monitoring for those on zidovudine. Provided that haematological values are normal before treatment, monthly monitoring was safe and did not result in unexpected leucopenia or anaemia.

The improvement in health induced by zidovudine has on a number of

occasions resulted in individuals feeling well enough to return to IDM. Continued IDM does and will occur in patients on zidovudine treatment. Thus it is important to keep up the 'harm reduction message'.

A number of our patients have started on zidovudine while being in prison and others have spent time there after commencing treatment. It might be expected that this would result in difficulties with therapy but this has not occurred. Prison authorities and their medical staff have allowed these patients to continue with their treatment and attend follow-up appointments.

Thus it is possible to treat IDM-related HIV with zidovudine. Our preliminary results with clinical monitoring of zidovudine-treated IDM-related HIV suggest that it is safe in a variety of drug misuse situations including recent injection drug use. Attendance is no different between those judged to be still misusing and those thought to have discontinued IDM. In the absence of initial haematological abnormalities monthly monitoring appears safe and the patients came to no harm as a consequence of their intermittent treatment. Selection for treatment could be made on the grounds of prior regular attendance and lack of injecting but do we have the right to withold treatment on the grounds of lifestyle. Perhaps the most important factor is patient realisation of toxicity and the need for monitoring.

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Implications of the Edinburgh AIDS epidemic for the United Kingdom

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Introduction

The acquired immunodeficiency syndrome (AIDS) was described only in 1981 yet there are now nearly 200000 confirmed cases known worldwide.[1] The true figure is likely to be much greater than this because Africa (from which as many cases have been reported as from Europe) does not have the administrative infrastructure required to diagnose and record all cases. In the U.S.A., where the illness was first described, 2/3 of cases have been in homo/bisexuals and 1/3 in persons injecting drugs intravenously.[1] In the U.K., at present, 89% of patients are homosexual, 4% inject drugs intravenously but only 4% cases result from heterosexual intercourse alone. By contrast, in Africa, AIDS is truly a heterosexually transmitted infection.[2] While over 2000 cases have been reported from the U.K. as a whole, only 124 have been reported from Scotland and only about 50–60 from Edinburgh.[3] This would suggest that, as a city, Edinburgh has a fairly small problem but unfortunately this is not so.

In Edinburgh, for various socio-economic reasons an epidemic of intravenous injection of drugs including heroin took place in the early 1980s. Most of those concerned were young, one third were female and two thirds were male. They were mostly unemployed and living in large council estates.[4] Unfortunately, at the peak of this epidemic of IV drug injection, HIV arrived and spread rapidly throughout this community where infection with the virus is now endemic.[4–7] Although it is easy to be wise after the event, attempts to control the IV injection of drugs appears to have increased the spread of HIV. For instance, an attempt was made to limit the supply of injecting equipment which seems to have led to widespread sharing of needles and syringes.[4] It is now known that HIV spreads rapidly as a result of the sharing of injecting equipment.[5,6] This event has been likened to that of attempting to stop people from drinking alcohol by limiting the sale of drinking glasses.

By July 1989, over 1000 persons or 0·1% the population of Lothian (750000) had been infected with HIV mostly by intravenous injection of drugs.[8] This prevalence is of the same order as that for the worst affected part of England, namely the north west Thames region (Gill, personal communication). Most infected persons in Lothian live in the City of Edinburgh which has a population of around only 300000 (1981 census). Thus the prevalence for the City of Edinburgh is 0·3% or three times that of the worst affected English region. Some 77% of infected persons in Edinburgh are in the 15 to 35 years age group (120000 in the 1981 census). Therefore, a more

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realistic prevalence rate for HIV is one in every 150 (0·64%) of the population aged 15–35 years. Edinburgh may therefore have the greatest density of HIV infections in the U.K.

Are there likely to be even more persons in Edinburgh infected with HIV from the IV injection of drugs? At the peak of the epidemic of IV injection of drugs it was estimated by SCODA (Standing Committee on Drug Abuse) that six per 1000 or 0·6% of persons aged 15–35 years were injecting opiate drugs.[9] Reports from 1985–1986 suggest that between 50 and 65% persons injecting drugs were infected with HIV. This would therefore suggest that at least 360–480 persons or 0·3–0·4% adults aged 15–35 years in Edinburgh are now infected with HIV. In fact, to date, 490 persons infected with HIV as a result of IV injection of drugs have been identified in Edinburgh.[8] Thus, the calculated and observed numbers of HIV-infected persons are very similar and confirm the serious nature of the problem for Edinburgh. Because the peak of the spread of HIV was in 1983, and the average time from acquisition of HIV infection to AIDS is around 8 years, 1990–1991 will mark the arrival of the AIDS epidemic in Edinburgh. Due to the very long incubation period before the onset of AIDS, it is difficult for most people to understand the enormous threat that AIDS poses to society. HIV-infected persons who inject drugs IV are probably infectious until death (a period of perhaps 10–15 years), most are heterosexual and 40–70% may, at the height of their sexual activity, have a heterosexual relationship with someone who is not injecting drugs IV. Despite awareness of this risk and fairly intensive counselling, transmission of infection is still taking place among such people because they do not practise 'safe sex'. Furthermore, women carrying the virus who become pregnant may pass the virus on to their children. For these reasons, HIV is already spreading in Edinburgh into the general heterosexual population. Because it takes 8–10 years for an infected person to develop AIDS, however, it is likely that a substantial heterosexual AIDS epidemic will not be generally apparent until 1995. By then it will be too late to take effective action. This unawareness of an impending heterosexual epidemic undermines present attempts to change sexual behaviour in our society.

AIDS, related to the intravenous injection of drugs, is forecast to become the commonest cause of AIDS in Europe in the 1990s because acquisition of infection by this means was widespread in 1986 (Downs, personal communication). Many heterosexual persons, therefore, must adapt their sexual practices to take account of this virus. In Edinburgh, we are currently living in a society where, as in Africa, HIV infection is being heterosexually transmitted. London, by comparison, is not yet in this predicament.

From the apparently safe haven of England with few HIV-infected persons injecting drugs IV, it may well appear that the apprehension of a heterosexual epidemic is excessive. Headlines have reported 'medical experts' commenting that the forecasted heterosexual epidemic of AIDS has not arisen and that such an epidemic has already 'peaked'. Even the government seems to have fallen into the trap by disbanding the Ministerial Group on AIDS. Why else would the prime minister cancel a research project into sexual behaviour when the major thrust of the government's education campaign until now has been 'Don't Die of Ignorance'. The prevalence of HIV infection in Edinburgh

among female sexual partners, as elsewhere, is currently around 20% while the transmission rate is 3–5% per year with a death rate among those who inject drugs IV of only about 1–2% per year.[10,11] Once a critical mass of infected heterosexuals has been reached in a society, even with an infectious disease that is 100% fatal, it requires only the transmission rate to equal the death rate each year for the infection to become self-perpetuating.[12] At present, the source of large numbers of infected heterosexuals is most likely to result from the IV injection of drugs. Thus, we need to teach people, both in words and deeds, the facts about the dangers of drugs and multiple sexual partners. While every family may not be infected with HIV by the year 2000, the adult members of every family ought to be well aware of the presence of HIV in society, hopefully well before the year 2000.

The lesson for the government is that HIV infection, as opposed to AIDS, is already a heterosexual public health problem in parts of the U.K. and is gradually spreading throughout the country. The problem may not yet be affecting London but we, in Scotland, ought not to tolerate the complacency currently being shown by the government towards heterosexual transmission of HIV. Perhaps the prime minister and her advisers should reconsider their decision on studies of sexual behaviour. It might then be possible to explain the low use of condoms among HIV-positive heterosexuals and possibly to formulate strategies to combat this in the general heterosexual population. Homosexual men have adapted to the presence of HIV in society; heterosexuals need to do the same. Homosexuals and haemophiliacs consider that the government did too little too late. Will future heterosexuals infected with HIV feel the same?

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Hospital health care for HIV infection with particular reference to injecting drug users

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Abstract *Models of health care developed for HIV and AIDS tend to reflect the experience of San Francisco or London where the majority of patients affected have been homosexual or bisexual. The services developed in these areas may not be appropriate for other risk groups such as injecting drug users. The author, who has been closely involved in developing an HIV service in Edinburgh mainly for injection drug users, undertook a travel fellowship to compare and contrast HIV medical services in Amsterdam, New York and San Francisco with particular regard to what was available for injecting drug users. The provision of drug related and HIV medical services at the same site by the same doctors appears to provide the most efficient service but has yet to be systematically evaluated.*

Introduction

Injecting Drug Use (IDU) related AIDS is the second largest risk group in the U.S.A. and Europe and the fastest growing risk group in Europe (Centres for Disease Control, 1989; Communicable Diseases Scotland, 1987; WHO, 1989). Spain and Italy, where IDU related AIDS is the commonest risk activity, have been particularly affected whilst other countries, notably France, Switzerland, and Ireland all have a major problem with IDU related HIV (Rodrigo *et al.*, 1985; Lazzarin *et al.*, 1986; Carcaba *et al.*, 1988; Ferroni *et al.*, 1985; Costigliola *et al.*, 1986; Bottolotti *et al.*, 1986; Bourchard *et al.*, 1986; Federlin *et al.*, 1986; Mortimer *et al.*, 1985; Schupbach *et al.*, 1985; Dolivo *et al.*, 1988; Shattock *et al.*, 1986). In England and Wales by comparison IDU related AIDS or HIV infection is not yet a significant problem (Anonymous, 1989). In Scotland however as in Southern Europe it is the major risk activity as far as HIV is concerned (Communicable Diseases Scotland, 1989a,b,c). The South East of Scotland notably Edinburgh, Dunfirmline in Fife and Dundee all suffered an epidemic of injection drug use which started in the early 1980's and peaked around 1983. This was coincident with an influx of relatively cheap heroin, the use of Edinburgh as a distribution point for the rest of Scotland and very high levels of equipment sharing as a consequence of a lack of needles and syringes. The users were young, mostly unemployed and the majority were living on council estates (Pearson *et al.*, 1985; Brettle & Nelles, 1988). Unfortunately HIV was introduced into the South East of Scotland at the peak of heroin use resulting in very rapid spread amongst injecting drug users (Peutherer *et al.*, 1985; Robertson *et al.*, 1986; Brettle *et al.*, 1987; Urquhart *et al.*, 1987).

The shape of any medical service is very much related to local demography and as a consequence the services for AIDS have developed along different lines in New York and

San Francisco. In New York City, IDU has been implicated in 34% of the male and in 60% of the female patients where as in San Francisco only 1.7% of San Francisco's cases have been in drug users although a further 11.5% have involved drug use in homosexual/bisexuals (Joseph, 1988; Lifson, 1988). New York has had to cope with over three times as many patients with very different characteristics (Joseph, 1988). In San Francisco 82% of the patients have been white, 99% male, 97% gay and only 1.7% heterosexual drug users (Lifson, 1988). By comparison in New York only 46% of the patients have been white, 90% male, 64% gay and 28% heterosexual drug users (Joseph, 1988). The medical problems are also very different for instance, 15% of IDU related AIDS have developed tuberculosis and this obviously requires very different nursing facilities (Drucker, 1988). In addition there has been a dramatic increase in non-AIDS deaths such as pneumonia, tuberculosis, endocarditis etc amongst injecting drug users (Stoneburner *et al.*, 1989).

It is estimated that New York has some 200,000 injecting drug users for its 7.5 million inhabitants and that around 50% have been infected with HIV (Joseph, 1988). There are around 35,000 places for drug treatment, approximately 30,000 methadone treatment slots and about 5,000 drug free treatment slots (Drucker, 1988). San Francisco by comparison to New York has a much smaller injecting drug problem of approximately 14,000 users for a population of 750,000 (Moss, 1988). As in New York however the majority are Black or Hispanic.

Methadone maintenance treatment programmes (MMTP) in the USA are regulated by the Federal Drug Administration (FDA) and perhaps the most stringent rule is that for every 50–60 patients attending a programme there should be one drug counsellor. In addition it is required that there be various support services such as day programmes. By law MMTP must also provide patients with an admission medical examination as well as an annual medical examination. The medical examinations varied however from a few minutes to 45–60 minutes depending upon the centres. The majority of patients attend daily to receive their methadone dose on site. In order to get into MMTP the patients need a 1–2-year history of drug use from court or medical reports, previous failed detoxification attempts and had to be greater than 18 years of age. For most patients there was a 3–4 month waiting list and at the admission physical the doctor would then decide on the dose of methadone which was usually about 30 mg. He would also decide on the final dose depending upon the patient's history and every 2–3 days the dispensing nurses could increase the dose by 10 mgs provided the patient was having withdrawal symptoms backed up by clinical signs such as dilated pupils, sweating etc. The doctors in the clinic provided primary care and referred to local hospitals if the patients were at all ill. Payment for the MMTP service was according to income and the support system used relies on role model counselling, from ex-addicts or stable addicts. The underlying philosophy was resocialization and to this end they allowed take home privileges as far as methadone was concerned in an attempt to restablize or resocialize the patients (Drucker, 1988; Sorenson, 1988).

It must be remembered that many HIV-infected individuals have given up drug use for instance in our own hospital approximately 50% of those attending are no longer involved in IDU. Thus any IDU related 'service' will have to cope with considerable diversity. To date the delivery of Health care to HIV positive individuals in Europe and the USA has been based on the model developed for homosexual men and it is the purpose of this article to review HIV medical services with particular reference to IDU related HIV infection. Whilst New York City has had the largest number of AIDS patients in the USA, it was in San Francisco that an AIDS dedicated medical service began.

Method

From 1985 the author has been intimately involved in developing medical services for HIV patients in Edinburgh. During October and November of 1988 the author undertook a travel fellowship to compare and contrast medical services for injecting drug users with particular reference to HIV and AIDS; by visiting Amsterdam and a number of centres in the USA notably the Montefiore Medical Centre, Beth Israel Hospital, St Lukes-Roosevelt Hospital, Memorial Sloan Kettering Cancer Hospital, Beth Abraham Hospice and Bailey House residential facility in New York as well as the University of California San Francisco Medical Centre, San Francisco General Hospital and San Francisco Department of Health. This report is based on discussions held with many individuals (unfortunately too many to all mention by name). Much of the factual information contained in this article was provided by Dr A. Moss, Dr G. Friedland, Dr R. Elison, Dr E. Drucker and Dr R. Coutinho. The views expressed are however, the author's own and are necessarily biased by the fact that the author is an Infectious Disease Physician providing medical care for IDU related HIV patients rather than a specialist in drug addiction. Whilst there are many other areas in Europe dealing with the problem of IDU related HIV Amsterdam was chosen because of their model of care for IDU, San Francisco because of their model of care for AIDS and New York because of the size and length of their experience with IDU related HIV. The work is largely descriptive because as yet there has been virtually no attempt to audit the various systems.

San Francisco

The San Francisco General Hospital (SFGH) AIDS Care system goes back to 1979–80 when Dr Abrams and Dr Volberding began a clinic for gay men with unexplained lymphadenopathy. The AIDS Clinic was set-up in Ward 86 of the SFGH in 1981–82 initially as an oncology clinic and then also as an opportunistic infection clinic.

It is now open 5 days per week, has 2,000 attendances per month, over 120 staff and provides the following functions: a Nurse Screening Clinic, an AIDS/ARC Clinic, an Opportunistic Infection Clinic, a Kaposi's Sarcoma Clinic and a Prescription Refill Clinic. In addition procedures such as blood transfusions, intraveneous rehydration, intravenous chemotherapy, etc. can be performed to avoid admission (Gorter, 1988).

Whilst injecting drug users do receive medical and HIV care at this clinic, because of Federal regualtions they have either to attend a separate clinic in the same building for methadone or alternatively a methadone clinic elsewhere in the City. Not surprisingly therefore follow up of injecting drug users is make more difficult by the need for multiple attendances (Soreson, 1988).

In 1983 the inpatient Unit was established initially with 12 beds and latterly because of the increased workload with 18 beds. The hospital has about 30 AIDS patients in each day (or 27% of medical beds) and the AIDS Unit is virtually always full (Clement, 1988).

Patients are admitted via the AIDS clinic or arrive via the emergency room and are admitted under the care of one of the general medical teams. There are eight such teams providing medical care for general as well as AIDS patients. The Consultants for the medical teams rotate monthly and provide inpatient care for between 2–4 months of each year. Thus patients with multiple admissions could find themselves under different medical teams for each admission (Clement, 1988).

In 1985–86 SFGH created an inpatient AIDS Team made up of an AIDS Specialist (from the AIDS clinic) together with a third year resident (usually a visiting elective resident from another medical school) and visiting medical students. The AIDS Team

provides back-up advise for the general medical teams and the AIDS Specialist did 2 ward rounds per week with these teams (Clement, 1988).

By comparison the rest of the care provided for the AIDS patients is very much via dedicated workers. For instance there are specialised social workers, counsellors, drug counsellors, physiotherapists, psychologists, etc.

It is important to remember that SFGH is a City Hospital and therefore many patients with private health insurance would not utilize these impatient services until they had exhausted their medical insurance. Patients with private health care insurance might utilize the expertise of the AIDS clinic but still attend their private physician and be admitted to private hospitals for their inpatient care (Clement, 1988).

New York

In March 1988 1513 or 6.4% of the acute medical and surgical beds in the municipal or voluntary hospitals were occupied by AIDS patients. At that time the Municipal system was caring for 36% of the AIDS patients although in fact it only had 16% of the medical and surgical beds in the City. Whilst overall only 13% of AIDS patients in New York hospitals were related to IDU, in the Health and Hospital Corporation facilities 75% of the cases were related to IDU. Thus a disproportionate share of the IDU problems gravitated to the Municipal hospitals (Joseph, 1988).

In 1986 the New York State Department of Health proposed a system of Specialized AIDS Units. The idea was to provide a comprehensive care model for AIDS patients and by 1988 22 Specialized AIDS Units had been designated together with their associated AIDS Teams. In order to persuade hospitals to set up AIDS Units and Teams the Department of Health offered an increase rate of reimbursement if the patients were consulted on by an AIDS team.

In setting up AIDS centres the New York State Department of Health formulated a set of standards which facilities had to meet in order to be designated an AIDS unit. Essentially in order to claim increased reimbursement for the care of AIDS patients hospitals had to designate a Unit for the care of AIDS patients which could provide a 24 hour emergency service and an outpatient facility. These units were expected to offer a broad range of services for a range of AIDS patients with differing needs including diagnostic services, inpatient care, hospice and residential care, counselling and educational programmes. The care of the patients in the Units was to be via a multi-disciplinary team providing individual case management. The Units were also expected to participate in clinical research, provide educational programmes for the general public including those at increased risk of acquiring HIV (Friedland, 1988).

The teams were headed by an AIDS specialist who would rotate monthly but the rest of the staff were dedicated full time to the AIDS patients. There were social workers and nurse practitioners on all teams but the rest of the teams composition then depended upon the particular Unit. Most teams had dietitians, psychiatrists and or psychologists, the Unit head nurse and an administrator the latter because of the importance of identifying AIDS patients in the hospitals in order to obtain increased reimbursement. Others also had occupational therapists or lawyers (because of the problems of Do Not Resuscitate Orders and or living wills).

St Lukes and Beth Israel Hospital utilized dedicated medical staff that rotated monthly but other Units such as the Montefiore Medical Centre in the Bronx did not have dedicated medical staff and as in SFGH each general medical team cared for its own AIDS patients in the Unit. In both systems there were a large number of Consultants involved in the care of

the patients and the AIDS team coordinated their care (O'Mahony, 1988; Saltzman, 1988; Friedland, 1988, Clement, 1988).

Some Units such as at Montefiore utilized a written admission policy not only for AIDS but also for substance users, whilst others did not. They all tended to admit the sickest and most difficult patients or any patient that might benefit from admission to the Unit. Becasue the Units were designated as AIDS wards all patients had to volunteer for admission because it revealed their diagnosis.

Security was a problem for many Units and it was not uncommon for the hospitals to have security guards who might visit the Units as often as two hourly. The security staff were however rarely called upon and in fact had a good relationship with many of the patients. Their presence was however appreciated by the staff.

The outpatient AIDS clinics in New York provided care for the non-private patients. The New York Health Department's plan was to provide a similar structure to the inpatient model of care for outpatient care but by December 1988 most of the AIDS Units had not fully established these specialized clinics. In general anyone not being followed by a private physician or a Methadone Treatment Programme was seen after discharge in an AIDS clinic.

Amsterdam

By 1988 Holland had reported 605 AIDS patients and of these 2.5% were drug users in 1986, 5% in 1987 and 8% in 1988. There were no special facilites available for AIDS in Amsterdam and at that time none were planned (Bunning, 1988).

The Municipal Medical Health Care Service has five major departments, one of them known as the Public Health and Enviornment Department (GG&GD) which has the function of running outpatient clinics, offering vaccinations, controlling infectious diseases, running laboratory services, combating AIDS and drug treatment for drug users.

Amsterdam's programme of drug treatment has three levels described as low, middle and high threshold. The Methadone bus is the low threshold system, the Methadone clinics are the middle system and drug detoxification, therapeutic communities etc the high threshold system. The low level system has little in the way of regulations whilst the high level system was very strict as far as the use of other drugs was concerned. the GG&GD estimate that they reach 70% of the 6000–8000 addicts in Amsterdam (approximately 1/3 of Dutch users) and 40% of these are injecting drugs. Eight hundred individuals or 1/3 of the injecting drug users in Amsterdam have been found to be seropositive and are in touch with authorities. Approximately 50% of these are German or Italian (Bunning, 1988).

The Health care system of the Netherlands is based on an insurance system such that if one is in receipt of social security then the social security system directly pays for the services used by the patient. There are however a large number of uninsured individuals (very often foreign drug users) and if admitted to hospital then the insurance is initailly paid by the social services only if it is a life-threatening illness. As the patients get better however they become liable for the bills and therefore often self discharge.

A team of psycho-social nurses visit all the drug users in the general hospitals and see between 300 and 400 patients per year. The team provide crisis intervention for the patient during the first 2–3 hours in order to avoid a lack of methadone and because the patients drug problem is usually of such a long standing nature they try to persuade the staff not to embark on detoxification (Sluijs, 1988).

The patients may well have aggressive, paranoid features or even frank psychiatric problems. The nurses evaluate the drug history, psychiatric history and social circumstances and manage numerous crises between patients and staff. The major problems seen in

hospitals with drug users centre around their visitors, their interaction with other patients and continued injection drug use. The nurses try to place the patients in treatment programmes and whilst previously they discharged them as soon as they left the hospital, with AIDS patients they offer outpatient follow up.

Some years ago Amsterdam experienced the effects of poisoned heroin and all those cases were managed in one ward to facilitate care. Thus they have already developed a model for how to deal with drug users in hospital utilizing a concentrated model of care but as yet they have not yet utilized this model for AIDS or HIV infection (Sluijs, 1988). Similarly at present the methadone bus clinics are not directly involved in HIV health care.

Edinburgh

Whilst Edinburgh has a voluntary sector for dealing with injecting drug users, from the late 1970'a and early 1980's there was a gradual reduction in the prescribing of substitute drugs by general practitioners and psychiatrists based on the assumption that spontaneous resolution eventually occurred with a mortality of around 1% per year. Thus when the epidemic of injection drug use occurred in the early 1980's there were little or no medical provisions for dealing with the problem.

The HIV medical clinic at the Infectious Disease Unit was started in October 1985 to cope with the problems associated with voluntary HIV testing. The majority of its clients were injecting drug users and when in 1986 it was suggested that continued injection drug use was associated with a greater loss of CD4 lymphocytes we began to prescribe methadone (Des Jarlais *et al.*, 1987). The HIV medical clinic had been faced with large numbers of HIV-infected drug users with no management options other than abstinence. There were very few general practitioners or psychiatrists willing to prescribe oral opiate substitutes and it was obvious that the previous philosophy of awaiting spontaneous resolution was no longer practicable with the advent of HIV.

Patients were evaluated for their HIV problems and those found to be injecting were offered initially reducing regimes of a methadone mixture but latterly maintenance methadone has been adopted. This is provided via a hospital prescription which is taken to any retail chemist and the cost is paid for by the hospital rather than the general practitioner budget. The majority of prescriptions are written for daily dispensing but variations such as two or three times per week are also used. No other substitute prescibing occurs but patients are provided with other medication such as zidovudine, antibiotics, etc.

Patients are offered routine medical surveillance for their HIV infection, methadone maintenance therapy as well as first aid for numerous drug problems. As far as possible a number of other facilities such as counselling, contraceptive advice, contraceptive supplies, inhaled pentamidine, refunding of bus fares and dental care are also provided on site. Paediatric follow up is available in the community or via a combined family HIV clinic from the same out patient department.

The majority of IDU related AIDS or HIV problems have when necessary been admitted to the Infectious Disease Unit and partly because of the mixed sexes are nursed in single rooms. The patients are admitted via their General Practitioners, via the local Accident and Emergency Departments or via the HIV medical clinic to the Infectious Disease wards which also cater for Infectious Diseases and General Medicine of all ages. There is no written admission policy and there are no security staff. There is a dedicated HIV team both medical and paramedical but as yet no dedicated drug dependence staff. The paramedical team consists of a dedicated physiotherapist, occupational therapist, dietitian, counsellors, psychologist, and social workers. Each week there are two multi-disciplinary

meetings, one for inpatients and one for outpatients, which is attened by the medical and paramedical team together with inpatient, outpatient and liaison district nurses. The Consultant staff provide the medical continuity of care for both in and outpatients. Continuity of nursing care is achieved by wherever possible re-admitting patients to the same ward. The majority of the paediatric HIV patients in Edinburgh have also been admitted to the paediatric ward of the Infectious Disease Unit, initially under the care of the Infectious Disease Consultants but latterly under the care of the Community Paediatrician providing the paediatric HIV outpatient care. This has allowed on occasions both mother and child to be admitted to the same Unit. However when the mother has advanced or serious disease she is usually to ill to care for the child. Whilst in emergency situations an admission to the Unit is offered for the child the preferred solution has been the identification of a longterm foster mother available at only a few moments notice via Social Services.

The problems encountered on the wards have been more to do with drug use than HIV. The concern about HIV amongst general patients has not been so much of a problem as the unsociable and disruptive behaviour connected with drug use which has caused considerable distress to other patients as well as difficulties for the staff. The need for a specialized AIDS Unit may be as much to do with this difficult behaviour as the need to provide specialized HIV medical care. Continued non-prescribed drug use either orally or by injection cannot be eliminated whatever the level of supervision. Not surprisingly it is less of a problem the more seriouly ill is the patient but even then total immediate withdrawal is impossible despite respiratory failure. Unlike Drug Detoxification Units, restricted visiting and body searches are not possible for visitors and or patients who are seriously ill.

Other major problems are verbal abuse towards other patients and staff, unsociable behaviour at unsociable hours, theft of other patients, as well as the wards property and violent behaviour. This later problem is not often directed towards the staff. Commonly there are old scores to settle between patients and unfortunately staff have been injured in the attempt to halt the fighting. In general because of similar problems to the impatient wards it has been necessary to divide the medical clinics according to current and non use of drugs of addiction.

Conclusions

The model of health care developed for HIV and AIDS has been developed in San Francisco and London and reflect the fact that the majority of patients have been homosexual or bisexual. The evolving HIV health care system has been characterized by the involvement of voluntary groups, most but not all from the homosexual community, an emphasis on home and/or community care to return the patient to a non-hospital environment, a rapidly evolving health consciousness over HIV and a positive response to risk reduction measures.

The model of care developed may not necessarily apply to injecting drug users since the current drug user has, a continuing involvement in illegal or criminal activities, manipulative tendencies in dealing with statutory agencies, a dislike or distrust of official organizations of the clients. As a group they exhibit poor utilization of existing services although some of this chaotic behaviour is more a characteristic of their community than drug use *per se*. There are in addition a relative lack of self-help groups within the community and a relatively weak community voice. Their home environment is often not ideal or suited to home care although in Edinburgh because of the close proximity of families and a well developed primary care service limited home care has been possible. To date behaviour change with

respect to HIV has been modest and difficult to initiate (Stimson *et al.*, 1988a,b; Donoghue *et al.*, 1989).

The medical care of patients with AIDS is complicated by a number of medico-social problems which are further compounded by the problem of IDU. Homelessness is extremely common in New York and San Francisco anyway, and the accommodation of those that are not homeless is often unsatisfactory in relationship to their medical condition. Thus the existing situation is simply worsened with the development of AIDS and consequently many patients remained in hospital solely because of their unsatisfactory accommodation.

In the USA continuity of care does not necessarily occur within the voluntary or municipal medical system unless the individual has private medical insurance. Private medical insurance ensures that the same doctor cares for the individual as both outpatient and inpatient but this is not the case for those lacking insurance. Deteriorating health often results in an inability to generate an income or eventual umemployment. When combined with high medical costs this often results in a lack of basic health insurance. Amongst injecting drug users there is not only the problem of the high cost of medical care but also a lack of initial basic health care insurance. This lack of health insurance further reduces continuity of care because individuals may move from hospital to hospital using false names in order to avoid the problem of payment. Without doubt in both New York and San Franisco as in the rest of the world the cracks in the medical system are exposed by drug users. Continuity of care in the New York or San Francisco was almost non existent for IDU related HIV unless the patients were in a methadone programme and in this respect they may be better off than the ex-user or heterosexual.

The inability to generate an income affects not only those in regular employment but also those with an illegal income. In the case of an injecting drug user this might be because of an inability to continue criminal activities. The resulting poverty often precipitates an additional crisis when the individuals can no longer afford their drug habit. Consequently IDU related AIDS and HIV patients were more often in need of drug treatment programmes as their health deteriorated. As a consequence of the shortage of places in methadone treatment programmes and the priority given to IDU related AIDS or HIV these programmes are rapidly being saturated. Since these programmes were not established to deal with medical problems it creates further problems for an overstretched service. In addition it further reduces the available places for the uninfected drug users and this in turn further reduces the effectiveness of the prevention aspects of methadone programmes.

The San Francisco model for AIDS care provides excellent outpatient medical care but even here continuity of care was not available for the numerous inpatient admissions unless the patient had private medical insurance. The SFGH inpatient model of care was adopted because it was felt that AIDS should be looked after by general physicians (despite the presence of an AIDS clinic). It was an attempt to avoid burnout in the carers and to educate more doctors in the principles of care of AIDS patients but does not address the problems of the patients. Continuity of care could not be provided by the Consultants since they were only on service for an average of about 2 months per year. The junior doctors also rotated frequently and thus it was quite possible for an individual to have number of admissions and to be looked after by numerous different doctors.

The New York health care system now provides some continuity of care via the AIDS teams but even here the AIDS specialists rotate. Thus true continuity of care for inpatients is not available because subsequent admissions are under different Consultants. This is in contrast to the UK system where Consultants are on service for the majority of the year and provide both inpatient and outpatient care. A lack of continuity of care or its provision has

not been evaluated as a possible factor in the difficulties of delivering health care to injecting drug users.

At present there are relatively few specialized AIDS outpatient services in New York but the AIDS teams are an improvement on the way patients are generally managed in the United States in the public sector system. When viewed from this perspective it is of course an extremely good system. However when viewed from a private health care system or a European perspective there is no doubt that it still has considerable deficiencies which could be remedied. For instance the creation of dedicated inpatient medical teams supervized by AIDS specialists as seen in some of the New York AIDS Units would provide better care for the patient without sacrificing the training of staff.

As a consequence of the enormous psycho-social problems, the drug dependence problems and the relative lack of a community network or movement to deal with these problems more than any other group the management of IDU related HIV requires a multi-disciplinary approach. IDU related HIV is a chronic debilitating disease of the young who are in addition socio-economically deprived and their care is as much about HIV as about how to deliver that care in the presence of extreme poverty.

The USA experience does emphasize the importance of a dedicated HIV service to cope with the problems. In Europe it will be necessary to further expand specialized HIV outpatient services in order to efficiently cope with the number of patients with HIV and to provide essential back-up for General Practitioners. The San Francisco experience suggests that it is more efficient to provide all the relevant specialties in one area. Thus Infectious Diseases, Oncology and Neurology should be considered in the outpatient department.

The Amsterdam Municipal Medical Health Care Service provides excellect continuity of care for drug problems but has not yet been utilized for IDU related HIV problems. This despite the fact that Amsterdam has previously used a specialized inpatient service for an epidemic of poisoned heroin. The SFGH and Amsterdam experience of using specialized substance abuse counsellors or psycho-social nurses to help the patients and staff seems to be well worth considering for General Hospitals in the UK. Alternatively inpatient services which are experienced in the care of both HIV and injection drug use are required because the problems and solutions are so different from the services already established.

In Edinburgh, a lack of specialized medical services for drug users has required the development of a service which provides not only inpatient and outpatient continuity of care but also delivers both drug and HIV services at the same site. The major concern and criticism of the situation in Edinburgh was the lack of a similar services for the HIV negative drug users. This has partly been offset by the creation in April 1988 of the Community Drug Project which had attempted to re-involve the majority of general practitioners in drug dependency.

The system used at the Montefiore Medical Centre in the Bronx and in Edinburgh of drug prescribing and HIV services delivered from the same site by the same doctors seems to provide the best model of care for injecting drug users. The San Francisco and Amsterdam experience of providing these services at two distinct physical sites reveals this to be an inefficient system providing either a poor medical and or a poor HIV service for drug users. Thus HIV and drug dependancy specialists need to exchange and acquire each others skills as well as utilizing the primary care services.

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LEADING ARTICLE

AIDS in Edinburgh drug users: observations on the epidemic and implications for its future management

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Summary

We are now witnessing the anticipated explosion of cases of AIDS resulting from the epidemic of HIV infection among Edinburgh drug users in the first half of the last decade. We expect the number of new cases of AIDS to continue to increase, although the rate at which they do so may be mitigated by intervention which slows the rate of progression to AIDS. There is evidence that current management of patients may postpone a diagnosis of AIDS until later in the natural history of HIV infection when immunity is very low as manifested by CD4+ lymphocyte counts. Health care planners need to provide resources for an increasing number of HIV-infected persons who have not yet fulfilled the definition of AIDS but who nevertheless require extensive resources both in the community and in hospital.

Introduction

In the U.K. Edinburgh has the highest proportion of drug users infected with HIV, reported seroprevalence rates being up to 65% in some groups at risk through the use of drugs.[1,2] The overall seroprevalence rate for all persons in Edinburgh between the ages of 15 and 35 years has been calculated to be 0·64%.[3] The number of drug users who have been at risk of infection is estimated to be 2000–3000, hence up to 1500 drug users may be HIV seropositive, most of these having been infected in 1983 and 1984.[1,2]

As of 30 June 1990, a total of 565 HIV seropositive drug users have been identified in Edinburgh[4] but, in the absence of widespread serological testing, it is impossible to be sure of the true prevalence of HIV infection in the community. The number of cases of AIDS, however, is more certain since these are clinically identifiable and reliably reported. They are still widely used to estimate the extent of the HIV epidemic. Most HIV seropositive persons among Edinburgh drug users have been managed at the Regional Infectious Diseases Unit (RIDU), over 400 of them having been reviewed to July 1990. This has enabled us to follow the evolution of the epidemic, not only recording the epidemiological features of new cases but also to study them immunologically. We have also assessed the impact of the current management of patients and have tried to determine its implications for future health care.

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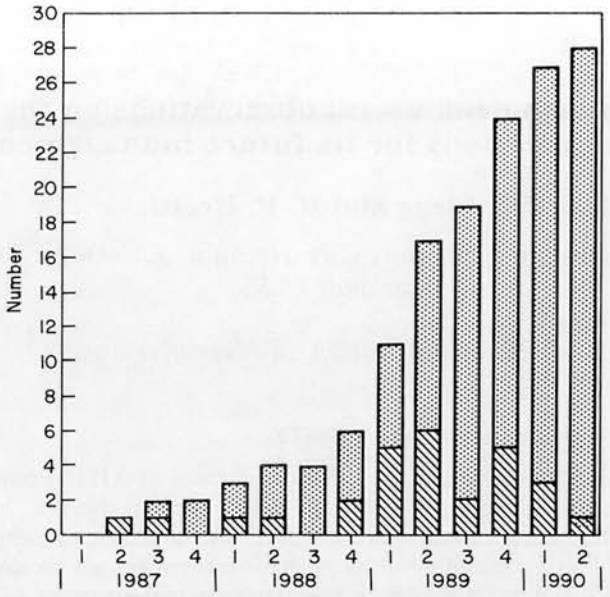

Fig. 1. Cases of AIDS by quarter of diagnosis. (▨), New cases; (▩), total cases.

Dynamics of the epidemic

By 30 June 1990, 44 cases of AIDS acquired through the use of drugs had been reported in Scotland.[5] The first case of AIDS in an Edinburgh drug user arose in June 1987. Since then, there has been a rapid rise in the number of new cases, a total of 28 cases by 30 June 1990 having been seen in the RIDU (Fig. 1). This rise closely correlates with an exponential epidemic curve ($r = 0{\cdot}98$). Analysis of the curve gives a doubling time in cumulative incidence of 7 months. The diagnoses of AIDS among the 28 cases have been made on the basis of the following conditions: *Pneumocystis carinii* pneumonia (PCP), 23 cases (82·1%); oesophageal candidiasis, three cases (10·7%); disseminated *Mycobacterium tuberculosis*, one case (3·6%); AIDS dementia complex, one case (3·6%). There have been eight (28·6%) deaths, one from PCP, two from liver failure associated with chronic active hepatitis B, one from primary cerebral lymphoma, one from AIDS dementia complex, one from disseminated cytomegalovirus infection and two as a result of a probable drug overdose associated with bacterial pneumonia.

The doubling times in the cumulative incidence of AIDS cases within the U.K. have been steadily extended from a period of approximately 7 months in 1981–1983 to 11 months in 1983–1985,[6] and 13–14 months in 1987.[7] The doubling time for the drug users seen at our unit reflects the early national rates. It has been shown that during the first few years of an AIDS epidemic the number of cases rises exponentially.[6] Hence, it should be possible to make short-term predictions of the number of future cases. When applied to the RIDU data, an exponential regression equation predicts a cumulative total number of cases of 69 by the end of 1990, and 221 by the end of 1991. A recent revision of estimates of the cumulative number of drug-related cases of AIDS

for the whole of south-east Scotland gives an 'optimistic' estimate of 109 and a 'pessimistic' estimate of 241 cases by the end of 1991.[8] Taking into account the above-mentioned from our unit alone, the number of cases of AIDS in 1991 may be closer to the 'pessimistic' prediction, assuming that an exponential increase continues as has been experienced in the early phases of other epidemics.

Even these short-term predictions, based on simple epidemiological models, may prove to be inaccurate. It is already evident from the Edinburgh AIDS data that the number of new cases has fallen from 11 in the first 6 months of 1989 to four in the first 6 months of 1990. This reduction in the number of new cases is not statistically significant and it would be unwise to read too much into figures based on such small numbers. It is probably too early to state that there is no longer an exponential rise in new cases. The small reduction may, however, be of some clinical importance as well as influence future decisions on numbers of beds and the allocation of resources.

How then can this apparent flattening of the curve of the Edinburgh AIDS epidemic be explained?

The impact of new therapeutic strategies

It is unlikely that the epidemic of AIDS has peaked in view of the many HIV-infected drug users in Edinburgh. With a median incubation period of 8–10 years between infection and development of AIDS, we would expect that the number of cases among drug users would still be increasing after only 5–7 years into the epidemic. Hence, it might be assumed that the worst is yet to come.

It is more likely, however, that changes in current medical practice are having a dramatic impact on the shape of the epidemic curve. For instance, recent advances in therapy for infected persons (such as the prescribing of zidovudine for early symptomatic disease and the prophylaxis of opportunistic infections such as PCP) may have contributed to a slowing in the rate of progression to AIDS. In our unit, primary prophylaxis for PCP in the form of nebulised pentamidine or oral co-trimoxazole has been recommended since the middle of 1989 for all persons with CD4+ lymphocyte counts persistently below $0{\cdot}2 \times 10^9$/l. Early prophylaxis for PCP is likely to benefit our HIV-infected drug users, since the incidence of PCP (82·1 %) as the AIDS-defining diagnosis among our patients appears to be greater than that found in drug users in the U.S.A. (67 %).[9] The use of regular, effective antifungal therapy in the form of fluconazole for those with recurrent oro-pharyngeal candidiasis would also be expected to reduce the likelihood of oesophageal candidiasis and cryptococcal meningitis, thereby averting fulfilment of the AIDS-defining criteria. Zidovudine therapy for persons in the U.S.A. Centers for Disease Control stage 4 (symptomatic disease) is increasingly being used and since July 1990 we have given the drug to 79 drug users without AIDS. Progression to AIDS has occurred in only five of our drug users already on zidovudine therapy. Recent data on the use of zidovudine in asymptomatic persons in the U.S.A. suggest that it delays progression to symptomatic disease and AIDS.[10] It is therefore likely to be used increasingly for this

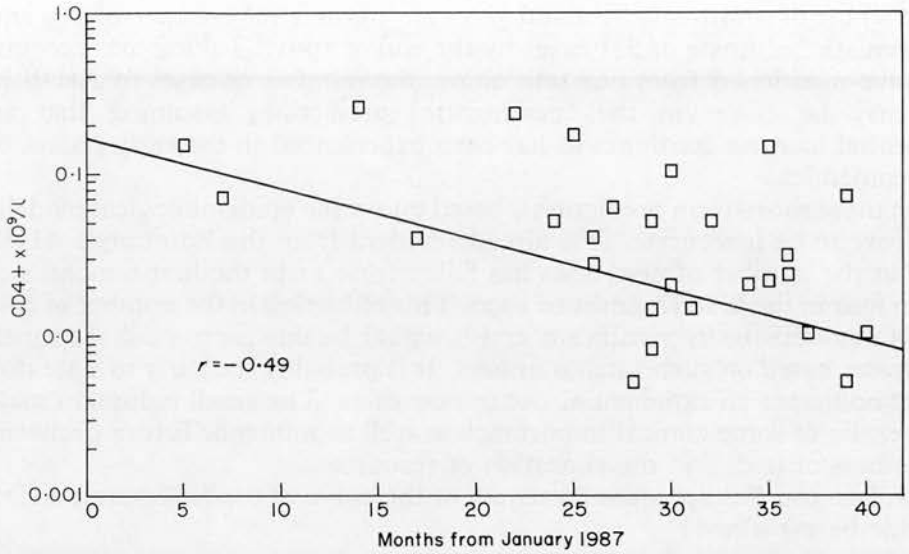

Fig. 2. CD4+ lymphocyte count at the time of diagnosis of AIDS.

purpose, so leading to further distortion in the future projected numbers of cases of AIDS.

We believe that these and other measures have contributed to fewer new cases of AIDS seen in our unit and in Edinburgh as a whole. In England and Wales, initial forecasts of cases of AIDS, as predicted in the Cox report,[11] are now judged to have been too pessimistic.[12] One of the reasons given for the departure from the predicted exponential growth of the epidemic is the effect of the introduction of zidovudine and of other improvements in the management of patients, thereby prolonging the incubation period.

Other than the falling incidence of cases is there any other evidence that the onset of AIDS is being delayed?

CD4+ lymphocyte counts when AIDS is diagnosed

We have analysed the CD4+ lymphocyte counts at the time our patients have presented with AIDS. There was a trend for CD4+ counts at that time to be lower the more recently the diagnosis was made (Fig. 2). The residuals obtained on regression analysis suggest that an exponential model fits this declining trend in CD4+ counts at diagnosis better than a linear model. These data support our hypothesis that the recent improvements in the management of patients are delaying the onset of AIDS. It would appear that 'early' opportunistic infections indicative of AIDS, such as PCP, are being postponed until a later stage in the natural history of HIV infection when CD4+ counts have declined even further. At this point, an opportunistic infection such as PCP breaks through despite prophylaxis or an alternative AIDS-defining condition develops. Indeed, it is remarkable how low the CD4+ counts may fall in some patients who have not yet developed any indicator disease. Currently, we are studying several persons with such counts persistently

$< 0{\cdot}02 \times 10^9/l$ and who have not yet developed an AIDS-defining illness. Unfortunately, analysis of CD4+ counts over a peirod of time for the cohort as a whole suggests that we have not altered the underlying immune deficiency state by improved management of patients since counts are continuing to fall at the same rate (unpublished observations).

Future implications

The term 'AIDS' often implies a rather loosely defined advanced stage of HIV infection. Furthermore, the incubation period is highly variable and subject to many influences. A diagnosis of AIDS, therefore, is a relatively artificial end-point and perhaps should not be used to study the dynamics of the HIV epidemic. Rightly or wrongly, however, identified cases of AIDS remain the most commonly used indicator for studying the evolution of the epidemic. Their numbers alone often provide the basis for future planning of health care. We believe that, in developed countries, monitoring of CD4+ counts may provide a better way of identifying patients who need interventive management than reliance upon clinical markers of progression to AIDS.

As far as future planning of health resources is concerned, the apparent reduction in the number of new cases of AIDS in drug users should not give rise to undue optimism. It is true that delay in an individual's fulfilment of the AIDS diagnostic criteria will have some benefit, both for the patient (who may have a better quality of life) and for the providers of health care (since the number of admissions to hospital may be reduced). Even so, the medical requirements of these HIV-infected persons will not diminish since they will continue to need intensive monitoring and interventive therapy as outpatients. It may be that the costs of community and outpatient hospital care for HIV infection, extended over a period of many years before a therapeutically delayed onset of AIDS, will be greater than the current lifetime costs of caring for a patient with AIDS.

The apparent reduction in the number of new cases of AIDS that we have reported in Edinburgh may lead health care planners to reduce financial outlay for HIV infection. Currently, funding is linked directly to the number of cases of AIDS and not to the number of persons infected with HIV. In the long-term, this will be detrimental to patients and will deprive them of many essential services because budgets will have to be stretched to provide the needs of the increasing number of HIV-infected persons who have not yet developed AIDS but who require expensive care.

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EDITORIAL REVIEW

HIV and harm reduction for injection drug users

Ray P. Brettle

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Keywords: Harm reduction, HIV, injection drug users, methadone, needle exchange, outreach programmes, safety, limitations, efficacy.

Introduction

Drug-use-related HIV is a continuing problem not only for important areas of the developed world, such as the USA and Europe, but also for countries in the developing world, such as east Asia and South America. It is a crucial issue because drug-use-related HIV in Europe, for example, is the fastest growing risk and, in addition, is associated with substantial vertical and heterosexual spread of HIV. A number of studies in the USA and the UK have shown that between 60 and 100% of heterosexually acquired HIV is related to injection drug use and that at least 40% of injection drug users (IDUs) are in relationships with non-users [1–4]. Approximately one-third of IDUs are female and so vertical spread to newborn children occurs [4–6]. Consequently, the reduction and control of drug-use-related HIV can have a substantial impact not only on transmission amongst drug users but also on the heterosexual and vertical spread of HIV.

The major public policy issues concerning the prevention of drug-use-related HIV are persuading society and governments (1) that drug use is a key element in the spread of HIV, (2) that AIDS is a greater threat than drug use itself, (3) that harm reduction as a strategy in preventing the acquisition of HIV is compatible with the aim of primary drug-use prevention and (4) that there is no single measure, such as methadone, needles or bleach, that constitutes a harm-reduction strategy; i.e. harm reduction must be multifaceted.

The importance of drug use in the spread of HIV was underlined by the Presidential Commission on HIV in the USA, which recognized that 'the future course of the HIV epidemic depends greatly on the effectiveness of our nation's ability to address IV drug use' [7]. In the UK, the Advisory Council on the Misuse of Drugs, in its report on AIDS and Drug Misuse, warned that 'the spread of HIV is a greater danger to individual and public health than drug misuse. Accordingly, we believe that services which aim to minimize HIV risk behaviour by all available means should take precedence in development plans' [8]. Thus, it is important to develop drug therapies and care systems that address the problems of injection drug use-related HIV and to reconsider our approach to drug use in the light of HIV. This new position was recently summarized by John Strang and Gerry Stimson [9], who said that 'we are at a point of change — a point of crisis between old ways of viewing drug problems and new ones forced on us by HIV'.

Before the advent of HIV infection, drug use itself had a relatively low mortality rate because of alternating periods of abstinence and drug use, and natural recovery [10–13]. In New York, however, there was a rapid increase in both AIDS and non-AIDS narcotic-related deaths such that by 1986, for every AIDS-related death in a drug user, there was one other as a consequence of such conditions as tuberculosis, endocarditis and bacterial pneumonia [14]. Similar data have been reported from Europe [15,16]. This increase in mortality for drug users is the driving force behind harm reduction and the reason we can no longer rely on spontaneous recovery for drug users.

Harm reduction was recently described thus: 'the harm minimization approach echoes the safer sex campaigns ... people will not want to abstain from sexual activity, therefore they must be encouraged to engage in safer sex. The idea has now been extended to drug injectors — if they won't stop injecting, they should and could inject drugs in a safer way' [17]. There are legitimate but unproven concerns, however, that harm reduction for injection drug use-related HIV will help to initiate new drug users. Similar concerns are voiced about increasing the

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availability of drug-injecting equipment or teaching safer injecting techniques.

The intense debate over injection equipment availability, especially in the USA, has interesting parallels with the debate that surrounded methadone maintenance treatment programmes (MMTP) in the management of drug dependency. In 1957, the Council on Mental Health of the American Medical Association concluded that 'The advisability of establishing clinics ... to dispense opiates to addicts cannot be settled on the basis of objective facts' [18]. This debate was in fact primarily centred on the health of society rather than that of an individual and is still continuing [19]; the question is whether we can wait for definitive proof where HIV is concerned.

Previous reviews have tended to concentrate on only one harm-reduction modality such as methadone or injection equipment availability [20,21]. This review seeks to examine not the evidence for and against harm reduction with regard to the treatment of drug dependency, but whether harm reduction can have a substantial impact on the spread of HIV. It is necessarily biased because the author is an infectious disease physician concerned with the problem of HIV and AIDS rather than a specialist in drug dependency.

The history of harm reduction

Methadone maintenance treatment programmes

The use of methadone, a long-acting opiate, allowed the development of maintenance programmes because they were no longer based on the self-administration of opiates. MMTP have been evaluated frequently since their establishment, but studies have concentrated upon retention rates, frequency and prevention of illicit drug use, reduction of criminal behaviour, the return to normal social activities and/or the possibility of curing drug use [18,19,22–26]. MMTP were seen very much as harm reduction for society, usually in terms of the reduction of crime or social reintegration of drug users. Harm reduction for the individual was considered in terms of psychosocial issues such as emotional stabilization, improved work record or retention in the programme.

Whilst some improvement in physical health was assumed, it was rarely mentioned in reports other than with respect to the safety of methadone maintenance [18,19,22–26]. For instance, reports of the medical side effects of methadone such as constipation or the death rate were published but measures of improved physical health were not [26]. In addition, the initial criteria for selection into MMTP concentrated on defining addiction and specifically excluded patients with serious medical problems, although separate programmes for patients with tuberculosis eventually were established [18,19,22,26]. Lack of venous access or health problems related to injection drug use were not considered entry criteria.

Amsterdam

The concept of harm reduction for physical health grew out of Amsterdam's approach to the drug problem. Amsterdam's approach to injection drug use recognizes the fact that it is a relapsing disease and that harm reduction means providing medical and social care whilst waiting for natural recovery from injection drug use in order to avoid some of its more harmful consequences [27,28].

Amsterdam's programme of drug treatment has three levels described as low, middle and high threshold. The methadone bus is the low-threshold system, the methadone clinics are the middle-threshold system and drug detoxification, therapeutic communities, etc., the high-threshold system. The low-level system has few restrictions concerning the use of other recreational drugs whilst the high-level system is very strict.

Needle exchanges in Amsterdam began in 1984 after the Junky Union (a voluntary organization representing drug users) agitated for and then initiated the first needle exchange [27,28]. There were initially 10 centres for distributing needles, which included the methadone bus, methadone outpatient clinics and the Junky Union, although the latter site now has been discontinued. There was no enrolment or clinical examination but this was eventually instituted in order to evaluate the return rate of equipment.

Amsterdam takes a pragmatic and non-moralistic attitude towards drugs and this has resulted in a pleuriform system which now offers harm reduction and/or anti-drug-free treatment. The primary goal was to make contact, to provide information on a personal level and to produce attitudinal and behavioural change through the use of condoms, drug-free treatment programmes with short waiting lists, methadone and needle-exchange systems.

The link between injection drug use-related HIV and equipment availability

Whilst there is as yet no direct evidence that increased injecting equipment availability stems the tide of injection drug use-related HIV, there is evidence of what happens when the supply is very limited. Edinburgh has perhaps one of the best documented examples of a temporal relationship between a policy of restricting injecting equipment and subsequent epidemics of hepatitis B and HIV. The epidemic of injection drug use started in Edinburgh around 1980 and peaked in 1983–1984 [29–31]. Drug users had no prior tradition of injecting heroin and knew little about how to avoid the complications of injection drug use. Further evidence for this injection drug use epidemic and the associated sharing of injecting equipment is provided by the concurrent epidemic of injection-related medical conditions, including hepatitis B, between 1980 and 1985 [32].

Drug users reported that needles and syringes were in short supply from around 1981/1982 to 1985 when a surgical supplies shop ceased trading and pharmacists were generally unwilling to supply drug users. In an attempt to restrict the injection drug use epidemic in 1982 the pharmacists' professional association advised its members to restrict needle/syringe sales to those indi-

viduals requiring them for therapeutic reasons [33–35]. Users also reported that equipment was commonly removed from them by the police during searches and then destroyed. Possession of equipment contaminated with heroin could be used as evidence of illicit use and users might then give evidence against a supplier. This resulted in suppliers forcing users to use drugs on site so that on leaving the premises they were free of any incriminating evidence. Because of the limited supply of equipment, considerable sharing occurred; for instance, only one or two sets of equipment were available for all a drug pusher's (dealer's) clients, which could number from 20 to 40 users. There were also large gatherings of users, from five to 20, in the style of American 'shooting galleries', in which one set of equipment was passed aroung the group.

Glasgow has a smaller injection drug use-related problem despite a larger number of drug users than Edinburgh, and comparisons of self-reported habits between Edinburgh and Glasgow or Edinburgh and London reveal considerably more sharing of needles and syringes in Edinburgh [5,30,36,37]. The absence of an epidemic cannot necessarily be used as proof of effectiveness, but it is interesting to note that many conurbations in England and Wales with larger drug populations than Edinburgh have not had an HIV epidemic. In the main, these areas did not restrict equipment availability, and some areas, such as Liverpool, had a well-developed strategy for dealing with drug users which enabled them to adapt rapidly to the problem of HIV [38]. In 1986, as a consequence of the AIDS epidemic, the restriction on the sale of needles and syringes imposed by the pharmacists' professional association was withdrawn [33,34]. The Advisory Council on Drug Misuse in its report on AIDS and Drug Misuse in 1988 noted that 'the opportunity to take preventative action must be seized now if the tragedy of Edinburgh is not to be repeated throughout the UK' [8].

Similar restrictions on equipment availability existed in other countries such as Australia and New Zealand until 1987 and 1988 [20,39]. They remain in force in many parts of the USA where the connection with blood-borne virus epidemics amongst drug users has not been so well documented [20].

A significant link between needle sharing and the risk of acquisition of HIV has been established [6,31,36,40–46]. More recently, HIV has been cultured from needles and syringes collected from a shooting gallery in Miami, Florida, confirming the infection risk [47]. Less well recognized is the importance of the type of drug used; for instance, links between HIV infection and the use of intravenous cocaine or amphetamines have been reported [48–56]. Drug users often inject cocaine mixed with heroin intravenously far more frequently than heroin alone [4]. The sharing of equipment seems to be associated more often with cocaine use and the difficulty in obtaining such equipment [57–60].

Is harm reduction effective?

Whilst there is strong and compelling evidence linking the spread of HIV amongst drug users with the use of contaminated equipment, is there any evidence suggesting that harm-reduction measures are effective in preventing the spread of injection drug use-related HIV or even in changing high-risk drug-use behaviour?

Methadone

There are data which support the effectiveness of oral opiate substitute programmes in reducing high-risk injecting behaviour as well as reducing the risk of acquisition of HIV or AIDS.

Modification of injecting behaviour

In a 3-year study of MMTP in New York, Philadelphia and Baltimore, 71% of clients who remained in MMTP for more than 1 year gave up injection drug use [61]. By comparison, 82% of those who left the programme continued to inject drugs, and 10% of clients in MMTP shared equipment during the study period compared with 27% amongst dropouts. This latter figure increased to 48% once individuals had been out of treatment for more than 1 year. In the Treatment Outcome Prospective Study organized by the National Institute on Drug Abuse (NIDA), 4184 clients from 12 MMTP, 2891 clients from 14 residential programmes and 2914 clients from 11 outpatient drug-free programmes were interviewed on admission between 1979 and 1981. One-year follow-up interviews were reported on 1310 clients from 1979, and 2300 clients from 1980 [62]. Whilst none of the treatment approaches had much effect on cocaine use, continuous long-term maintenance methadone was the most effective method of reducing the risk of heroin use, 74% effective compared with 68% for residential treatment of more than 3 months and only 56% for outpatient drug-free treatment. These differences were statistically significant at $P < 0.001$ level. The authors' conclusion was that the decline in regular drug use after treatment, particularly for longer treatment stays, indicate that drug-use treatment can be effective in reducing major risk behaviour for HIV [62].

Another New York study looked at clients on the waiting list for MMTP [63]. These clients were randomly divided into two groups, one which received counselling, methadone and biweekly urine toxicology, and another which received counselling and biweekly urine toxicology only until they were admitted to the regular MMTP. Initial needle use was identical for each group at 95 injections per month, but at entry into MMTP only 33% of those on methadone were injecting compared with 82% of those in the counselling group. In San Francisco self-reported needle sharing amongst 7660 drug users admitted to 28-day outpatient methadone detoxification clinics decreased from 50% in 1986 to 28% in 1988 ($P < 0.001$) [60]. A study of 42 HIV-positive individuals in a San Francisco MMTP assessed via self-reporting as well as urine tests and clinical examination, found that heroin use decreased significantly during the first 3 months, and that the early gains were generally maintained 12 months af-

ter entry ($P < 0.0001$) [64]. A Seattle study noted that individuals in MMTP for more than 6 months shared needles less than those who were in treatment for less than 6 months, and a study of New York and New Jersey drug users in MMTP noted that older users with more years in treatment were more likely to have changed their needle-cleaning habits [60,65]. In West Germany the majority of 30 HIV-positive drug users in MMTP stopped injection drug use whilst in Vienna, of 180 drug users in MMTP, more than one-third of poly-drug users and more than one-quarter of HIV-positive drug users were using only methadone after an average of 11.2 months of treatment [66,67].

Effect on HIV acquisition

A survey of 28 MMTP clinics in New York City revealed that HIV seropositivity in established clients was 27.2% compared with 45.9% in new clients [68]. In 68 long-term MMTP patients in New York with a mean length of treatment of 16.9 years but 10.3 years of injection drug use before enrolment none had HIV antibodies [69]. In San Francisco there was a significant difference between HIV serostatus for individuals in MMTP for more or less than 60 months (8 versus 14%, $P < 0.001$), although this difference was only for white and Hispanic drug users [70]. There was, however, no difference for black drug users. This is a matter of concern because it further underlies the fact that behavioural characteristics of drug users vary with race and geographical location and must be taken into account in harm reduction [71].

In Swedish MMTP, the HIV seroprevalance was only 3% for those admitted in 1983, 16% for those admitted in 1984–1986, and 57% for those admitted in 1988, suggesting a highly protective effect for the acquisition of HIV related to MMTP [72]. In Geneva, the HIV seroprevalence for those admitted to MMTP before 1980 was only 12% compared with 47% between 1980 and 1986 ($P = 0.02$) [73]. In addition, the HIV seroprevalence of drug users admitted to MMTP between 1987 and 1989 had fallen to 22%, coincident with a dramatic fall in needle-sharing behaviour, which fell from 90 to 5% for HIV seropositives and from 80 to 29% for seronegatives. During this time only one out of 155 seronegative patients seroconverted to HIV, suggesting that MMTP is able to modify high-risk injection drug use-related behaviour [73]. Similar results were obtained from another methadone programme which demonstrated prospectively a reduction in high-risk behaviour and a correspondingly low seroconversion rate for HIV [74]. HIV serostatus was recently evaluated for low-threshold MMTP in Amsterdam, which enables contact to be made but has little in the way of counselling, and showed that long-term clients did not have lower HIV seroprevalence [75].

Effect on progression to AIDS and immune activation

There is a suggestion that continued injection drug use may accelerate progression of HIV to AIDS. One study reported a relationship between the frequency of injection drug use and the loss of CD4 lymphocytes, whilst another study noted a similar increased rate of decline of CD4 lymphocytes amongst a group of injectors compared with a group of non-injectors [76,77]. There was also a lower probability of disease progression amongst methadone users or ex-users compared with those that continued injection drug use reported from Switzerland. Progression to AIDS after 3 years was 24% in the methadone group, 19% in the ex-users, but 41% in the persistent injection drug use group ($P < 0.05$). Multivariate analysis showed a relative risk of 1.76 for persistent users [78]. However, other groups have not found an increased risk for continued injection drug use [79–81]. The incidence of AIDS in the Bronx was reported to be lower (11.4 versus 33 per 1000 patient years) for entrance to the Montefiore MMTP before and after 1983 [82]. Similarly the proportion of drug users attending MMTP in Italy was inversely related to the cumulative incidence of AIDS. The highest AIDS incidence rates were seen in the regions with the lowest proportions of IDUs attending MMTP. Nearly 40% of the variability of AIDS incidence was explainable by attendance in MMTP [83]. The reasons why continued drug use might predispose a drug user to accelerated immune decline are unknown, but one suggestion is that the drift in molecular composition demonstrated in different HIV isolates could result in an individual acquiring more infection with differing strains of HIV, which might hasten disease progression [84].

Another possible explanation is that injection drug use itself significantly affects the immune system; for instance, frequent injection drug use was associated with depressed lymphocyte function irrespective of HIV serostatus. Injection drug use has been associated with higher levels of β_2-microglobulin and activated T cells, and injection drug use-related HIV is associated with more immune stimulation [85–88]. HIV serostatus may not be known for most patients, and therefore measures such as the cessation of injection drug use, if necessary via MMTP that are thought to reduce progression to AIDS, should be applied to all drug users.

Harm reduction measures

Injecting equipment

The most controversial harm-reduction measure, especially in the USA and certain parts of Europe, surrounds the availability of sterile injecting equipment.

Modification of injecting behaviour

It appears that drug users change their high-risk injecting behaviour if given both information and equipment. In Amsterdam this behaviour change was more effective and more likely to occur in the context of individual counselling than in the context of mass campaigns [89]. Specifically, over time there was a reduction in risk behaviour amongst those enrolled in a cohort study but no reduction over the new entrants to the cohort. Others have shown that information and counselling alone can produce risk reduction but equipment alone seems not to be enough, since in New Orleans and Portland, Oregon, areas where needles are not controlled by prescrip-

tions, needle sharing still occurred [90–92]. Similarly the widespread availability in Italy of sterile injecting equipment and water, which was introduced as a preventative strategy to combat the injection drug use-related hepatitis B epidemic in the mid-1970s, failed to prevent not only hepatitis B but also the spread of HIV [93].

Behaviour change has, however, been shown to occur more often amongst attenders of needle exchanges than amongst non-attenders. In Amsterdam only 10% of attenders were sharing equipment in the previous 6 months compared with 24% of non-attenders. Similarly, 74% of attenders were using equipment only once, compared with 27% of non-attenders [27,94]. Comparable results have been reported from Glasgow, Scotland, where less risk reduction occurred amongst individuals obtaining supplies from pharmacies compared with needle exchanges [96].

Partly as a consequence of the Amsterdam experience, UK practitioners began to exchange injecting equipment and, under pressure from the Scottish Home and Health Department report, HIV in Scotland (McClelland report), which called for greater availability of injecting equipment, the UK Government set up 15 experimental needle exchanges in early 1987 which have now been evaluated [97–100].

The final report on 2449 clients concluded that these schemes reached a considerable number of IDUs, the majority living within 2 miles (3.2 km) of the schemes. Forty per cent had never been in a treatment programme and nearly 75% were not in a current treatment programme. The attenders were, however, older opiate users with a mean age of 27.8 years, mostly male (78%) and with an initial lower level of risk behaviour compared with injectors who did not attend. For instance, only 36% had shared equipment within the previous 4 weeks and only 19% had shared with more than two individuals in the last 4 weeks. By comparison, 62% of a group of non-attenders were injecting in the previous 4 weeks and 36% with more than two individuals. Thus, non-attenders at exchange schemes had riskier injecting behaviour despite the fact that this sample was interviewed after the Government's publicity campaign. The most commonly reported reason for sharing was the difficulty in obtaining equipment, a reason which did not differ between attenders or non-attenders. Non-attenders, however, paid more attention to the cleaning of equipment than the attenders.

The major problem for needle exchanges was the poor retention rate, which varied from as low as 25% in some centres to as high as 85% at others of clients returning for a second visit. The average retention rate was 61% for the second visit, falling to 17% for the 10th visit and only 1% returning for more than 40 visits. The exchange rate also varied from 23 to 100% with a mean of 62%. The number of syringes/needles issued per visit varied from three (the legal maximum per visit in Scotland) to 30, with a mean of nine per visit.

Amongst clients who continued to attend there was evidence of self-reported reduction in needle-related risk behaviour. For instance, sharing in the previous 4 weeks declined from 34 to 27%, and the percentage sharing with two or more individuals declined from 17 to 11%. Over 70% of attenders and non-attenders reported that as a consequence of AIDS they had made some change in their drug use, usually a reduction in sharing or an increase in using clean equipment.

Interestingly, clients in Scotland, possibly because the schemes ran under stricter legal controls with fewer needles and syringes given out per visit and shorter opening hours, showed greater sharing compared with their English counterparts. For instance, 76% of Scottish injectors had shared equipment in the previous 4 weeks compared with only 52% of English injectors. In Scotland injectors found equipment harder to obtain and were more likely to find exchanges closed or to share in custody.

An evaluation of a central London exchange scheme was able to demonstrate after 3 months a fall in median injecting from 56 to 48.5 per month ($P < 0.001$), sharing from 15 to 11% of the time, equipment borrowing on two or more occasions from 8 to 6% and equipment lending on two or more occasions from 10 to 6% [101]. This improvement in high-risk behaviour was associated with a self-reported decrease in skin abscesses in the previous 3 months from 14 to 9% [101].

The first North American needle-exchange scheme in Tacoma, Washington State, was also able to demonstrate change toward safer injecting practices. Lending equipment either to a close or casual friend significantly declined from 64 to 44 times per month and 48 to 32 times per month, respectively ($P < 0.05$) [102]. There are reports that stimulant users, who are known to inject more often and to be more at risk for HIV, are additionally more resistant to behaviour change, an important area that requires additional information [96].

Effect on acquisition of HIV

Diabetic drug users in Baltimore were noted to have a lower-than-expected incidence of HIV, which may be explained by these individuals' preferential access to clean injecting equipment [103].

Data are emerging which show that needle exchanges can prevent acquisition of HIV. These data are mostly in the form of stable HIV prevalence rates over time and it is difficult to use the absence of an event as positive data. For instance, in London the prevalence of HIV in attenders at a needle exchange was 6% initially and 7% after 1 year of follow-up [101]. In Australia the seroprevalence as judged by anonymous testing of returned equipment remained stable at 1.5% in 1987 compared with 1% in 1986 [104,105]. The seroprevalence rates in Amsterdam have risen from 3.4% in 1983 to between 27 and 31% in 1987, even in the face of harm reduction [27]. But how fast would the seroprevalence of HIV have risen without these measures and how much of this is new infection as opposed to the movement of infected IDUs into Amsterdam? Careful longitudinal studies are required to answer these questions.

Outreach education, intervention programmes and cleaning of equipment

One of the major criticisms of harm-reduction measures based on treatment facilities is that many drug users are not in contact with treatment facilities. Amsterdam's Municipal Health Service Drug Department (GG&GD) is unusual because it is in contact with least 70% of its estimated 6000–8000 drug users [27,28]. Unlike the gay community, collective organizations of drug users with an educational role have not flourished with the exception of the Junky Union in the Netherlands [27,28].

Modification of injecting behaviour

Outreach intervention programmes have been developed most extensively in the USA, probably as a consequence of the early involvement of drug users in the AIDS epidemic, the paucity of treatment facilities and the political climate in relation to either increased treatment facilities or other harm-reduction measures [106]. In the early 1980s New Jersey began to hire ex-addicts to teach safer injecting techniques, which resulted in increased demand for drug-treatment facilities. New Jersey had instituted fees for drug treatment in the early 1980s but, in response to the increased demand, began to issue coupons for free treatment through outreach workers. Of 1 884 drug users interviewed by the Newark and Jersey City Health Behavior Project, 49% subsequently entered methadone treatment programmes [107]. Outreach intervention programmes were also developed in San Francisco and New York City to provide basic information concerning safer injecting practices initially, and then to distribute condoms, cleaning solutions and even injecting equipment, despite the fact that this latter event remains illegal [106]. In San Francisco the early message of 'Don't Share Needles!' utilized by the Haight-Ashbury Free Medical Clinic in 1983 was extended by the San Francisco AIDS Foundation in 1985 into a larger campaign to raise the general consciousness of drug users towards AIDS [108]. This was then augmented by the use of Community Health Outreach Workers (CHOW) to develop trusting relationships with drug users and deliver both the message and simple practical help in the form of bleach [108].

The campaigns to teach cleaning of injection equipment have concentrated on commonly available disinfectants such as bleach, alcohol, and detergent. Whilst whole blood is protective against disinfection of HIV, dilute household bleach, 70% isopropyl alcohol and dilute detergent remain effective even in the presence of whole blood, and such compounds should be available to the majority of injection drug users [109,110]. Street-based education, utilizing CHOW and free 1-ounce (28.4 g) bottles of bleach have successfully improved 'safe' needle hygiene [108,111,112]. In San Francisco the combination of CHOW and bleach raised the use of bleach for equipment cleaning from 3 to 76%. Compliance with the bleach disinfection protocol was associated with access to CHOW [108].

A NIDA-funded study of drug users not enrolled in treatment was able to demonstrate that outreach and intervention could influence entry into drug treatment and reduce high-risk drug-injecting behaviour [107]. The study enrolled 30 000 drug users and their sexual partners, and the preliminary report was on 1584 injection drug users, the majority black and male, in five US cities (Chicago, Houston, Miami, Philadelphia and San Francisco). The recruitment was via CHOW and those eligible were those injecting drugs for at least the previous 6 months and not enrolled in a treatment programme during the previous 1 month. The interventions used included some or all of the following: both individual and peer counselling, efforts to build peer support for behaviour change, demonstrations and practice of safer injecting techniques. The safer injecting practices that were encouraged included not sharing equipment, use of sterile equipment and or the cleaning of equipment with disinfectants. At follow-up 6 months later, 14–35% of the drug users had entered a drug-treatment programme, and between 49 and 75% reported either stopping or reducing their frequency of drug injecting. Amongst those who continued to inject 20–39% reported an increase in the cleaning of equipment. There are also data to suggest that intervention programmes improve the behaviour of users not directly involved in the programmes [107].

Much more in the way of outreach and contact is required, however, because in a study of over 15 000 US drug users, whilst 85% were aware of the benefits of clean equipment only 17% always cleaned their equipment and only 20% always used new equipment, leaving 63% using high-risk injecting techniques [113].

Effect on acquisition of HIV

There are as yet few scientific data to prove that outreach is effective in preventing injection drug use-related HIV, although it is popular with clients. In San Francisco, where individuals self-reported an improvement in risk behaviour, this improvement was noted to coincide with an aggressive prevention campaign directed at drug users which began in mid-1986. Subsequently, a levelling off of the hepatitis B and HIV seroprevalence curves has occurred amongst drug users [114,115]. Similar stabilization of HIV incidence in drug users has been reported from Baltimore and Amsterdam [116,117]. It may be that campaigns detailing cleaning techniques could be used effectively in areas such as prisons where needle exchange is unlikely to occur for security reasons. Perhaps the innovative use of graffiti, demonstrated to be effective at reaching drug users in Denver, should be considered by others [118].

Skin cleaning, whilst not protective for HIV, has been shown to reduce the risks of endocarditis and skin abscesses. In 110 active drug users in San Francisco reporting on skin cleaning and past infections, only 4.2% of those who skin-cleaned some of the time reported endocarditis compared with 14.5% in those who did not skin clean. Forty-eight per cent of those who never skin-cleaned had suffered skin abscesses compared with 24% for those who sometimes cleaned [119]. In view of the seriousness of these infections, harm-reduction measures for bacterial infections are needed, especially for HIV-

seropositive users, in view of their increased susceptibility to bacterial infections [120–122].

Safety of harm reduction

A major concern of harm reduction for HIV is the concern that it may encourage existing as well as primary or new drug use. There was no evidence of an increase in the total number of IDUs as a consequence of one needle-exchange programme [123]. Neither do needle exchanges appear to encourage more drug use amongst existing users. In Amsterdam those attending exchanges were compared with those recruited from other areas such as hospitals or police stations. Only 29% of attenders compared with 50% of the non-attenders had increased their injecting during a 6-month period [89,94]. Similarly, increased injection behaviour in attenders was not reported in UK exchanges [20,97–101]. The opening of a needle-exchange scheme next door to an MMTP did not increase or decrease the number of illegal substances found in the urine of the MMTP patients [124].

Reports from Amsterdam have also shown that new users, that is people who had never injected before, were not attracted into the system. The mean age of those attending rose with time from 26.4 years in 1981 to 30.1 years in 1987 and the proportion under 22 years fell from 14.4 to 4.8% [27]. If new, younger users were being attracted to drug use, one would expect the average age of the group to fall with time. The length of injection drug use was also greater at 9 years for exchangers compared with 7 years for non-exchangers [27]. Comparable data have been reported from the underground needle-exchange scheme in San Francisco [114]. The use of bleach for disinfection of injecting equipment has met some resistance, especially in the UK on the grounds of safety, despite the fact that even full-strength bleach has been shown to be relatively non-toxic when injected intravenously in small amounts [125].

Reasonable return rates have been recorded even for underground and illegal exchanges, although static sites were better than mobile sites (60 versus 30%) [126]. Return rates and public safety can be assured by public-health initiatives such as disposal bins in public places and by providing portable plastic disposal containers to exchangers. These techniques increased the return rate from 25 to 64% over 14 months in Sydney [127]. More importantly, there are studies on the infectivity of discarded needles which suggest that lymphocytes can only be infected with HIV from needles exposed to room temperature for 4 h or less [128].

Limitations of harm reduction

Harm reduction for injection drug use is not the only solution for injection drug use-related HIV, but it is a useful intermediate goal, although for many, progression beyond safe injection drug use or oral opiate therapy is unlikely [123]. It is important to remember that injection drug use itself is an immunostimulant which, in the context of HIV, is a disadvantage, and that opiates not only increase susceptibility for bacterial infections but also promote the growth of HIV in cell cultures [85–88,130].

Blanket harm-reduction measures applied in the absence of effective counselling and health education are not effective in achieving behaviour change. Needle sharing still occurred in New Orleans and Portland, Oregon, despite the fact that needles were not controlled by prescriptions [91,92]. Similarly, the widespread availability in Italy of sterile injecting equipment and water, which was introduced as a preventative strategy to combat the fast-growing heroin and hepatitis B epidemic in the mid-1970s, failed to prevent not only hepatitis B but also the spread of HIV [93]. The data from Amsterdam would suggest that it is not methadone availability alone that is protective but the programme as a whole, whilst the data from New York suggests that counselling alone is equally ineffective [63,75,89].

The development and marketing of harm-reduction strategies also has to take into account the particular drug problem prevalent in a community, as well as the demographic and legal characteristics of that community. For example, MMTP are not successful in managing stimulant drug problems, or, it seems, in preventing the acquisition of HIV in black drug users in San Francisco. In those circumstances other measures such as clean equipment or the distribution of stimulants in a non-injectable form might be more effective, but one also has to remember the variations in safe injecting practices in differing racial groups around the USA [62,70,71,131]. In an assessment of 7835 out-of-treatment injection drug users in 15 US cities, blacks in the northeast and the west reported significantly ($P < 0.05$) greater use of new needles than whites or Hispanics whereas in the southwest both blacks and Hispanics were reporting the use of more new needles than whites [71]. In the same study the use of cleaning agents was significantly ($P < 0.05$) more likely amongst blacks in the northeast or blacks and whites in the southwest and west [71]. In the UK the original needle exchanges failed to attract young or female IDUs and were less effective at reducing high-risk behaviour in Scotland, presumably because of greater legal restrictions [98–100]. Only time will tell whether behaviour change brought about by harm-reduction campaigns can be maintained, although individuals retained in the UK needle exchanges continued to modify their behaviour [99,100].

Despite major efforts with the homosexual community there is evidence that the incidence of rectal gonorrhoea is rising again. This suggests that the safe sex message with regard to anal intercourse has not been maintained [132]. Harm reduction for injection drug use cannot prevent sexual transmission of HIV and, in many communities such as the UK, the rate of increase in heterosexual AIDS has equalled or overtaken the rate for injection drug use-related AIDS [133,134]. It appears that the gen-

eral heterosexual population, as evaluated by the sexual behaviour of college women in the USA between 1975 and 1989, has not as yet changed significantly [135]. It is not surprising therefore that drug users are slow to take on board the need to modify sexual behaviour.

Outreach programmes, especially those based on ex- or stable drug users, also have their problems. Whilst outreach may be viewed as work and part of a drug user's reintegration into society it often suffers from being part-time, associated with low pay and a high turnover of staff. There is also the concern that the ex-drug user will be drawn back into drug use as a consequence of the work. There are no estimates of the risks involved for such workers, but they are not considered insubstantial. This must be taken into account in the overall cost benefit analysis of such harm reduction programmes [106].

Perhaps the major limitation concerning injection drug use harm reduction concerns the methodology used to assess its effectiveness. Much of the work quoted here is only in abstract form and close scrutiny of methodology is impossible, although the studies do illustrate the speed of change and the recent nature of the work.

The evidence concerning the MMTP and the acquisition of HIV is mostly retrospective but consistent differences continue to emerge. Prospective data on the effectiveness of MMTP with regard to low rates of acquisition of HIV, corroborated with a self-reported reduction in high-risk behaviour, are now available [68–70,72–74].

Many of the data from needle exchanges and outreach intervention programmes on behaviour change for IDUs are, however, subject to the criticism that they are based on purely self-reported behaviour change. Such studies often do not assess the changes that occurred in a control group and are thus unable to distinguish general from specific behaviour change. The evaluation of the UK and Amsterdam needle exchanges did attempt such assessments [27,89,94,98–100]. There are as yet few prospective data available on the acquisition of HIV. San Francisco, however, has noted a fall in annual seroconversion rates amongst drug users from 9 to 3% as a consequence of a general media campaign, HIV testing, increased availability of drug treatment and outreach programmes [136]. The newer and, one must hope, more acceptable methods of anonymous testing, such as salivary or urine HIV testing or HIV testing of blood from returned injecting equipment, need to be utilized to assess the effectiveness of intervention campaigns [101,104,137–139].

Self-reported data are used for assessing the sexual behaviour changes of heterosexuals or homosexuals but are usually backed up by more objective measurement parameters such as rates of sexually transmitted diseases or rectal gonorrhoea [132]. Injection drug use-related research needs to find similar objective measures of reduced risk behaviour. Frequency of injection drug injuries and/or skin injections can be used as markers of injection drug use. A self-reported decrease in abscesses was associated with self-reported reduction in injection drug use [101]. Serum β_2-microglobulin levels have recently been shown to be increased in HIV-negative drug users compared with non-drug users. They are also increased in HIV-positive IDUs compared with HIV-positive non-IDUs [85–88]. Whilst absolute levels in HIV-positive individuals could not differentiate injectors from non-injectors, trends would provide confirmation of self-reported behaviour change. Hair analysis has been shown to be an effective method of detecting drug use and could be utilized on a wider scale to corroborate self-reported behaviour change [140].

Another major difficulty is finding objective measures of reduced equipment sharing as opposed to injection drug use. Hepatitis B infection rates are sometimes quoted, but these data must be treated with caution because of the saturation effect in a community as a consequence of the develoment of immunity [114]. Falling rates of hepatitis B need to be quoted together with the prevalence rates for markers of past hepatitis B infection. Studies of returned equipment from needle exchanges have tended to concentrate on the isolation of HIV in order to demonstrate the potential for spread [47]. However, the detection of more than one blood group from such equipment would provide an objective assessment of sharing and, if used randomly, could be used to corroborate self-reported behaviour change.

Conclusion

It appears to me that harm reduction measures such as oral opiate substitution therapy and needle exchange, when provided in the context of counselling and health education, are able to initiate contact with drug users, to maintain that contact and to convey health-education and prevention messages. There are preliminary data to show that such measures are safe in that they do not increase drug use or initiate drug use, and are effective in changing high-risk drug behaviour, and in that the prescription of oral substitutes such as methadone protects against acquisition of HIV and may also protect against progression to AIDS. It seems, however, that methadone or needles provided without counselling or health education are not effective. The evidence that needle exchanges protect directly against the acquisition of HIV is not yet available. However, there is indirect evidence in the form of reduction in high-risk behaviour, and highly suggestive evidence from places like Edinburgh, where needle availability was actively reduced. Not only did reduced needle availability fail to prevent an injection drug use epidemic, it facilitated an injection drug use-related hepatitis B and HIV epidemic.

Thus, a harm reduction strategy for injection drug use-related HIV should incorporate outreach health education and counselling to initiate contact with and reduce high-risk behaviour amongst drug users not in treatment, increased needle availability in the context of exchanges to reduce the sharing of equipment, increased availability of

oral substitute prescribing to reduce injection drug use and increased availability of drug treatment, which may achieve eventual abstinence. At present there would appear to be no overwhelming reasons for society to avoid harm reduction for injection drug use and in view of the consequences of injection drug use-related HIV for drug users, as well as for vertical and heterosexual transmission of HIV, every reason to increase such harm-reduction programmes. Those of us involved in the care of individuals infected with HIV remain extremely concerned over society's continued opposition, either overtly or by ommission, to harm reduction. It is perhaps significant that a recent report, 'Treating Drug Problems' from the Institute of Medicine of the National Academy of Sciences dealt with effectiveness, cost benefit and the recommendations for both public and private treatment systems [141]. However, there was no discussion of the importance of drug treatment with respect to the control of HIV and what effect the HIV epidemic might have on need for drug-treatment facilities!

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EDITORIAL REVIEW

The natural history of HIV and AIDS in women

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Introduction

Increasing numbers of women are being infected with HIV. Up to one-third of injecting drug users may be women and the spread of infection from HIV-positive individuals to heterosexual partners, especially women, is occurring with increasing frequency. To date, at least 500 000 women with HIV or AIDS have been reported to the World Health Organization (WHO) and in New York State and New Jersey, AIDS is now the leading cause of death among black women aged between 25 and 44 years [1,2]. Whilst women make up only 6, 13 and 10% of the AIDS cases in the United Kingdom, Europe and the United States, respectively, in Haiti at least 28% and in Africa 40–50% of AIDS cases are women [2–6]. By the end of June 1991, the number of women infected with HIV in the United Kingdom was still relatively low at 11% of 15 712 [7]. In comparison with the rest of the United Kingdom, there are many more women affected in Scotland: 27% of individuals infected with HIV by 30 June 1991 and 17% by July 1991 were women [4,9]. In addition, there was a 96% increase in the number of women infected with AIDS from August 1990 to July 1991 in the United Kingdom, compared with an 18% increase for men during the same period [4].

In the same way that HIV-infected drug users may differ from homosexual men in presentation, progression, and management, it cannot be assumed that HIV will necessarily present in the same way in men and women. Consequently, given the increasing frequency of HIV infection in women, it is important that physicians are aware of the possible variations in natural history and management of HIV in women. The speed of progress in understanding HIV, and the more recent interest in HIV infection of women, has meant that much of the work referred to in this review has only recently been presented in abstract form. Whilst such information is not generally available for scrutiny, it is important because of the paucity of published material.

Although the majority of women globally have probably been infected with HIV by heterosexual intercourse, the clinical problems and natural history of HIV in women have been documented largely in Europe and the United States, where injection drug use (IDU) is the risk factor; IDU was implicated in 56 and 51% of the notified women with AIDS in Europe and the United States, respectively, [3,8]. In the United Kingdom IDU has accounted for only 24% of the notified cases of AIDS in adult women; however, in Scotland the picture is much more like the rest of Europe or the United States, with 76% of adult women having IDU-acquired AIDS [4]. We have been involved in caring for women with HIV acquired directly (via IDU) or indirectly (via heterosexual intercourse with an injecting drug user) and it is necessary, before attempting to understand any variations in the clinical course or natural history of HIV in women, to consider the possible confounding effects of IDU.

Progression from HIV to AIDS

Several factors have been implicated in the progression from early HIV infection to AIDS, including the biological properties of the HIV itself, genetic susceptibility, gender, pregnancy, risk activity, coinfection with other viruses, age, and smoking [10–39]. Additional immunosuppressive factors, such as the use of opiates, stimulation of the immune system via soluble antigens, coinfection with DNA viruses and the acquisition of different HIV strains may also be important [40–44]. A number of markers or predictors of this progression to AIDS have been noted, including the

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age of the patient, low numbers of CD4 lymphocytes, immune thrombocytopenic purpura, the presence of HIV antigen in serum and rising levels of β_2-microglobulin (β_2M) [45–50].

Extensive data on the time course of progression from HIV to AIDS are now emerging from various cohorts which present various known risk groups and seroconversion dates. These reports reveal the following rates of progression to AIDS: 0–2% at 2 years, 5–10% at 4 years, 10–25% at 6 years, 30–40% at 8 years, and 48% at 10 years [51]. Recently published data on the San Francisco City Cohort revealed a median progression rate of 51% by 10 years [52,53]. The majority of these data are based on men and to date there have been few cohort studies of progression in either drug users or women. Studies published to date have often not controlled for important variables such as duration of infection with HIV, gender and concurrent IDU. Since many women in the United States and Europe have been infected by IDU, its effect on disease progression should be considered.

The effects of IDU on progression

Kaslow *et al.* [54] found no evidence for a role of alcohol or other psychoactive drugs in accelerating the progression of immunodeficiency in HIV-seropositive homosexual and bisexual men. Whilst there appears to be no relationship between opiate use and disease progression, it has been suggested that continued IDU may accelerate progression of HIV to AIDS. One study reported a relationship between the frequency of IDU and the loss of CD4 lymphocytes, while another noted a similar increase in the rate of decline of CD4 lymphocytes among a group of drug users compared with a group of non-injectors [32,33]. A study from Switzerland reported a lower probability of disease progression amongst methadone-users or ex-users compared with persistent injection drug users [34]. Progression from Centers for Disease Control (CDC) stage II or III to stage IV after 2 and 3 years of follow-up were 11% [95% confidence interval (CI), 3–19%] and 29% (CI, 15–43%) in the methadone-using group, 21% (CI, 10–32%) and 29% (CI, 14–43%) in the ex-users, but 36% (CI, 24–48%) and 60% (CI, 45–76%) in the persistent IDU group, respectively. The progression rate in the persistent IDU group was significantly higher than that in the methadone-treated and the former IDU group ($P<0.01$ and <0.05, respectively). Multivariate analysis showed a relative risk of 1.78 for the persistent IDU group, 0.48 for the methadone-treated group, and 0.66 for the former IDU group [34]. However, other studies have not found an increased risk for continued IDU [29,55,56].

The reasons why continued IDU might predispose to accelerated decline of the immune system are unknown, but one suggestion is that the drift in molecular composition demonstrated in different HIV isolates could result in an individual being exposed to additional infection with different strains of HIV which might hasten disease progression [44]. Another possible explanation is that IDU itself significantly affects the immune system; for example, frequent IDU has been associated with depressed lymphocyte function irrespective of HIV serostatus. IDU has also been associated with higher levels of β_2M, and activated T cell- and IDU-related HIV has been associated with increased immune stimulation [57–59]. Finally, smoking has been associated with progression to AIDS; the relative hazard for cigarette smokers has been reported as being 1.63, compared with non-smokers [35].

The effects of gender and pregnancy on progression of HIV infection

Perhaps one of the greatest concerns for both women and their physicians is the interaction of pregnancy and HIV infection, not only because of the possibility of transmission of the virus to the child, but also because of the possibility that pregnancy may hasten the onset of AIDS in the mother. The mean time from HIV infection to the development of AIDS is between 10 and 11 years and the majority of infected women are in the reproductive age group: in Scotland 86% are in the 15–44-year age group and in Europe 76% are in the 15–49-year age group [3,9]. Many HIV-infected women may therefore become pregnant unless there are obvious contraindications. Despite the large number of at-risk pregnancies that have occurred and the large number of women now infected with HIV, the natural history of HIV infection in women and its influence on outcome of pregnancy is still poorly understood.

The effect of pregnancy on HIV was studied in 16 mothers who were identified by the birth of a child with AIDS: only four (25%) of the mothers remained healthy after a mean of 2.5 years after delivery [36]. In addition, 11 of the 16 women had a subsequent pregnancy during this time although there was no mention of their total parity. In five of these 11 subsequent pregnancies, the women developed AIDS or AIDS-related complex (ARC) during the subsequent pregnancy. In another study, 34 mothers, again identified by the birth of an infected child, were followed-up for a mean of 27.8 months [37]. At that time, 15 out of the 34 (44%) mothers had symptoms of AIDS or ARC, and 14 of the mothers had gone on to further pregnancies. Minkoff *et al.* [37] concluded that there was a significant chance of maternal ill health associated with AIDS or ARC after delivery of a child. These original studies suggested that pregnancy, and possibly a second pregnancy, accelerated progression from asymp-

tomatic HIV to AIDS; however, a selection bias cannot be excluded since the women were identified by the development of AIDS in an HIV-infected child. Furthermore, there were no non-pregnant controls and the duration of infection with HIV was unknown.

However, two further studies have also suggested that pregnancy accelerates progression of HIV. In a study from Paris, France three groups of patients were studied: those going through a pregnancy; those undergoing a spontaneous abortion; those without pregnancy [38]. Progression to CDC stage IV occurred most among the pregnant group, 15% compared with 3.6 and 5.7% in the other groups. In addition, possession of high-risk markers, as defined by a CD4 count $< 150 \times 10^6$/l, p24 antigenaemia, and loss of p24 antibody, was greatest in the pregnant group, after the follow-up period. For example, an increase from 8 to 21% for the pregnant group compared with 10 to 13.5% and 9 to 12.5%, respectively, for the other groups [38]. In a study from Port au Prince, Haiti with 21 months of follow-up, progression to HIV-related ill health or AIDS was greatest for patients having a live-birth pregnancy (47 compared with 26%) [39]. The cumulative proportions of patients with symptoms at 5 years were 84 and 53% for the pregnant and non-pregnant groups, respectively [39].

In contrast, there have been other studies which have shown that pregnancy has no effect on the progression of HIV disease [60–67]. In 1987, Nachman [60] followed 71 women, of whom 44% were HIV-seropositive, and found no disease progression during pregnancy, although methadone users, whether HIV-infected or not, had depressed CD4 levels compared with non-methadone users (HIV seropositive, mean 358×10^6/l; HIV-seronegative, mean 804×10^6/l) [60]. A prospective study of HIV in pregnant IDU women in Italy (28 HIV-seropositive and 16 HIV-seronegative individuals) did not show worsening disease during follow-up, although the length of follow-up was not indicated [61].

Schoenbaum *et al.* [62] compared the incidence of ill health and AIDS in women according to the number of pregnancies [62]. A group of 141 women, 56 with no live-births, 36 with one live-birth and 49 with two or more live-births were followed for a mean of 2.6 years. There was no excess of symptomatic disease or AIDS among the women with live-births. On regression analysis controlling for CD4 count and CD4:CD8 ratio, the presence of oral thrush or AIDS was predicted by both an earlier onset and longer duration of symptoms, but not by live-births ($P < 0.0001$ and $P = 0.59$, respectively).

Berrebi *et al.* [63] reported 60 HIV-positive asymptomatic pregnant women and compared their outcome with 68 age- and sex-matched non-pregnant asymptomatic controls. Over a period of 3 years, no difference in the progression of HIV disease was observed between the two groups. Transient appearance of p24 antigen was observed during pregnancy, but did not appear to be an adverse prognostic marker. In 1991, an update on their cohort of HIV-positive women, which by now consisted of 54 women who had had a live-birth, 65 women who had had an abortion and 81 women who had not been pregnant, showed no difference in immunological or clinical outcome over 3 years of follow-up [64].

Our experience is of 107 HIV-seropositive women infected between 1983 and 1985 with follow-up periods ranging between 6 and 54 months. Thirty-one were infected after HIV seroconversion. The women were categorized by obstetric history according to: no live-births; only live-births before seroconversion; live-births after seroconversion to HIV. No excess progression was noted for the patients with live-births post HIV seroconversion or for patients with live-births versus no live-births ($\chi^2 = 3.26$; $P = 0.07$). In addition, virological and immunological markers did not differ significantly for the three groups [65].

Bledsoe *et al.* [66] reported that progression to AIDS for a pregnant group from Bethesda, USA was only 1.8% compared with 7.8% for a non-pregnant group. Another small study from Belgium compared 13 pregnant prostitutes, with 13 non-pregnant prostitutes (matched for CD4 cell counts) and 10 pregnant married women. They were all HIV-seropositive but had been followed-up for a total, including the pregnancy, of 15 months only. No significant differences were observed in the progression of HIV [67].

Perhaps the most important piece of evidence on the effect of pregnancy on HIV is the lack, to date, of any obvious gender effect in natural history studies [68,69]. No major difference between the sexes in the rate of progression from HIV to AIDS has been reported. Gender was not a significant factor in a study of progression in 58 male and 18 female Spanish IDU, and a Swedish transfusion study noted shorter progression times for men, although this was not statistically significant [68,69].

Clinical problems for HIV infected women

Non-opportunistic infections

Women with HIV infection appear to be at higher risk of developing lower genital tract infection, although well-controlled studies with HIV-negative community controls are rare. For example, prevalences of 46% of lower genital tract infection have been reported for HIV-positive compared with 20.5% for HIV-negative drug users, although the major infections were genital warts [70]. A higher prevalence of human papilloma virus (HPV) was also reported among 24% of 160 and 54% of 224 HIV-negative and HIV-positive drug users, respectively ($P < 0.01$) [71]. Genital her-

pes, candidiasis and pelvic inflammatory disease were of particular concern in a study of 178 HIV-seropositive women [72]. This study also reported that these infections were more prevalent, more aggressive and often recurrent in HIV-positive women. In a study of 40 HIV-infected women (75% in CDC stage 3), 80% had evidence of recurrent vaginal candidiasis [73]. The prevalence of reported genital infections in 465 HIV-positive women, of whom 23% had AIDS, over a 1-year period, was 31%. This included vaginal yeast infections reported by 10% (4% with recurrent yeast infections as defined by more than four attacks per year), genital herpes infections, trichomonas infections and pelvic inflammatory disease reported by 5, 4 and 1% of women, respectively [74].

Any increased susceptibility to genital infection may in part be related to the overall susceptibility of HIV patients to bacterial infections. Encapsulated bacteria such as *Streptococcus pneumonia* and *Haemophilus influenza* are frequent respiratory pathogens and causes of bacteraemia in HIV-seropositive individuals [75]. IDU-related HIV patients have a higher prevalence of recurrent bacterial infections such as pneumonia: 12% with a mortality of 2.2% compared with 3% with a mortality of 0% in HIV-negative drug users [76]. The annual incidence of pneumonia was 9.7% for HIV-seropositive drug users compared with $<2\%$ for a population of mainly homosexual men with AIDS [77,78]. There is a rising mortality from pneumonia in young adults in New York City, primarily as a consequence of IDU-related HIV, and other cities in the United States are showing similar trends [79]. In a study of bacteraemia in Nairobi, HIV-seropositive individuals were five times more likely to suffer a bacteraemia (26 versus 6%), particularly with *Streptococcus pneumoniae* and *Salmonella typhimurium* [80].

Our own experience of a cohort of 501 patients with a male-to-female ratio of 3 : 2 was that admissions for urinary tract infections increased among women (male-to-female ratio, 4 : 11) whilst admissions for other infections showed no difference in the male-to-female ratio [81]. Only four of the 168 women required admission with pelvic inflammatory disease. The majority of both men and women were, as has been reported for drug users in the United States, admitted for respiratory disorders, especially recurrent bacterial infections [76–78,81].

Neoplasms

Kaposi's sarcoma (KS) is the most common neoplasm associated with AIDS and occurs in 15% of the reported cases of AIDS. KS is mainly associated with homosexual men since it has been reported in approximately 3% only of drug users [82]. By comparison, the most common malignancy associated with IDU appears to be malignant lymphoma, which was reported in 8% of surgical specimens from drug users [83]. Approximately 3% only of women have developed KS in Europe or the United States [84], but it is suggested that when KS occurs, the patients are more immunodeficient and have a shorter survival period. In one series of 12 women, 11 of whom were Caucasians, 50% had a CD4 count $<100 \times 10^6/l$ at presentation and 67% had died by 12 months [85]. In another series, of 23 Italian women, the median survival was only 6.25 months, and 70% had died after 1 year [86]. This was of a similar order to a median survival of 3–4 months for seven women in the United States [87]. By comparison, 70% men with KS survived for 1 year [88]; however, it has been reported that the most recent cases of KS in men were more immunodeficient and had poorer prognostic markers [89]. In Africa, KS seems to affect women quite frequently, and the male-to-female ratio of epidemic KS is 2 : 1 instead of the 5 : 1 ratio seen for endemic KS prior to 1983 [90]. In a study of 101 patients with KS, 18% of cases were women and, by comparison to the European and United States studies, only 35.8% had died by 2 years [85–87,91]. It may be therefore that the studies reporting poor prognosis for women are too small. It has also been suggested that KS is a sexually transmitted agent, since it was four times more likely to be present in female partners of bisexual women than other risk groups, and because it is so much more common in Africa [82,91]. Another study reported that the initial lesions of KS were in areas of sexual contact [85]. However, more recent studies have not confirmed this association with bisexual men or sufferers of KS since the majority were drug users or heterosexual contacts of non-bisexual men, all without KS [86].

The other problem which particularly affects women is neoplasia of the genital tract. In a study of HIV-infected women who were clinically well, 18 out of 109 had abnormalities of their lower genital tract. Seven of these women had intraepithelial neoplasia and disease at more than one site was detected, and the need for colposcopy was stressed [92]. Generally, HIV-positive women from a variety of sources have an incidence of cervical intraepithelial neoplasia (CIN) varying between 35 and 80%. In one study the incidence was 9% for HIV-negative drug users but 36% ($P<0.01$) for HIV-positive drug users [71]. The relative risk of CIN in HIV-seropositive individuals was 6.3 (95% CI, 3.5–11.2) [71]. Increasing immunosuppression, as estimated by lower CD4 counts or poorer CDC clinical staging, is also significantly associated with worsening CIN [71,93–95]; for a reported 46.6% incidence of CIN of for CDC stage III or IV compared with only 17.6% for CDC stage II ($P<0.026$) [94]. Recent studies from New York have confirmed previous suggestions of increasing cervical and more severe dysplasia occurring with increasing immunosuppression [95]. This increased cervical dysplasia was related to HPV since it did not occur if the patients were HPV-negative [96]. Further controlled studies are required however since these New York studies were neither

blinded nor well-matched for HIV-negative community controls. Despite these concerns there has not as yet been an increased incidence of cervical cancer in New York and cervical cancer is rarely listed as a cause of HIV-related death.

Opportunistic infections

Other than genital tract infections and neoplasms, there have not been many reports to suggest that HIV-infected women have a particular disease spectrum that differs from men. In a small series of 24 women with AIDS, there was a lower incidence of *Pneumocystis carinii* pneumonia (PCP) as the AIDS-defining illness among women compared to men with AIDS in the same area [97]. There was, however, a large proportion of women with *Candida albicans* oesophagitis (38%) and HIV-related wasting syndrome (25%). Similar findings were reported by a Danish study which included 35 women among 618 AIDS patients [98]. A further study group, 7.7% of which were women, noted more likely presentations of oesophageal candidiasis for women than men (19 versus 9.7%), atypical mycobacteria (16 versus 8%), and the wasting syndrome (10 versus 3%) [99]. The relative risk for candida oesophagitis in women was 1.5 in another study [100]. The numbers in these reports were small, however, and these findings need to be confirmed before any significant conclusions can be made on the possible effect of gender and hormones on the natural history of HIV infection.

Pregnancy

The effect of HIV on an individual pregnancy, as with the effect of pregnancy on HIV outcome, is in similar dispute. A number of reports found no increase in obstetric complications for HIV-positive pregnant women, although some of the studies contained quite small numbers [101–104]. For example, an Italian study compared 28 HIV-positive with 16 HIV-negative pregnancies [101]. Other studies, however, contained reasonable numbers of patients: from France, 68 HIV-positive drug users were compared with 3017 other pregnancies; from Italy, 106 HIV-positive were compared with 50 HIV-negative IDU mothers; from Kenya, 135 first trimester abortions were matched with 135 pregnancies >20 weeks [102–104]. None of these studies found any association between HIV and increased obstetric complications, although in the Kenyan study the incidence of HIV in the early abortion group was greater than that of 20-week pregnancies (10.4 versus 5.2%), but this was not statistically significant [104].

By comparison, other reports have suggested an increased spontaneous abortion rate for HIV-positive women. For example, in a Scottish study of 136 pregnancies, the only difference between HIV-positive and HIV-negative pregnancies was an increased spontaneous abortion rate (18 versus 5.3%; $P<0.02$) [105]. Similarly, a retrospective study of US Army women compared 69 HIV-positives with 276 matched controls and found that the relative risk of a complicated pregnancy and of spontaneous abortion was 2.0 and 4.4 (CI, 1.4–2–8 and 1.5–13, respectively) [106]. Of 461, respectively consecutive pregnancies in Malawi, which presented an overall HIV seroprevalence rate of 17.6%, spontaneous abortions were associated with syphilis and HIV infection; however, after logistic regression analysis and stratification for syphilis serology, HIV retained a significant association with spontaneous abortion [odds ratio (OR), 2.5; $P = 0.007$] [107].

An association between HIV infection and other complications of pregnancy has also been reported. An Italian study of 74 HIV-positives, 48 HIV-negative drug users and 22 HIV-positive non-drug users suggested that seropositive patients had a higher incidence of small-for-gestational-age babies, although this difference was not statistically significant [108]. A further study of 18 Italian HIV-positive and nine HIV-negative drug users and 20 HIV-positive and 18 HIV-negative non-drug users found that the gestational age and mean birth weight for babies of HIV-positive drug users was significantly reduced ($P<0.01$) but that this was not the case for HIV-positive non-drug users [109]. The prevalence of intrauterine growth retardation, preterm deliveries, premature rupture of membranes and perinatal complications all increased among the drug users [109]. The conclusion was that HIV was perhaps additive to the effects of IDU on pregnancy.

As with progression of HIV, most studies have not controlled for the effect of IDU on pregnancy. However, two African studies have suggested a role for HIV in pregnancy complications. In Uganda, 605 pregnant women, of whom 206 were HIV-positive, were studied [110]. HIV infection was associated with one complication of pregnancy (47 versus 33%; $P = 0.001$) such as fever (18 versus 12%; $P = 0.05$), urinary tract infection (10 versus 4%; $P = 0.05$), smaller weights at birth (2.94 versus 3.13 kg; $P<0.001$), prematurity (82 versus 93%; $P<0.001$) and perinatal death (8 versus 3%; $P = 0.01$). A study from Kenya also noted associations of intrauterine growth retardation, small for gestational age, intrauterine fetal death and intrapartum fetal death with HIV infection (OR, 2.1, 2.3, 2.7 and 2.9, respectively) [111].

Other problems

Loss of endocrine function has been reported in patients with AIDS. Overall deficiencies of adrenal or thyroid function have not been found, except in relation to severe illness [112]. As far as sex hormones are concerned, most of the studies to date have concentrated on testicular function; for example Raffi, although studying 25 women, presented no data with respect to women [112].

Another common problem with HIV infection is thrombocytopenia, which appears to occur in approx-

imately 5% of individuals [113]. In a cohort of 435 individuals, the male-to-female ratio was 3.8:1, whilst for those with platelet counts $<150 \times 10^9$/l the ratio was 13.5:1. This difference was not, however, statistically significant [113]. In addition, it has been reported that women are more likely to be anaemic than men [114].

Finally, as with IDU, the increased susceptibility to bacterial infections may increase the mortality of non-opportunistic events such that many patients die before the advent of AIDS [115–117]. Thus it will be important to look at total survival for women rather than meerly survival after the development of AIDS. In a follow-up of 55 HIV-positive compared with 55 HIV-negative mothers in Africa, 16% of the HIV-positive women had died by 5 years, compared with none of the HIV-negative women, exemplifying the increased mortality for infected women [118].

Survival after AIDS diagnosis

In one study approximately 50% of patients with AIDS survived 1 year, but only 20% survived 3 years after the development of AIDS [119]. Whilst it is generally assumed that the survival for drug users with AIDS is shorter, a report on 5833 cases of AIDS from New York, which adjusted for various factors (i.e. age) found no difference between homosexuals and IDU in terms of survival. IDU itself may be an adverse factor, since the combination of IDU and homosexuality led to a shorter survival. A proportional hazards model showed a significant interaction between IDU and PCP as factors shortening survival [119]; the prognosis appeared to be worse for drug-using women, since in New York, the cumulative probability of survival at 1 year was 75.4% for white men with KS but only 37% for black drug-using women with PCP [119].

The apparent poor survival for drug users with AIDS may be connected with reports of poor survival of women; 16.3 and 10.9% of women and men die at diagnosis of AIDS, respectively [119]. A greater risk of respiratory failure was observed for women with PCP as well as a two fold increase in their mortality, compared to a matched group of men [120]. In New Jersey, among 345 women, 95% of whom were black and 63% drug users, the mean survival was only 14.5 weeks [121].

However, reports of poor outcome for women with HIV/AIDS in the United States, especially among drug-using women, may have a greater association with access to medical care than with HIV infection alone. Studies demonstrate that US women present late for medical care; 39% of women had a CD4 count $<200 \times 10^6$/l at presentation and in Minnesota two-thirds of women with HIV were detected by neonatal screening rather than as a result of medical care [122,123]. In New Jersey, women presented with more advanced disease, with more symptoms and a greater duration of symptoms than men (59.75 versus 24.5 weeks) [124]. The importance of being in medical care, as far as survival is concerned, was underlined by the fact that patients attending an outpatient clinic had a better survival (70.4 compared to 27.5 weeks for non attenders) [121]. Similarly, in a series of 24 white women from Rhode Island, the mean length of survival was 19 months, but only five had PCP as an index diagnosis [97]. Unfortunately, since the majority of women with HIV in the United States and Europe have, to date, been drug users, it may take some time to separate the interactions of IDU and gender.

In a survival analysis of 4805 patients treated with zidovudine, drug users had a slightly better prognosis than homosexual or bisexual men; however, the numbers in the IDU group were small. Survival did not differ significantly according to gender or race [125]. Similarly, survival analysis of 4323 patients with AIDS in San Francisco between July 1981 and December 1987 did not confirm previous reports of poorer prognosis for women and IDU [126]. In Denmark, the survival of women has been shown to be less than that for men (mean 306 versus 504 days; $P<0.05$), whilst in Amsterdam a comparison of 25 women with 682 men did not show a significant difference in one year survival between women and men (50.0 versus 56.3%) [127,128].

It has also been suggested that the development of PCP during pregnancy has a particularly poor prognosis since four women, initially reported, died during acute illness [129,130]. Similarly, of 11 women who were asymptomatic during pregnancy, one died during pregnancy and three within 3 months of delivery [131]. By comparison,a further three patients with PCP during pregnancy and 25 symptomatic women (20 with ARC and five with AIDS) survived pregnancy, suggesting that these original observations may suffer from ascertainment bias [132–134].

Conclusions

The increasing numbers of women infected with HIV and ultimately dying of AIDS will undoubtedly have serious implications for all societies. The psychosocial issues for women with HIV may, or may not, be different to those for homo- or heterosexual men. Illness and death of one or both parents, and the death of infected children are important issues that must be considered by society as a consequence of this epidemic.

At present, there does not appear to be a significant difference in the natural history of women infected with HIV, although the majority of studies have concerned patients with early HIV infection, and as time passes other problems may emerge. Of concern for

countries such as the United States is the fact that there appears to be a different natural history due to differential access to medical care. The effect, if any, of pregnancy on outcome of HIV could be the result of a variety of pathologies, for instance, hormonal, immunosuppression or antigenic stimulation. However, the lack of an overall effect of gender on progression of HIV would suggest that pregnancy is unlikely to have a significant effect on the natural history of HIV in women.

The confused state of knowledge with regard to HIV infection in women raises important questions which can only be answered by careful long-term studies of the natural history of HIV in women. Natural history studies need to consider a number of important interactions, some of the current confusion surrounding women, pregnancy, and HIV, may exist because confounding factors such as length of HIV infection, age, smoking, drug use, gender and, pregnancy have not always been considered.

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Journal of Infection (1992) **24**, 101–102

PERSONAL COMMENTARY

Observations on the problems of HIV infection in Malaysia

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Oceania (South-East Asia and the Western Pacific) with only 2803 (0·97%) out of 288337 reported cases of AIDS by 1 November 1990 has not yet figured prominently in the worldwide AIDS epidemic,[1] although recent information suggests that there is now an HIV epidemic in South-East Asia with the potential for an enormous AIDS epidemic in about 7–10 years. The current focus of concern is Thailand, where an explosive HIV epidemic began in 1987 such that by the end of 1990 there had been 76 cases of AIDS out of a total identified HIV population of 25342, 50% acquired via injection drug use (IDU) Mr John K. Roberts, Wellcome Thailand Ltd, Bangkok, Thailand and Dr Surapol Suwanagool, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand, (personal communication).[2,3] HIV is spreading to neighbouring countries, probably as a consequence of the mobility of drug users and heterosexual contacts of prostitutes which has been reported elsewhere in the world.[4,5] For instance, they may travel to south-west China where 29·6% of over 400 drug users were HIV seropositive Professor Y. Zeng, Institute of Virology, Chinese Academy of Prevention, presented at 1st International Conference on AIDS and Reproduction, December 1990, Genoa, Italy, (personal communication) and to Malaysia which, by December 1990, had 19 patients with AIDS and over 750 cases of HIV infection, 76% acquired via IDU Professor Rokiah Ismail, Faculty of Medicine, University of Malaya, Kuala Lumpur, (personal communication).

There has not yet been any systematic serological survey of at-risk populations in Malaysia to determine the prevalence of HIV, and there is currently no easy way to obtain a fully confidential HIV test. There is a reluctance to discuss sexual and drug-related matters which is partly based on the teachings of Islam and makes it difficult for medical and paramedical staff to be effective as counsellors and health educators. The seriousness of the epidemic suggests that a more pragmatic approach to these matters might allow the introduction of harm-reduction measures that have been found effective in the U.S.A. and Europe.[6] Malaysia, however, needs more information about the extent of HIV infection in addition to the drug and sexual habits of the population. This can only be obtained by local research, since intervention strategies must be based on accurate knowledge of local high-risk activities. At present, however, the legal situation is such that it is difficult to interview at-risk populations without fear of their arrest and detention.

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A non-government organisation could undertake research as well as providing a fully confidential HIV counselling service and promoting a harm-reduction programme to help reduce the spread of HIV. Clinical epidemiological research must be given a high priority since such information, especially that concerning drug and sexual habits, could be used to modify education campaigns either by targeting those at greatest risk or by trying to modify high-risk behaviour.

Once there are sufficient experienced counsellors in place the government could undertake a large-scale media campaign. Finally the government should consider very seriously the current legal situation with regard to the drug problem, which will without doubt exacerbate the HIV problem. Strict non-voluntary rehabilitation or detention cannot control the spread of HIV, because it is not possible to identify all those who carry it. Malaysia has to find a solution to the epidemic of HIV infection which is acceptable to an Islamic society, but in doing so one would urge them to consider very seriously measures that have previously been shown to be effective in the U.S.A., Europe and Africa.[6]

(The views expressed here are my own and were formed during a visit to Kuala Lumpur, Malaysia on the occasion of the First AIDS Counselling Course organised by Professor Rokiah Ismail, the Malaysian Society of Infectious Diseases and the Faculty of Medicine, University of Malaya. The visit was made possible by the support of the British Council and the Myre Sim Travel Fund of the Royal College of Physicians, Edinburgh.)

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REVIEW

Infection and injection drug use

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Introduction

The complications of recreational drug use are many and varied and include the excessive or withdrawal effects of such drugs as well as a number of associated medical conditions. The related health service workload is not inconsiderable; a survey from Dundee revealed that heroin drug users had twice the general practice consultation rate of matched controls (7/year *vs.* 3·25/year).[1] In Glasgow 0·6% of all consultations at an accident and emergency facility were by injection drug users and two thirds of these consultations were deemed to be medical or surgical and only one third 'psychiatric'.[2] A second Scottish accident and emergency department survey revealed that drug users accounted for 0·16% attendances of which 47% required admission. Sixty percent of the attendances were related to the effects of drugs (37% related to an excess of drugs or overdoses and 23% related to withdrawal from drugs), 21% to infections, 8% to trauma and 10% to other medical conditions.[3] Hospital and post-mortem surveys have suggested that between 31–58% admissions and 19% deaths of recreational drug users were related to associated infections.[4–6]

There is thus no doubt that drug users utilise a substantial amount of medical resources and the clinical spectrum of disease includes injection drug use (IDU) related infection.

Injection drug use related infections

Infections related to drug use usually occur in association with injections although the use of animal excreta in the cultivation of marijuana and subsequent outbreaks of Salmonella gastro-enteritis are notable exceptions.[7] IDU-related infections occur because of the use of either non-sterile equipment (needles, syringes, spoons, cups etc.), or solutions. Both of these allow micro-organisms direct access to subcutaneous tissues, muscle or blood and result in either local or systemic infections.

The use of opium via inhalation or its consumption in food or drink is centuries old and although it is often assumed that IDU is a modern problem this is not the case.[8] The 'hypodermic injection of morphia' during which a lancet dipped into a solution of morphine was inserted beneath the skin, was described by Dr Lafargue of St Emilion in the 1830s.[8] The use of the hollow hypodermic needle and syringe to introduce a solution of morphine under the

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skin was described in the 1840s and the first reports of an associated infection in patients addicted to morphine given by this method were of tetanus in 1876.[8–14] Tetanus in drug users was related to subcutaneous injections (skin popping) of opiates or adulterated heroin, usually in the region of the abdomen and/or thighs, and was at first relatively rare.[14–16] Doane comments that during an 8-year period he had seen only three cases among 4000 patients with drug addiction.[14] However, by the late 1950s drug addiction accounted for the majority of cases of tetanus in New York and was the cause of between 5 and 8% of deaths in drug users.[5,14,17,18] The rise in incidence was probably accounted for by a resurgence of the subcutaneous route as a result of a lack of venous access from prolonged intravenous drug use.[15] The use of street heroin 'cut' with quinine was also considered important since this could produce skin abscesses suitable for the growth of *Clostridium tetani*.[15] It is possible that the widespread practice of immunisation with tetanus toxoid in childhood has been an indirect but successful harm reduction measure for IDU since in recent surveys tetanus is now a rare IDU-associated infection.[1–4] This success might be a useful model for the prevention of hepatitis B in drug users.

Although the intravenous use of drugs, including opium, was reported as early as the 17th century its widespread practice and cutaneous stigmata were first reported in the English literature from Egypt in 1929. This was closely followed by reports from a number of cities in the U.S.A. in the early 1930s.[8,19–22] Intravenous heroin in the 1930s was injected via crude syringes made from medicine or eye droppers attached to hypodermic needles and used in succession by several individuals without intervening washing or sterilisation.[22]

Two particular practices associated with the sharing of injection equipment or associated paraphernalia seem to favour the spread of blood-borne micro-organisms. Firstly washing the drug out of the syringe into the blood stream, by repeatedly drawing back the plunger and injecting the user's own blood (booting), results in heavy blood contamination which can be passed to the next user. This practice may have resulted from the original use of medicine droppers as syringes. Secondly, there is the practice of washing the equipment between shots in a communal glass or bowl of water which rapidly becomes contaminated with blood.

The first blood-borne organism to be associated with equipment sharing was malaria and was recognised in Egypt in 1929 and in the U.S.A. in the 1930s and 1940s.[19–23] Another possible example of harm reduction for IDU may have been the practice of using quinine as a 'cutting' agent for street heroin. This practice was reported as having been deliberately introduced by the users in New York during the 1930s so that artificially transmitted malaria was not seen there after 1943.[5]

The association of subcutaneous or intravenous IDU with hepatitis B virus (homologous serum hepatitis) was first reported in 1950.[24–27] One report described the spread of hepatitis through a tight-knit group of long-term users after a new individual joined the group.[28] Multiple attacks of hepatitis at first attributed to chronic hepatitis were described in 1960 and it is now known of course that hepatitis C is also commonly associated with IDU.[29–31]

More recently human immunodeficiency virus (HIV) has been shown to spread to drug users. Although the risk factors have not been well elucidated, a link with the frequency of equipment sharing is well established and in the U.S.A. there is also a link with IDU in areas where equipment is rented (shooting galleries).[32–43] Less well recognised, but also of importance is the type of drug used; for instance cocaine alone or mixed with heroin is injected far more frequently than heroin.[44] A link between HIV infection and intravenous cocaine has been reported and in addition equipment sharing is more often associated with cocaine use and/or the difficulty of obtaining equipment.[45–57]

IDU-related HIV and AIDS are noted for their geographical clustering; 75% of IDU-related AIDS in the U.S.A. has occurred in the New York City metropolitan area and 70% of the European cases have been reported from Italy, Spain and France.[58,59] There are as yet no convincing explanations for this clustering although it has been linked to the intense sharing of equipment in localised areas together with the mobility of a small number of users.[60] Scattered pockets of IDU-related HIV in Europe may be explained by the movement of small numbers of very mobile users between areas of varying drug availability.[34,60] In Italy a relatively high sero-prevalence amongst drug users near U.S. Air Force bases has been suggested as one means of entry of the virus into Europe.[61]

This pattern of the sudden appearance of pockets of HIV among drug users may well continue in developing countries with the reports of HIV sero-prevalence amongst drug users of 44% in Bangkok, 22–48% in Argentina and 54% in North-East India.[62–65] The pattern has, however, been described before; malaria, which was not endemic in Washington DC, suddenly appeared among drug users there in 1943 and until 1946 was of the falciparum type though in 1947 cases of quartan malaria began to be detected.[23] The high prevalence of hepatitis D (delta agent) in drug users from Italy, Copenhagen, Basel, Dublin and Edinburgh is another example of the international spread of blood-borne viruses by IDU.[66,67]

Epidemiology of injection drug use infections

It is difficult to determine how common IDU-related infections are for a variety of reasons; drug use is illegal in many countries, the severity of the infection determines whether medical help is sought, few doctors record drug use as an associated factor for infection and the number of drug users in any one particular location is often not known. As an example, between 1943 and 1947 infection was a factor in 80% heroin addicts admitted to one Washington hospital whereas it had been so in only 6% during the years 1938–1942. The increase was attributed by the authors to a lack of antisepsis and the use of a communal needle.[23] This epidemic of IDU and consequent infection has similarities to the events that occurred in Edinburgh and suggests that whether infection will occur and how often varies with the type and frequency of drug use.[33,34,42]

From published series it is apparent that the frequency and spectrum of infections among drug users is very variable. Examples of the frequency of

drug use related infection as a medical problem are shown in Table I. A study of 1561 narcotic-related deaths between 1950 and 1961 showed that 298 (19%) were related to infection; 34·5% were bacterial sepsis including endocarditis, 44% were tetanus and 10% viral hepatitis. By comparison during 5 months in 1973, of 200 consecutive admissions to the medical inpatient unit of a New York hospital devoted to drug addiction, 30·5% were acute viral hepatitis and 27·5% were a consequence of other infections.[5] Among the latter, which were identified, were endocarditis (3·5%), bacteraemia without an obvious source (11%), chest infections (29%) and skin infections (43·5%). In Basel, Switzerland between 1980 and 1986, 0·78% of all admissions to a University Hospital involved narcotic drug users and 31% were infection-related; 24% were for lower respiratory tract infections, 20% for viral hepatitis, 6% were soft-tissue infections and 3% secondary to bacteraemia including endocarditis.[4] The survey of accident and emergency consultations by drug users in Edinburgh during 1983 revealed that 73% of their infections were described as local, 17% as some form of hepatitis and only 10% as a consequence of systemic infection.[3]

Thus, it appears that IDU-related medical problems account for between 0·1 and 1% of hospital medical problems and that 20–60% of admissions are related to infections, i.e. 0·1–0·6% of all hospital admissions. Combined with the fact that 10–15% of IDU-related infections are serious systemic infections we can conclude that at the most 0·1% hospital admissions are related to serious IDU-related infections. However, none of these series gives any indication of the size of the population at risk and therefore prevalence or incidence data cannot be calculated.

In Edinburgh during 1983 and 1984 the prevalence of opiate-related IDU was 0·6% for those between the ages of 15 and 35 and there were an estimated 2000 injection drug users.[68] During a 4-month period 23 drug users attended the accident and emergency department because of infection. This suggests an incidence of clinical IDU infection requiring medical attention of about 3·5% (20% of which was viral hepatitis and less than 1% a consequence of serious infection).[3,68] During 1984 there were 100 admissions to Lothian hospitals for conditions such as hepatitis, endocarditis, pneumonia and skin infections out of a population of 2000 drug users. This suggests an incidence of 5% for IDU infections requiring admission.[32,68] Eighty-one percent of these infections were bacterial and 15% were serious (pneumonia or endocarditis). Thus, the incidence of clinical IDU infection for a drug using population is probably somewhere between 3·5 and 5%, with about 20% of these being viral. The incidence of serious drug-related infections is between 0·35 and 0·75%.

What are the risks, however, from the drug user's point of view, i.e. the attack rate for the various infections? A general practice survey in Edinburgh noted that 50% drug users had suffered some form of infection during their IDU career.[69] The majority of the recognised IDU infection problems at that time were hepatitis B, skin infections (14%) and endocarditis (10%). Thus, serious systemic bacterial infections such as endocarditis seem to have an incidence of around 0·75% but perhaps a lifetime attack rate of 5%. This compares with an 80–90% attack rate for blood-borne viral infections such as hepatitis B as determined by serological surveys.[70]

Table I *Frequency of IDU-related infections*

Year	Series	Number of patients	% Infections	References
1950–1961	Narcotic related deaths	(1561)	19	5
1983	Attendance at A&E department	(107)	21	3
Drug related hospital admissions				
1943–1947	Washington	(139)	6	23
1973	New York	(200)	58	5
1989	Basel	(404)	31	4

The effect of HIV on injection drug use related infections

Estimates of IDU-related infection may increase since it has now been shown that susceptibility to bacterial infections is increased by HIV infection.[71–83] In New York the rate of tuberculosis was 4% among HIV-positive patients compared with 0% in HIV-negative drug users and the 36% increase in reported cases of tuberculosis between 1984 and 1986 in the U.S.A. has been largely ascribed to infection among HIV-positive drug users.[73,74] IDU-related HIV patients have a higher incidence of bacterial infections such as pneumonia, 12% with a mortality of 2·2% compared with 3% with a mortality of 0% in HIV-negative drug users.[77] The annual incidence of pneumonia was 9·7% for HIV-seropositive drug users compared with under 2% for a population of mainly homosexual males with AIDS.[78,79] A rising mortality from pneumonia in young adults in New York City is primarily a consequence of IDU-related HIV and other cities in the U.S.A. are showing similar trends.[80,81]

The morbidity and mortality of bacterial endocarditis in HIV-seropositive individuals are greater than for those who are seronegative; the mortality was 24% compared with 4%. The poorer outcome was related to more frequent embolisation, a greater diversity of organisms, more prolonged fever, persistent bacteraemia and greater immunological dysfunction. It was not related to recognised opportunistic infections.[82,83]

The combined effect of progressive immunodeficiency and attempts at harm reduction has had an influence on the predominant medical problems of drug users. For instance a review of narcotic-related deaths in New York from 1978 to 1986 revealed, not surprisingly, a rise in deaths attributed to AIDS.[84] There was also an increase in deaths from other infections such as meningitis, pneumonia or endocarditis equal to the number of AIDS deaths but there was no increase in the non-infective causes of death.[84] A survey of methadone maintenance patients from the Bronx in New York from 1986 to 1987 revealed that infection now accounted for 62% of the admissions but infection that might be related to injecting, such as endocarditis or cellulitis, only for 17% admissions.[85]

Estimates of the effect of HIV on IDU admissions are also available from Edinburgh where the epidemic of IDU started in about 1980 and peaked in 1983 to 1984.[33,42,67] The earliest known drug user, infected with HIV as a

consequence of drug use in Spain and Italy, seroconverted in January 1983.[60] The annual rate of admissions for pneumonia in Edinburgh during 1986 for individuals aged 15–44 years was 0·6/1000 while the admission rate for pneumonia in drug users aged 15–44 years rose from 1·4/1000 between 1983 and 1985 (i.e. as HIV was spreading through the drug community) to 12/1000 between 1985 and 1989, an eight-fold increase in, at the most, 5 years after infection with HIV.[86] In San Francisco the increase of pneumococcal bacteraemia in all HIV-infected individuals has been shown to be 100 times that of the general population.[81]

The reasons for bacterial infections amongst HIV patients are not entirely clear. Although unsterile IDU exposes an individual to episodes of bacterial infection, the susceptibility is not specific for drug users since bacteraemia is also increased in HIV-positive individuals in Africa.[76] In drug users and in Africa it might be argued that lack of access to medical services is an additional contributory factor. However, antibody production is impaired in HIV-infected patients, and low levels of IgG_2 have been associated with bacterial infection.[87,88] Additional susceptibility factors for drug users may be that opiates themselves depress the cough reflex as well as the immune system.[89–92]

Prevention of injection drug use related infections

Drug use itself has a relatively low mortality (1–2 %) since there are alternating periods of abstinence and use, together with natural recovery from addiction.[68,93–95] The increased mortality and morbidity of HIV infected drug users is the reason why spontaneous recovery from addiction can no longer be relied on. Harm reduction has recently been described thus: 'the harm minimisation approach echoes the safer-sex campaigns ... people will not want to abstain from sexual activity, therefore they must be encouraged to engage in safer sex. The idea has now been extended to drug injectors—if they won't stop injecting, they should and could inject drugs in a safer way'.[96] The concept of harm reduction for physical health originated with the Amsterdam Municipal Health Service Drug Department's approach to IDU which recognised the fact that harm reduction means providing medical and social care while waiting for natural recovery from IDU.[97,98] Evidence is now appearing that harm reduction may be able to halt the spread of HIV; oral methadone can reduce the frequency of injecting and needle exchanges reduce infection. Both seem to reduce the acquisition of hepatitis B and HIV.[99] However, drugs of addiction may also have an effect on HIV and both morphine and cocaine have been shown to potentiate HIV replication *in vitro*.[100,101]

As important as preventing the spread of blood-borne viruses is the prevention of bacterial or fungal infections by improving aseptic techniques. An evaluation of a central London exchange scheme was able to demonstrate a fall in median injecting from 56 to 48·5 per month ($P < 0{\cdot}001$), sharing from 15 to 11 % of the time, equipment borrowing on two or more occasions from 8 to 6 % and equipment lending on two or more occasions from 10 to 6 %.[102] This improvement was associated with a self-reported decrease in skin abscesses in the previous 3 months from 14 to 9 %.[102] Skin cleaning, while not

protective for HIV, has been shown to reduce the risk of endocarditis and skin abscesses. In 110 active drug users in San Francisco reporting on skin cleaning and past infections, only 4·2% of those who skin cleaned some of the time reported endocarditis compared with 14·5% in those who did not skin clean. Forty-eight percent of those who never skin cleaned had suffered skin abscesses compared with 24% of those who sometimes cleaned.[103] In view of the seriousness of these infections harm reduction measures for bacterial infections are needed and even more so for HIV-seropositive users in view of their increased susceptibility to bacterial infections.[75,77–80,82–84]

Conclusions

Infections related to IDU continue although the particular organisms involved have varied over time depending upon injecting practices and the use of unsterile equipment. Patients are susceptible to bacterial and fungal infections which become more of a problem in the setting of HIV infection. The sharing of injection equipment facilitates the spread of malaria, various forms of hepatitis and, latterly, HIV. Harm reduction measures seem to be able to reduce the spread of HIV as well as the morbidity associated with IDU.

The incidence of clinical IDU infection for a drug using population is probably between 3·5 and 5%, about 20% of these infections being viral. The incidence of serious drug related infections is between 0·35 and 0·75%. The attack rate for bacterial infection may be of the order of only 20% during IDU with perhaps 5% for serious bacterial infections and this compares with 80–90% for blood-borne viral infections.

As a consequence of the immunodeficiency secondary to HIV infection, medical admissions for drug users are likely to increase and it is therefore important that physicians be aware of IDU-related medical problems, especially their greater susceptibility to bacterial infections.

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ORIGINAL ARTICLE

Outpatient medical care of injection drug use related HIV

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Summary: By the end of March 1990 470 HIV positive patients, 77% injection drug use (IDU) related, had attended the outpatient department of the Regional Infectious Disease Unit with a cumulative loss to follow-up of only 20%. Coincident with the prescribing of oral methadone and a specific all-day IDU-related HIV medical clinic the total number of appointments increased from 28/month in May 1986 to 300/month in May 1989 ($P<0.001$) and the number of defaulted appointments decreased from a maximum of 60% (17/28) to 16% (48/294, $P<0.001$) in these months.

There was a significant initial increase in the number of defaulted appointments for the infectious disease (ID) clinics from 11% (77/726) to 16% (124/797, $P<0.01$) which returned to previous levels once a specific IDU-related HIV clinic was established. There was also a significant decline in the number of new patients referred which was greater for the urinary tract infection clinics (108 to 56 per 6 months, $P<0.0001$) than for the ID clinics (119 to 88 per 6 months, $P<0.05$).

Keywords: Human immunodeficiency virus, injection drug users, methadone, outpatient medical care, models of health care

INTRODUCTION

Models of health care developed for HIV and AIDS tend to reflect the experience of San Francisco or London where the majority of affected patients have been homosexual or bisexual[1,2]. The services developed in these areas may not necessarily apply to injection drug users. As a group injection drug users exhibit poor utilization of existing services although some of this chaotic behaviour is more a characteristic of their community than drug use per se[3]. Their use of health care facilities is often characterized by a high default rate and an immediate or crisis type of presentation. The medical services dealing with drug users have, until recently, concentrated on the management of their addiction rather than their physical problems and to date behaviour change with respect to HIV has been modest and difficult to initiate[4–6].

This paper describes the experience of initiating and maintaining a medical surveillance clinic for HIV patients, the majority of whom were injection drug users, in an area with little in the way of services for drug users. It considers not only the success of various initiatives but also the effect of this new HIV service on existing clinics.

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PATIENTS AND METHODS

The Regional Infectious Disease Unit (RIDU) has since the early 1960s provided urinary tract infection (UTI) clinics (renal infection and cystitis) which are held on one specific day staffed primarily by the consultant staff. On other days infectious disease (ID) clinics provide outpatient consultations and care for patients with suspected infections including patients returning from abroad. These clinics are staffed by consultants and junior medical staff.

A voluntary self-referral clinic was established in the Edinburgh RIDU in October 1985 to provide open access counselling and HIV antibody testing[7]. As an essential prerequisite to providing voluntary HIV testing, medical clinics for patients found to be HIV seropositive were also established, initially within one of the general ID clinics. The clinic was held in the outpatient department of the RIDU of the City Hospital, Edinburgh and was initially staffed by a consultant (RPB) and one part-time medical officer but latterly also by two research registrars and another full-time medical officer.

The provision of long-term maintenance methadone from the HIV clinics began in June 1986. Methadone initially in daily instalments of 'DTF' 1 mg/ml solution—an elixir which includes chloroform to induce vomiting if injected is provided via a hospital prescription which can be taken to any dispensing pharmacist. Other drugs of addiction such as dihydrocodeine, buprenorphine, prochlo-

perazine or benzodiazepines are not provided but help with establishing contact with general practitioners is provided. Although initially the majority of patients were in receipt of hospital prescriptions, with time more general practitioners have now taken on long-term prescribing.

As a consequence of the disruption to the general ID clinics and the continuing high default rates for IDU-related HIV patients it was decided to offer, in November 1986, IDU-related HIV medical care on separate days from the ID clinics. Provided the patients attend during that day they are seen by a doctor. This overcame the problem of patients arriving late for morning clinics, being sent away and classified as defaulting patients. The busiest time for the clinic is between 11.00 h and 15.00 h and consultations often continue through the lunchtime period.

Additional health care features which were gradually introduced are on-site dental and contraceptive services, on-site care for both parents and children, the services of a dedicated physiotherapist, occupational therapist, dietition, social worker, liaison district nurse and health visitor together with a combined medical and obstetric clinic held at the antenatal clinic. Patients requiring admission, whether as an elective or emergency, remain under the care of their outpatient consultant and wherever possible are admitted to the same hospital ward to ensure continuity of care from the nursing staff.

A retrospective analysis of outpatient records was undertaken from 1985 to 1989 with the objective of assessing the effectiveness of this service. Detailed records of attendance were compiled for May and November of each year since these months are least affected by holidays as well as all months between November 1985 and May 1987.

RESULTS

By the end of March 1990 contact had been made with 470 HIV seropositive patients, 77% (363) of whom were IDU related, 13% (62) were homosexual and 8% (37) were heterosexually related, with 4 cases related to blood transfusion and 4 unknown. The male to female ratio was 2 : 1 (312/158), the median length of follow up was 21.5 months and 25% of the patients had been followed up for at least 36 months. Only 49 (10%) patients had attended for only a single clinic visit whilst 274 (58%) patients had attended for at least 5 visits and 48 (10%) patients for at least 20 clinic visits.

One hundred and sixty-nine (47%) of the drug using individuals were considered by the doctor to be definitely injecting at their initial clinic visit compared to 36 (10%) at their last clinic visit. One hundred and twenty-nine (36%) of the drug users were in receipt of methadone prescribed from the clinic at their last clinic visit.

An additional 71 HIV seronegative but at-risk individuals had also been seen during this time, 66% (47 of whom were drug users, 4% (3) were homosexuals and 21% (15) were heterosexuals, mostly the partners of seropositive patients. The male to female ratio for seronegatives was 1.8 : 1 (46/25).

The overall mean age of the patients was 27.5 years (SD 6.5, range 16–57) and 90% of the patients were between 19 and 39 years of age. The mean age of the patients was 27.7 years for the HIV seropositives compared to 26.8 years for the HIV seronegatives. The mean age for male HIV seropositives was 28.6 years compared to 25.9 years for the HIV seropositive females. This difference is largely accounted for by the fact that the mean age for the male homosexuals was 34.5 years. The mean age for IDU related HIV seropositive patients was 26.9 years for males and 26.0 years for females.

There were 158 (25%) patients who had failed to attend for at least one year and 83 (15%) patients who had not attended for 1.5 years by the end of March 1990. However, a total of 79 patients were known to have reappeared after a one year absence and 37 patients after a 1.5 year absence. The cumulative loss to follow up of HIV seropositive patients between 1985 and 1988 was 20%. Thirty-four (6%) patients are also known to have died, 20 after the diagnosis of AIDS, 12 of drug overdoses and 2 of unknown causes.

Of the living patients, 80 (18%) had been classified as being in CDC stage II, 187 (43%) in CDC stage III and 142 (33%) in CDC stage IV at their last clinic visit.

The total attendance for 2 months (May and November) of each year from 1985 to 1989 together with the number of default appointments are shown in Table 1. In November 1985 HIV appointments accounted for only 3% (13/426) of the outpatient workload but by November 1989 this had risen to 39% (246/637). The default rate for the HIV clinic is not constant ($\chi^2_{(8)}=52.6$, $P<0.001$) whereas over the 4 year period the default rate has remained constant for the UTI ($\chi^2_{(8)}=10.26$) and ID ($\chi^2_{(8)}=3.12$) clinics. Whilst there is a significant linear trend in the reduction of the HIV default rate ($\chi^2_{(1)}=21.6$, $P<0.001$) there is also a highly significant departure from linearity ($\chi^2_{(7)}=31$, $P<0.001$).

The data were examined to see if the default rate changed significantly after the introduction of methadone and the all-day HIV clinic. The change in the default rate after November 1986 was significant ($\chi^2_{(1)}=38.94$, $P<0.001$). The introduction of methadone and the all-day clinic explains the observed variation (residual variation $\chi^2_{(7)}=13.7$, $P>0.05$).

The data were examined in more detail for the time period November 1985 to May 1987 (Table 2). There was no homogeneity of the default rate across the 19 month time period ($\chi^2_{(18)}=83.96$, $P<0.001$). As far as the time periods November 1985–June 1986, (no methadone), July 1986–November 1986 (methadone) and December 1986–May 1987 (methadone and an all-day clinic) were concerned there were significant differences ($\chi^2_{(2)}=61.26$, $P<0.001$) not explained by the introduction of methadone

Table 1. Appointments made and defaults for 2 months of each year, 1985–1989

	UTI clinic		ID clinic		HIV clinic	
	Total	DNA	Total	DNA	Total	DNA
Nov 85	359	52 (14%)	122	16 (13%)	19	6 (32%)
May 86	306	52 (17%)	123	21 (17%)	28	17 (61%)
Nov 86	304	38 (13%)	127	20 (16%)	77	27 (35%)
May 87	283	47 (17%)	103	12 (12%)	172	31 (18%)
Nov 87	275	55 (20%)	112	13 (12%)	152	26 (17%)
May 88	321	50 (16%)	63	8 (13%)	192	42 (22%)
Nov 88	269	34 (13%)	153	24 (16%)	213	36 (17%)
May 89	225	33 (15%)	152	21 (14%)	300	45 (15%)
Nov 89	244	32 (13%)	205	26 (13%)	294	48 (16%)
$\chi^2_{(8)}$		10.26		3.12		52.6
P		NS		NS		<0.001

UTI, urinary tract infection; ID, infectious diseases; HIV, human immunodeficiency virus; DNA, did not attend

alone (residual variation after allowing for methadone and the all-day clinic $\chi^2_{(16)}=83.96-61.26=22.7$, NS at 10% level; residual variation after allowing for methadone alone $\chi^2_{(17)}=83.96-52.05=31.91$, $P<0.02$).

We now consider the effect of relatively large numbers of drug users with HIV on the other clinics. Table 3 documents the total number of appointments and the number of default appointments for the 2 6-month periods of 1986 and the first 6-month period of 1987. There was a significant decline in the total number of UTI appointments ($\chi^2_{(2)}=21.3$, $P<0.001$), a highly significant increase in the total number of HIV appointments ($\chi^2_{(2)}=442$, $P<0.001$) but little change in the total number of ID appointments. The default rates were unchanged for the

Table 2. Monthly HIV appointments and defaults November 1985–May 1987

Month	Total	Did not attend
Nov 85	19	6 (32%)
Dec 85	21	13 (63%)
Jan 86	27	12 (44%)
Feb 86	19	8 (42%)
Mar 86	32	14 (44%)
Apr 86	70	31 (44%)
May 86	28	17 (61%)
Jun 86	62	30 (48%)
Jul 86	51	16 (31%)
Aug 86	55	16 (31%)
Sep 86	57	18 (32%)
Oct 86	56	17 (30%)
Nov 86	77	27 (35%)
Dec 86	78	16 (21%)
Jan 87	97	22 (23%)
Feb 87	102	34 (33%)
Mar 87	172	36 (21%)
Apr 87	138	30 (22%)
May 87	172	31 (18%)
$\chi^2_{(18)}$		83.96
P		<0.001

Table 3. Total appointments made and defaults for each 6-month period from 1986 to 1987

	UTI clinic		ID clinic		HIV clinic	
	Total	DNA	Total	DNA	Total	DNA
Jan 86–Jun 86	2179	349(16%)	726	77(11%)	238	112(47%)
Jul 86–Dec 86	1978	322(16%)	797	124(16%)	374	110(29%)
Jan 87–Jun 87	1894	336(18%)	725	77(11%)	865	192(22%)
$\chi^2_{(2)}$	21.3	2.45	5.12	11.28	442	57.7
P	<0.0001	NS	<0.1	<0.01	<0.0001	<0.001

UTI clinic ($\chi^2_{(2)}=2.45$) and decreased for the HIV clinic ($\chi^2_{(2)}=57.7$, $P<0.001$) as previously noted.

The default rate for the ID clinic significantly increased for the second half of 1986 and then returned to the previous level ($\chi^2_{(2)}=11.28$, $P<0.01$). This coincided with the increased attendance of HIV patients in the general ID clinics as a consequence of the use of methadone between June 1986 and November 1986. The subsequent decline in the default rate in the general ID clinics coincided with the introduction of an all-day clinic for HIV drug users.

Table 4 details the numbers of new patients referred to the UTI and ID outpatient unit between 1985 and 1989. There appears to be a significant decline in the number of new patients referred to the UTI clinics over the period 1985–1989 ($\chi^2_{(8)}=60.72$, $P<0.001$). The decline in the UTI new patients is non-linear ($\chi^2_{(7)}=22.04$, $P<0.01$), being accentuated after June 1988. The decline in patients referred to the general ID clinics over the same period is only just significant ($\chi^2_{(8)}=17.96$, $P<0.05$) and less remarkable in terms of clinical workload. The 6-monthly acquisition of new HIV patients (Table 4) is not at a constant rate over the period ($\chi^2_{(8)}=36.3$, $P<0.001$). Much of the variation is however contributed by the first and last time periods. The number of HIV negative but at-risk patients (mainly HIV negative drug users seeking methadone) rose

Table 4. Number of new patients referred to the RIDU by half year, 1985–1989

	UTI	ID	HIV	HIV -ve high risk
Jul–Dec 85	108	119	21	0
Jan–Jun 86	142	102	47	3
Jun–Dec 86	116	130	58	16
Jan–Jun 87	107	122	65	24
Jul–Dec 87	105	107	40	3
Jan–Jun 88	114	114	56	6
Jul–Dec 88	61	96	43	6
Jan–Jun 89	85	85	63	7
Jul–Dec 89	56	88	33	2
$\chi^2_{(8)}$	60.72	17.96	36.3	70.6
P	<0.0001	<0.05	<0.001	<0.0001

significantly until June 1987 and then ceased. This coincided with a management decision that the prescribing of oral methadone should be restricted to HIV seropositive individuals.

DISCUSSION

The aim of an IDU service should be to initiate and maintain contact primarily in order to deliver health care and health education. This initiation and maintenance of contact may require a variety of initiatives such as needle exchange, methadone and social provisions, as well as medical care which may have to be delivered in ways that fit in with the injection drug user's life style. This concept has recently been more widely advocated by the Advisory Council on the Misuse of Drugs (ACDM)[8].

Unlike other UK centres, in the early 1980s Edinburgh had little in the way of specialist services for drug users[8]. Whilst Edinburgh had a voluntary sector for dealing with injection drug users, from the late 1970s and early 1980s there was a gradual reduction in the prescribing of substitute drugs by general practitioners and psychiatrists based on the assumption that the natural history of drug use was of spontaneous resolution with an overall mortality of around 1% per year[9–12]. The ACDM report in 1988 noted that in Scotland, and in Edinburgh in particular, there had been four notable features of the drug services. Firstly, a dearth of psychiatric input with virtually no specialist support which undoubtedly contributed to the unwillingness of general practitioners to provide care for drug users. Secondly, a limited range of treatment options; thirdly, limited community based services; and lastly, pilot syringe exchange schemes which were not 'user friendly'[8]. When the epidemic of injection drug use occurred in the early 1980s there were little or no medical provisions for dealing with the problem and as a consequence the initial management of IDU related HIV in 1985 and 1986 utilized only the offer of medical care at infectious disease clincs.

In June 1986 evidence suggesting that accelerated loss of CD4 cells was associated with continued IDU was presented at the 2nd International Conference on AIDS in Paris[13,14]. It had also become obvious that it was necessary to provide an underlying drug service before being able to provide health care for HIV. The provision of oral methadone from the HIV clinics after June 1986 coincided with not only the increased numbers attending but also a reduced default rate which achieved the aim of initiating the maintaining contact with IDU-related HIV.

As a consequence of disruption in the general ID clinics and the continuing high default rates for the HIV patients it became necessary to offer IDU-related HIV medical care on separate days from the ID clinics. The use of a specific IDU-related HIV clinic which lasted for the whole day, was not only associated with improved total attendance but also a reduction in the default rate. From an analysis of the default rates it appears that the organizational changes made in the HIV clinic are as important if not more important than the introduction of methadone in explaining the improvement in the default rate.

The additional features of dedicated personnel, continuity of medical and nursing care, etc now offered HIV patients were introduced gradually after November 1986 and are probably as important in maintaining contact but their individual effects are not as easily quantifiable. The overall package has, however, resulted in a continuing decline in the default rate until it is indistinguishable from other clinics.

The measures adopted have enabled us to initiate and maintain contact with over 400 HIV positive patients, 77% IDU related, and 47% injecting at their first visit in an area with no drug services. We have been able to establish long term follow up: the cumulative loss to follow up is only 20% which is not significantly different from our non HIV clinics. This is surprising in view of what is known of drug users and the health care system. The reasons for the loss to follow up are eventually to be quantified but include unforeseen prison sentences, dislike of the methadone being prescribed, a dislike of being associated with an HIV clinic for fear of losing confidentiality, and a dislike of other currently chaotic drug users.

Thus a medical care system which is experienced in the care of both HIV and injection drug use is able to deliver health care to injection drug users. The system used in Edinburgh and at the Montefiore Medical Centre in the Bronx of providing both drug services as well as HIV medical care from the same site by the same doctors seems to be an efficient model of care for injection drug users[15]. The San Francisco and Amsterdam experience of delivering these services at two distinct physical sites is less efficient and seems to provide either a poor medical and/or a poor HIV service for drug users[15].

As a consequence of the lack of drug services in Edinburgh there was a rise in the number of injection drug users uninfected with HIV seeking treatment until in June 1987 they were accounting for over one third of the referrals. Unfortunately the response of the management to this problem was to restrict the service to only HIV seropositives rather than to increase the available resources. This effectively created a two-tier drug service such that it was easier to obtain oral opiates if infected with HIV and resulted not surprisingly in critical comments from the ACDM[8].

> 'In practice this has led to the absurd position whereby treatment involving substitute prescribing is mostly available only to those already infected with HIV. Its use to prevent a seronegative drug misuser from engaging in HIV risk behaviour and acquiring the virus is virtually non-existent'.

Eventually this illogical situation was rectified with the creation of the Community Drug Project in April of 1988[16].

The establishment of IDU-related HIV medical services appeared to have an effect on existing medical clinics. The success of methadone prescribing resulted in an influx of chaotic drug users into the general ID clinics. Until the establishment of a specific IDU related HIV clinic day there was an increase in the default rate of general ID patients presumably as a consequence of the disruption at these clinics since no change was noted in the default rate for the UTI clinic which is held on a separate day. The establishment of a specific all day IDU-related HIV clinic appeared to reverse this trend by removing drug users from the ID clinics.

Over the 4 year period a gradual decline in the number of new patients referred by general practitioners for both the ID and UTI clinics was noted suggesting a possible reluctance by doctors to refer to, or patients to attend, the unit. This was particularly notable from the second half of 1988 and might be as a consequence of the City Hospital, and the ID Unit in particular, being identified with AIDS. It was also more notable for the UTI patients and one might expect such patients to be accommodated more easily in other medical/surgical units. The general ID clinics seemed to be affected less and this is perhaps because these services are not duplicated elsewhere in the region. The establishment of an IDU-related HIV service appears to have had an effect on other patient services and in order to avoid either separate facilities or separation of clinics, much more in the way of education for the general public is still required.

CONCLUSIONS

It is possible to adapt an existing health care system to be more 'user friendly' for injection drug users fulfilling the important aims of initiating and maintaining contact with health care services although there may be effects on the established service in terms of default rate for existing patients and the referral of new patients.

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AIDS

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SCIENCE

Clinical and epidemiological implications of the Centers for Disease Control/World Health Organization reclassification of AIDS cases

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Objective: To establish whether various accepted and proposed AIDS definitions have clinical and biological validity: because the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) reclassifications of AIDS are important not only for describing the epidemiology of HIV disease but also to individual patients.

Setting: Regional Infectious Diseases Unit, City Hospital, Edinburgh, Scotland, UK.

Patients: We analysed the disease progression of 532 HIV-seropositive individuals seen at the City Hospital, Edinburgh, up to the end of July 1991.

Main outcome measures: Annual numbers of potentially reportable cases from the Edinburgh City Hospital Cohort according to three proposed AIDS case definitions based on: (1) first lymphocyte count $\leq 1000 \times 10^6$/l; (2) first CD4 cell count $\leq 200 \times 10^6$/l; or (3) first of two consecutive CD4 cell counts $\leq 200 \times 10^6$/l. Lifetables to death (irrespective of cause) from month of satisfying the above case definitions, and proportion of patients who satisfied each definition in their calender year of enrolment in the cohort are reported.

Results: There is a threefold increase in patients in the Edinburgh City Hospital Cohort defined as having AIDS under the 1987 and the proposed 1992 CDC definitions — a substantial change for patients and epidemiologists alike. That they are describing different immunodeficiency states is clear from lifetable analysis, which reveals median survivals of 20 and 50 months under the 1987 and the proposed 1992 AIDS definitions, respectively. For epidemiological purposes, redefinitions based on the WHO proposed classification of HIV disease using *either* a lymphocyte count $\leq 1000 \times 10^6$/l *or* a CD4 cell count $\leq 200 \times 10^6$/l are broadly interchangeable. They are not equally effective for monitoring individual progression (CD4 cell count is superior). Both, for different reasons, lack biological plausibility.

Conclusions: We therefore suggest that the stricter, biologically more plausible, case definition used in Scotland of two consecutive CD4 cell counts of $\leq 200 \times 10^6$/l [$CD4^{200}$ ($\times$ 2)] should be adopted — not as a new definition of AIDS, but as an additional important state of severe HIV-related immunodeficiency (SHRID). Median survival under the $CD4^{200}$ ($\times$ 2) case definition was 40 months in the Edinburgh cohort. We have illustrated differences in $CD4^{200}$ case ascertainment between injecting drug users and other HIV-infected patients in the Edinburgh City Hospital Cohort. We recommend that surveillance centres should ascertain date of first immunological monitoring as well as date of SHRID diagnosis in order to identify differential case ascertainment.

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Keywords: 1992 CDC AIDS definition, $CD4^{200}$ ($\times$ 2) case definition, severe HIV-related immunodeficiency, lifetable to death, case ascertainment, injecting drug users.

[For editorial comment, see pp 585–587]

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Introduction

None of the staging systems for HIV disease and AIDS is entirely satisfactory. Some, such as those of the Centers for Disease Control and Prevention (CDC) [1], are purely clinical except for requiring confirmation of HIV status, and developed out of a surveillance definition. Others, such as the Walter Reed Staging and Classification system [2], are based on a combination of clinical and laboratory assessments. The Walter Reed classification uses skin reactivity to a panel of antigens and a dichotomy in CD4 cell count (above and below 400×10^6/l) as laboratory assessments, but dichotomizing the CD4 cell count tends to reduce its informativeness. In addition, this system is not very convenient from the clinician's or patient's point of view, since it requires repeated clinic visits to read the skin tests.

Table 1. World Health Organization Interim Proposal for staging of HIV infection.

	Laboratory ($\times 10^6$/l)						
	Absolute CD4 count	or	Total lymphocyte count	Clinical group* 1	2	3	4
A	≥ 500		≥ 2000	A1	A2	A3	A4
B	200–499		1000–1999	B1	B2	B3	B4
C	< 200		< 1000	C1	C2	C3	C4

*Clinical group 1: acute HIV infection/persistent generalized lymphadenopathy/asymptomatic/normal activity. Clinical group 2 (early-stage disease): weight loss < 10% of body weight, minor mucocutaneous problem, herpes zoster within 5 years, recurrent upper respiratory tract infection with normal activity. Clinical group 3 (intermediate-stage disease): weight loss > 10% of body weight, unexplained chronic diarrhoea and/or prolonged fever for > 1 month, oral candidiasis, oral hairy leukoplakia, pulmonary tuberculosis within 1 year, severe bacterial infections and/or bedridden < 50% of day during previous month. Clinical group 4 (late-stage disease): definitive or presumptive diagnosis of any AIDS-defining illness under the 1987 Centers for Disease Control surveillance definition and/or bedridden > 50% of day during previous month.

In 1990, the World Health Organization (WHO) proposed a simplified HIV classification system [3] based on four clinical criteria (acute infection or persistent generalized lymphadenopathy or asymptomatic; minor symptoms; major symptoms; and AIDS) combined with three laboratory groups, to provide 12 distinct stages. The laboratory groups were based on *either* lymphocyte *or* CD4 cell count (Table 1). This proposal had the merits of simplified clinical staging, a powerful predictor in the CD4 cell count, and a cheap alternative in the lymphocyte count. oreover, patients could be classified in the absence of either clinical or laboratory data.

CDC also began to develop a modified classification system for HIV [4] for surveillance purposes. Change was justified because treatment modalities have delayed the onset of illnesses included in the 1987 AIDS case definition and better prediction of health resource utilization was required. To avoid two di ferent schemes, CDC and WHO worked closely t combine the two proposals into a joint CDC/WH classification system for HIV disease in adolescent and adults. The joint CDC/WHO classification syste (Table 2) was based on three clinical groups (A, acut infection or persistent generalized lymphadenopath or asymptomatic; B, all symptomatic conditions othe than AIDS; C, the 1987 definition of AIDS) and thre laboratory groups (1, a CD4 cell count ≥ 500×10^6/ **or** a lymphocyte count ≥ 2000×10^6/l; 2, a CD4 ce count of 200–499 $\times 10^6$/l **or** a lymphocyte count 1000–1999 $\times 10^6$/l; 3, a CD4 cell count < 200×10^6/ **or** a lymphocyte count < 1000×10^6/l).

Perhaps more importantly, CDC also proposed that i addition to the clinical diagnosis of AIDS based on th 1987 revision (i.e., C1–3 of the modified CDC/WH classification system, see Table 2), there should b a definition of AIDS based on all patients with single CD4 cell count < 200×10^6/l irrespective symptoms (i.e., A3 and B3 of the modified CDC/WH classification system, see Table 2). This suggestion ha elicited considerable debate, and dissent [5], but fe data on the validity of these new definitions — eithe clinically or epidemiologically — have been publishe

Several arguments for changing the AIDS case def nition have been proposed. One of the most com pelling is to facilitate assessment of the number HIV-infected individuals who need intensive medica care, and are at highest risk of serious opportunisti illness. Second, with the increasing number of pa tients from diverse risk activities and regions, suc as Asia, being affected by HIV disease, expansion the clinical definition of AIDS will produce an enc less list of opportunistic events [6]. In Thailand, fo instance, it has been suggested that a fungal infectio *Penicillum marneffei*, should be considered an AID diagnosis [7].

Claims that the 1987 definition of AIDS excludes th clinical features of immunodeficiency that manifest i women and drug users have not been supported i reviews of AIDS diagnoses, which have revealed tha women present with the same opportunistic infection as men, and (except for Kaposi's sarcoma [8]) as d drug users. However, this reassurance is perhaps illu sory: any AIDS definition only counts those patient who satisfy it, and so it is not surprising that to dat no difference in presentation of AIDS has been note since other presentations are not considered.

While the natural history of AIDS does not appea markedly different for drug users [8], a more im portant question is whether HIV-infected patients di of non-AIDS conditions before they achieve an AID diagnosis. This appears to be the case for drug user In New York, Stoneburner *et al.* [9] have reported rapid increase in both AIDS and non-AIDS narcoti related deaths. By 1986, for every AIDS-related deat

ble 2. Centers for Disease Control/World Health Organization DC/WHO) classification of HIV infection.

Laboratory ($\times 10^6$/l)					
Absolute CD4 count	or	Total lymphocyte count	Clinical group* A	B	C
≥ 500		≥ 2000	A1	B1	C1
200–499		1000–1999	A2	B2	C2
< 200		< 1000	A3	B3	C3

linical group A (asymptomatic): acute infection with HIV; persistent neralized lymphadenopathy; asymptomatic. Conditions in groups B id C must be absent. Clinical group B (symptomatic): any symptomatic nditions not included in group C. Examples are bacterial infections, ndidiasis (oral or vulvovaginal) for > 1 month, cervical dysplasia or rcinoma, constitutional symptoms, oral hairy leukoplakia. Two dis-ct episodes of herpes zoster or involving more than one dermatome, iopathic thrombocytopenia purpura, *Mycobacterium tuberculosis*, pe-heral neuropathy. Clinical group C: any condition that meets the 1987 DC/WHO case definition for AIDS.

a drug user, there was another as a consequence of nditions such as tuberculosis, endocarditis and bac-rial pneumonia. Similar data have also been reported om Europe [10,11], supporting the argument that ie current AIDS definition does not adequately des-ibe the clinical problems of HIV immunodeficiency drug users.

s far as women are concerned, the Edinburgh ex-erience [12] is that only admissions for urinary act infections are increased among women, while dmissions for other infections show no sex differ-nce. Neoplasia of the genital tract is a major prob-m that particularly affects women, and while some udies suggest that women with HIV disease do have increased risk of progression, they are still too w for a definitive answer [13]. Other than genital act infections and neoplasms, only a few reports ave suggested that HIV-infected women have a dis-se spectrum that differs from that of men. However, any studies have not addressed gynaecological prob-ms. Reports comparing the survival of HIV-infected en and women have been mixed [11]. To date, the dinburgh data have not suggested any sex-related fference in survival for patients with known sero-nversion dates [14]. However, larger studies of the uses of death of HIV-infected women are needed.

the United States, the change of AIDS definition has een linked to the debate over access of HIV-infected dividuals to medical care. Patients with AIDS, but not IV-infected individuals, qualify for financial help with edical care, and so altering the clinical AIDS defini-on could increase the number of patients qualifying r financial assistance. Advocacy groups have urged ie CDC to expand their surveillance definition, and is pressure is likely to transfer to the Social Security dministration, which has decided not to accept the roposed new CDC definition of AIDS as a criterion r assistance [6].

Other problems with the proposed 1992 AIDS definition concern the cost of measuring CD4 cell counts. This expensive laboratory marker of HIV progression is not widely available, even in the United States, let alone in developing countries. While the clinical definition of AIDS relied upon patients presenting with ill health, the 1992 definition will depend upon individuals presenting to the health-care system and upon that health-care system being willing to pay for an investigation to confirm the diagnosis —especially for asymptomatic patients. Inequalities may be exacerbated, not reduced, as recognized in the reasons [5] given for the European rejection of CDC's proposal. These include (1) immunological monitoring of HIV disease requires patients to have enlisted in clinical care, (2) the propensity to do this differs between risk groups and over time, and (3) CD4 cell counting is not well standardized throughout Europe.

However, standardized and quality-controlled methodologies for lymphocyte subtyping have been in place throughout Scotland since 1988, and earlier still in Glasgow and Edinburgh [15]. Scotland has capitalized on CD4 monitoring of HIV disease for short-term predictions of the AIDS epidemic [15,16], using the date of the **earlier** of two consecutive CD4 cell counts of $\leq 200 \times 10^6$/l to define when a patient passes the $CD4^{200}$ ($\times$ 2) threshold. A patient whose immunological depletion has reached this point is designated a $CD4^{200}$ ($\times$ 2) case.

To date, AIDS surveillance centres in the United Kingdom have collected only limited information on CD4 cell count at the time of AIDS diagnosis. Pilot studies of more detailed immunological surveillance are now underway. In the interim, and to inform the discussion of proposed AIDS reclassifications, we provide data on annual numbers of 'AIDS cases' and their survival, based on clinical and immunological follow-up (to the end of July 1991) of the Edinburgh City Hospital Cohort of 532 HIV-1-antibody-positive patients, of whom 397 (75%) were injecting drug users (IDU).

Methods

The Edinburgh City Hospital Cohort was initiated by the referral of three patients in April, August and October 1984. The October patient was diagnosed with AIDS in the same month; the August patient developed AIDS-related complex (ARC) in September 1990; and the April patient developed ARC in November 1987, followed by AIDS in June 1989. Annual referrals thereafter were: 26 patients in 1985, 105 in 1986, 110 in 1987, 102 in 1988, 109 in 1989, 56 in 1990 and 21 in the first 7 months of 1991.

Annual numbers of potentially reportable cases from the Edinburgh City Hospital Cohort are documented according to a series of proposed AIDS case definitions as follows:

(i) according to the date of the first lymphocyte count $\leq 1000 \times 10^6$/l;
(ii) according to the date of the first CD4 cell count $\leq 200 \times 10^6$/l [CD4^{200}($\times$ 1) diagnosis];
(iii) according to the date of the earlier of two consecutive CD4 cell counts $\leq 200 \times 10^6$/l [CD4^{200} ($\times$ 2) diagnosis];
(iv) according to the date of AIDS diagnosis (1987 definition [1]).

For the duration of this study, CD4 counts were evaluated by a whole-blood lysis technique using directly conjugated specific monoclonal antibodies (Becton Dickinson, ountain View, California, USA) with cells enumerated on a FACScan (ountain View, California, USA) flow cytometry analyser.

The interchangeability of definitions (i) and (ii) as proposed by WHO was assessed for patients enrolled in the Edinburgh cohort. Lifetables to death (irrespective of cause) from month of satisfying case definition (ii), (iii) or (iv) are presented as a basis for doctors (and patients) to judge which of the modified AIDS case definitions appears to be valid [17] as a measure of severe HIV immunodeficiency. The proportion of patients who satisfied each definition in their calendar year of enrolment to the cohort is also documented.

Because three-quarters of patients in the cohort (to the end of July 1991) were IDU, among whom deaths from overdose have been as frequent as AIDS-related deaths, Kaplan– eier lifetables to death are presented separately for IDU and other patients satisfying case definitions (iii) and (iv). The deaths of patients who have been lost to clinical follow-up for at least 1 year are ascertained confidentially from the Registrar General, to whom all deaths are notified. Lifetables have therefore been calculated on the basis that enrolled patients were alive at the end of July 1991 unless known to have died. This convention reflects the best quality of information that is available to reporting clinicians, and so the best that surveillance centres might routinely have access to.

Results

Edinburgh City Hospital Cohort

Of the 532 patients in the cohort to the end of July 1991, 397 (75%) were IDU. The oldest patient was born in 1930, the youngest in 1973. edian year of birth for the cohort was 1961; a quarter of patients were born in 1956 or before, and a quarter in 1964 or later. ean age at referral was 28.2 years (s.d., 7.0 years), ranging from 16 to 60 years of age. One hundred and seven AIDS diagnoses have been recorded as follows: one each in 1984 and 1985, two in 1986, 12 in 1987, 16 in 1988, 30 each in 1989 and 1990, and 15 in the first 7 months of 1991. There have been 96 deaths: 58 (60%) were AIDS-related, 11 (11%) were medical non-AIDS, 23 (24%) were overdoses and fou causes are unclassified. Deaths were recorded as fo lows: one in 1984, none in 1985, four in 1986, seve in 1987, nine in 1988, 13 in 1989, 28 in 1990, and 3 in the first 7 months of 1991.

edian year of birth for the 397 IDU was 1961 (rang 1942–1972). Their mean age at enrolment in the co hort was 26.9 years (s.d., 5.3 years) and 205 (52%) ha enrolled before 1988. Fifty-six IDU developed AID before the end of July 1991; and there have bee 60 deaths, including 23 that were AIDS-related an 23 overdoses. Until now, no change has been mad to certified cause of death to reflect *postmortem* find ings of AIDS-related causes in sudden deaths certifie as overdose.

The median year of birth of the 135 non-IDU (o whom 71 were homosexual men and 55 heterosexu contacts) was 1959 (range, 1930–1973). Their mea age at enrolment in the cohort was older, at 31.9 yea (s.d., 9.7 years), and only 39 (29%) non-IDU had en rolled before 1988. Fifty-one non-IDU developed AID before the end of July 1991; and there have been 3 deaths, of which 35 were AIDS-related.

Cases according to modified AIDS case definitions

Table 3 shows the frequency distributions for num bers of reportable cases per annum in the Edinburg City Hospital Cohort according to the above serie of modified AIDS case definitions. One hundred an seven patients had developed AIDS (1987 definition of whom 54 (40 non-IDU) had done so in their ca endar year of enrolment to the cohort, 341 patien had a first lymphocyte count $\leq 1000 \times 10^6$/l and 30 patients a first CD4 cell count $\leq 200 \times 10^6$/l. od fied AIDS case definitions (i) and (ii) were met i the calendar year of enrolment by 158 (46%) an 145 (47%) of the respective cases. These proportion are, however, very significantly different by risk group modified AIDS case definition (ii) was met in the ca endar year of enrolment by 88 (39%) out of 225 dru user cases but by 57 out of 83 (69%) non-IDU case ($\chi^2_1 = 21.3$; $P < 0.001$); alternatively, by 88 (22%) ou of 397 enrolled IDU but by two-fifths of non-IDU pa tients in the cohort [by 57 (42%) out of 135 non-IDU

odified AIDS case definition (iii), as implemented b HIV immunology laboratories in Scotland [15], wa met by 205 patients in the Edinburgh City Hospit Cohort by the end of July 1991, of whom 81 (40% met it in their calendar year of enrolment. These 8 patients constituted 12% (46 out of 397) of IDU pa tients, but 26% (35 out of 135) of non-IDU. Through out the period of enrolment from 1986 (when CD cell count monitoring became established), there wa evidence of earlier disease presentation by injector only 7% (12 out of 184) of IDU in 1986–1987 pre sented as CD4^{200} ($\times$ 2) cases in their calendar yea of enrolment, compared with 13% (four out of 31) o non-IDU and in 1988–1990, compared with 17% (3

Table 3. Modified AIDS case definitions: reportable cases from the Edinburgh City Hospital Cohort.

Year	No. enrolled (no. with AIDS by July 1991)	Modified AIDS case definitions* (criterion met in calendar year of enrolment) (i) No. with first lymphocyte count ≤ 1000	(ii) No. with first CD4 count ≤ 200	(iii) No. with first of two consecutive CD4 counts ≤ 200	(iv) AIDS diagnosis	Deaths All causes	Deaths AIDS-related
Entire cohort'							
1984	3 (2)	1 (1)			1 (1)	1	1
1985	26 (9)	6 (6)			1 (1)	0	0
1986	105 (16)	31 (29)	21 (18)	6 (5)	2 (0)	4	2
1987	110 (20)	21 (17)	38 (23)	21 (11)	12 (8)	7	3
1988	102 (20)	47 (29)	65 (31)	39 (17)	16 (12)	9	6
1989	109 (20)	96 (37)	78 (39)	62 (26)	30 (15)	13	7
1990	56 (17)	90 (29)	74 (26)	50 (16)	30 (14)	28	15
1991†	21 (3)	49 (10)	32 (8)	27 (6)	15 (3)	34	24
Total	532 (107)	341 (158)	308 (145)	205 (81)	107 (54)	96	58
Drug users only							
1984	2 (1)						
1985	19 (3)	3 (3)					
1986	94 (12)	28 (26)	15 (14)	4 (4)		2	
1987	90 (12)	15 (13)	30 (17)	14 (8)	2 (1)	4	
1988	75 (10)	30 (17)	46 (18)	23 (8)	4 (2)	4	1
1989	77 (9)	72 (21)	59 (23)	47 (15)	18 (5)	9	3
1990	27 (8)	63 (12)	54 (11)	34 (8)	19 (5)	18	6
1991†	13 (1)	36 (5)	21 (5)	18 (3)	13 (1)	23	13
Total	397 (57)	247 (97)	225 (88)	140 (46)	56 (14)	60	23

*All counts measured in × 10^6/l. †Up to the end of July 1991.

out of 179) of IDU presenting as $CD4^{200}$ (× 2), 32% (28 out of 88) of non-IDU were $CD4^{200}$ (× 2) in their calendar year of enrolment. A period effect was also evident, with relatively more $CD4^{200}$ (× 2) presentations in calendar year of enrolment during 1988–1990 for both transmission categories than in 1986–1987, and a marked increase in the enrolment of non-IDU in 1988–1990 compared with 1986–1987.

Interchangeability of criteria (i) and (ii)

Table 4 presents data on the interchangeability of criteria (i) and (ii) based on single lymphocyte and CD4 cell count, respectively, for patients enrolled since 1988 in the Edinburgh City Hospital Cohort. (By 1988, CD4 cell count monitoring was available in most UK centres.) Ninety-eight out of 288 (34%) patients met neither criterion (i) nor (ii), 57 (20%) met one but not both criteria (37 met the lymphocyte criterion only, 20 the CD4 criterion); and of the 133 (46%) who met both criteria, 103 satisfied them in the same calendar year, 13 satisfied the lymphocyte criterion earlier and 17 the CD4 criterion earlier.

Lifetables

Of the 96 known deaths in the Edinburgh City Hospital Cohort to July 1991, 58 were AIDS-related. Among the 397 IDU, as many deaths were from overdose as were AIDS-related (23 deaths each), as reported for both European and American drug users [9–11]. Table 5 shows the six-monthly probabilities of survival after criteria (ii–iv). edian survival was 50, 40 and 20 months, respectively, with 80 and 71% of patients surviving at least 2 years after modified AIDS diagnoses (ii) and (iii), compared with 42% of patients still alive at 2 years after the current AIDS diagnosis.

Table 4. Cross-tabulation of when criteria (i) and (ii) were met by 288 patients enrolled in 1988 or later.

(ii) First CD4 count ≤ 200 × 10^6/l	(i) First lymphocyte count ≤ 1000 × 10^6/l: 1988	1989	1990	1991*	Not met	Total
1988	21	4	1	2	3	31
1989	4	40	4	0	8	56
1990	3	1	31	6	6	47
1991*	0	2	3	11	3	19
Not met	1	6	20	10	98	135
Total	29	53	59	29	118	288

*Up to the end of July 1991.

Table 6 presents selected lifetables for both IDU and non-IDU. Non-IDU were on average 5 years older at enrolment and more likely to have satisfied both the modified AIDS case definition (iii) and current AIDS definition in their calendar year of enrolment.

Non-AIDS mortality in HIV-1-antibody-positive IDU in the Edinburgh City Hospital Cohort was approximately 2.5% per annum, of which three-fifths was attributed to overdose (23 out of 37 non-AIDS deaths).

Table 5. Lifetables from (ii) first CD4 count $\leq 200 \times 10^6$/l, (iii) $CD4^{200}$ ($\times$ 2) diagnosis and (iv) AIDS diagnosis to death.

	Modified AIDS case definitions					
	(ii)		(iii)		(iv)	
Months	At risk	Pr(surviving)	At risk	Pr(surviving)	At risk	Pr(surviving)
0	308		205		107	0.99
3	286	0.98	187	0.98	95	0.88
6	270	0.96	177	0.95	79	0.78
9	251	0.94	162	0.91	71	0.74
12	232	0.94	137	0.87	57	0.68
18	189	0.88	109	0.78	43	0.54
24	148	0.80	86	0.71	28	0.42
30	101	0.72	49	0.59	9	0.22
36	72	0.69	28	0.54		
42	44	0.58	17	0.47		
48	24	0.53				
Median survival (months)	50		40		20	
No. deaths	77		68		65	
AIDS-related	58		50		58	
Medical non-AIDS	10		8		4	
Overdose	9		9		3	
Unknown cause	0		1		0	

Table 6. Selected lifetables for injecting drug users and other patients.

	Injecting drug users						Other patients			
	Enrolment to non-AIDS deaths		$CD4^{200}$ ($\times$ 2) diagnosis to death		AIDS diagnosis to death		$CD4^{200}$ ($\times$ 2) diagnosis to death		AIDS diagnosis to death	
Months	At risk	Pr(surviving)	At risk	Pr(surviving)	At risk	Pr(surviving)	At risk	Pr(surviving)	At risk	Pr(surviving)
0	397		140		56	0.92	65		51	
3	389	0.99	137	0.99	50	0.86	63	0.95	45	0.90
6	378	0.99	123	0.98	39	0.77	54	0.89	40	0.80
9	370	0.98	113	0.96	34	0.72	49	0.82	39	0.76
12	363	0.96	103	0.94	23	0.62	37	0.72	36	0.74
18	342	0.95	80	0.84	15	0.44	31	0.66	28	0.62
24	311	0.94	63	0.78	12	0.40	23	0.56	17	0.44
30	273	0.94	44	0.68			11	0.40		
36	262	0.93	25	0.64						
42	198	0.91	17	0.57						
48	156	0.90	12	0.48						
54	120	0.89								
60	89	0.87								
Deaths	37		36		30		32		35	
AIDS-related	Censored		19		23		31		35	
Medical non-AIDS	10		7		4		1		0	
Overdose	23		9		3		0		0	
Unknown cause	4		1		0		0		0	

Nine overdoses were recorded in patients who had passed the $CD4^{200}$ ($\times$ 2) threshold, and three after AIDS diagnosis. Among IDU who met modified AIDS case definition (iii), i.e., $CD4^{200}$ ($\times$ 2) diagnosis, only half the reported deaths were AIDS-related (19 out of 36 deaths), compared with 31 AIDS-related out of 32 deaths in other $CD4^{200}$ ($\times$ 2) cases. The time from $CD4^{200}$ ($\times$ 2) diagnosis to death from any cause was significantly longer for IDU than for non-IDU; but a common lifetable applied from AIDS diagnosis. If non-AIDS-related deaths among injectors are censored, the resulting lifetable from $CD4^{200}$ ($\times$ 2) diagnosis to AIDS-related death (data not shown) is approximated by the square root of the all-causes survival probabilities shown in Table 6. For example, the probability that an IDU did not die from

AIDS within 1 or 2 years of $CD4^{200}$ ($\times$ 2) diagnosis is 0.97 or 0.87, respectively (the latter with standard error of approximately 0.04).

Discussion

By July 1991, 107 (20%) patients in the Edinburgh City Hospital Cohort had been diagnosed with AIDS (1987 definition), but 205 (39%) would have been notifiable as $CD4^{200}$ ($\times$ 2) cases and 308 (59%) by the criterion of $CD4^{200}$ ($\times$ 1). Fifty-four (10%) patients were diagnosed with AIDS in their calendar year of enrolment; 81 (15%) were diagnosed as $CD4^{200}$ ($\times$ 2) cases and 145 (27%) patients had a CD4 cell count $\leq 200 \times 10^6$/l in their calendar year of enrolment.

The $CD4^{200}$ ($\times$ 2) case definition doubles, and the $CD4^{200}$ ($\times$ 1) trebles, the numbers of cases reportable from the Edinburgh City Hospital Cohort according to proposed new definitions of AIDS. This is a substantial change, and is in contrast to the findings of Velaquez *et al.* [18], who surveyed 305 HIV-infected Spanish patients, of whom 21% fulfilled the 1987 AIDS definition and 30% the criterion of any CD4 cell count $\leq 200 \times 10^6$/l, which CDC propose as the 1992 AIDS definition. At the 1992 International AIDS Conference, Cohn *et al.* [19] described a case series from Denver, Colorado, which suggested a 49% increase in $CD4^{200}$ ($\times$ 1) reports over the 1987 AIDS definition. In comparison, recent reports from France [20] and San Francisco [21] suggest a two- to threefold increase in reportable cases by adopting the 1992 proposed definition, which accords with the Edinburgh data. Clearly, the impact of the proposed new definitions on reportable cases will be greater in cohorts of patients who seroconverted in the mid-1980s rather than in the late 1970s, many of whom have already met the 1987 AIDS definition.

Lifetable analysis for the Edinburgh City Hospital Cohort, again unlike the Spanish report, clearly shows that the 1987 AIDS definition and the 1992 modified definitions are not identical in terms of patient survival. The probability of being alive 1 year after having met the 1987 AIDS definition was 0.68, compared with 0.87 after $CD4^{200}$ ($\times$ 2) diagnosis, and 0.94 after $CD4^{200}$ ($\times$ 1) diagnosis. Corresponding median survivals were 20 months from AIDS, 40 months from $CD4^{200}$ ($\times$ 2) diagnosis, and 50 months for patients who had had a single CD4 cell count $\leq 200 \times 10^6$/l.

We have drawn attention to the possible confounding of risk group and differential entry into health care on estimation of lifetables from redefined AIDS to death. When the Edinburgh City Hospital Cohort was subdivided according to injecting drug use or not, differences in both enrolment pattern and immunological progression at enrolment were evident. IDU constituted 184 (86%) of the 1986–1987 cohort of 215 patients and two-thirds of the 1988–1990 cohort of 267 patients. In both periods, IDU were only half as likely to be $CD4^{200}$ ($\times$ 2) cases in their calendar year of enrolment as were other patients; and were only half as likely to be dead within 2 years of $CD4^{200}$ ($\times$ 2) diagnosis as were other patients (44%). Younger age at enrolment, clinical care from an earlier stage of HIV disease [22] (as measured by immune depletion) and, because of previous immunological monitoring, earlier recognition of when the $CD4^{200}$ ($\times$ 2) threshold was passed may each have contributed to drug users' longer survival after reportable $CD4^{200}$ ($\times$ 2) diagnosis. Patients who have truly passed the $CD4^{200}$ ($\times$ 2) threshold before being enlisted in clinical care necessarily have their $CD4^{200}$ diagnosis delayed until after the start of immunological monitoring. Date of first CD4 cell count, as well as date of meeting modified AIDS criterion (ii) or (iii), is thus required for surveillance centres to recognize differential patterns of entry into health care by risk group. In the Edinburgh City Hospital Cohort, lifetables from AIDS diagnosis, as distinct from $CD4^{200}$ ($\times$ 2) case definition, were similar for injectors and other patients, but the clinical symptoms that qualified the patients as AIDS cases also differed by risk group, Kaposi's sarcoma being unusual in drug users. Complex survival patterns will not be resolved satisfactorily by surveillance data; this requires regression modelling [23] of survival and progression from the time of seroconversion for well-characterized clinical cohorts.

For surveillance purposes, we have shown that the proposed WHO reclassifications of HIV disease (i and ii), based respectively on single lymphocyte count $\leq 1000 \times 10^6$/l and single CD4 cell count $\leq 200 \times 10^6$/l, appear interchangeable. This suggests that lymphocyte counts, which are a relatively simple immunological assessment, can be used in centres without CD4 monitoring. But lymphocyte and CD4 cell counts are not equally effective for monitoring the progression of HIV disease in individual patients. We have several reservations about their apparent epidemiological exchangeability. First, if immunological staging is to be used, it should have biological plausibility. Lymphocyte counts do not equate with CD4 cell counts, because CD8 count fluctuates widely and unpredictably in HIV infection. Second, the relationship between CD4 cell count and absolute lymphocyte count in other, ethnically different, HIV-infected populations should not be extrapolated from the Edinburgh data; different lymphocyte count thresholds may be required. Third, and most important, the inherent variability of individual CD4 and lymphocyte counts, associated with biological changes and contributed to by measurement error, determines that in some individuals a single low count is obtained considerably earlier than genuine passage below a particular threshold. For this reason, consecutive counts provide a more reliable marker of disease progression

in individual patients. For example, in 1986, when CD4 monitoring was just beginning in the Edinburgh City Hospital Cohort, 21 patients had a single CD4 cell count $< 200 \times 10^6$/l, but only six were $CD4^{200}$ ($\times$ 2) cases (see Table 1).

The use of lymphocyte counts rather than CD4 cell counts, as proposed by WHO, is less expensive. However, its validity in different risk groups and areas has not been widely examined. In a cohort of homosexual men from Canada, ontaner *et al.* [24] showed that a modified WHO staging system was prognostically meaningful, and that the lymphocyte count was a valid alternative laboratory marker to CD4 cell count in describing survival. Based on their data, lymphocyte ranges of < 1000, 1000–1500 and $> 1500 \times 10^6$/l were suggested. Still cheaper and easier markers (that can be evaluated in stored sera), such as immunoglobulin A, β_2-microglobulin or neopterin, should also be investigated.

It is important that any staging system is broadly comparable between populations. CD4 percentage has been successfully evaluated using standardized procedures and quality control between laboratories, but the absolute lymphocyte count — upon which the CDC/WHO staging system would be based — has not yet been subject to similar scrutiny. Indeed, recent studies [25] suggest that the choice of an individual haematology analyser can result in wide variations in individual total lymphocyte counts. Adoption of the revised CDC and WHO classifications would require the introduction of national and international quality assurance of total lymphocyte determinations.

In summary, the $CD4^{200}$ ($\times$ 2) case definition has greater biological plausibility than immunological staging based on a single CD4 cell count $\leq 200 \times 10^6$/l, as proposed by the CDC/WHO classification. Survival analysis of the Edinburgh City Hospital Cohort indicates that the 1987 and 1992 redefinitions of AIDS are not identical, describing as they do patients at different stages of HIV infection. The CDC/WHO proposal and, *a forteriori*, the $CD4^{200}$ ($\times$ 2) case definition have merit as descriptions of imminent immunodeficiency and therefore an increased risk of ill health; this is useful in clinical practice. The current AIDS definition is essentially a functional assessment of the immune system, as described by a constellation of clinical symptoms. In contrast, CD4 cell counts yield a numerical assessment of the immune system, which is of value in identifying those at risk of developing clinical illnesses, against which prophylaxis and antiviral therapy have some success.

There is a strong argument for a reclassification of HIV disease that does not rely purely on clinical symptoms. Controversy [26] over the CDC reclassification of AIDS [27] is associated with the term AIDS, rather than the condition itself. Therefore, the reclassification should avoid the term AIDS. A definition of severe HIV immunodeficiency is clearly required (CDC/WHO have proposed A3 and B3 using lymphocyte or CD4 cell counts: see Table 2). Our main criticism of the CDC/WHO system is that the use of **consecutive** CD4 or lymphocyte counts provides a better definition of staging. HIV immunodeficiency described by **consecutive** CD4 cell counts $< 200 \times 10^6$/l could be called A3/B3, or perhaps severe HIV-related immunodeficiency (SHRID).

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Out-patient medical care in Edinburgh for IDU-related HIV

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Abstract *Using combined medical and drug clinics, by the end of 1990 we had initiated contact with 511 HIV positive individuals, 75% injection drug use (IDU) related. We have previously reported a significant reduction in the number of missed appointments from 1985–89 following the introduction of methadone and an all day clinic, but between 1989 and 1990 the appointment default rate rose from 17 to 25%. A significant percentage increase in missed appointments was, however, only seen in those not attending the all day clinic ($\chi^2_{(3)} = 121.3$, $p < 0.001$). An analysis of the patients missing appointments during 1989–90 revealed that 36–45% of patients attending each year missed only 1 or 2 appointments, that the majority of missed appointments each year were accounted for by less than 20% of the patients, around 60% of these patients missed appointments in both years and that only 2% of patients attending both years consistently miss 3 or more appointments per year. Laboratory monitoring of HIV, that is at least one sampling episode in a year, was achieved, however, in 92–95% of the patients attending each year. The annual number of patients lost to follow-up varied between 7 and 11% per year, but did not change significantly over time, whilst the cumulative number of HIV infected individuals lost to follow-up after 5 years was only 14%. Between 1986 and 1990 self-reported reduction in IDU was more likely in HIV positive than negative individuals; the number of HIV positive individuals who reported injecting for more than 50% of the year fell from 40 to 5% ($\chi^2_{(4)} = 15.23$, $p < 0.01$) whilst the number who reported at least one injection per year fell from 51 to 23% ($\chi^2_{(4)} = 62.06$, $p < 0.001$). By comparison amongst non-HIV-infected patients the percentage who reported opiate use for more than 50% of the visits during a year rose from 54% in 1986 to a peak of 70% in 1989 ($\chi^2_{(4)} = 10.22$, $p < 0.05$) and those who reported opiate use at least once during the year rose from 57% in 1986 to a peak of 75% in 1989 ($\chi^2_{(4)} = 14.3$, $p = 0.006$). Combined medical and drug clinics from 1986 to 1990 together with a multi-disciplinary team approach to medical care was successful in delivering health care to HIV-infected injection drug users. We have initiated and maintained contact with HIV infected drug users, undertaken laboratory monitoring of HIV in 95% of patients and noted a decrease in self-reported high risk injection drug use. Whilst such a system is relatively inefficient from the health service's point of view, it may be necessary in order to maintain contact with the most difficult drug users.*

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Introduction

In Scotland, as in Southern Europe injection drug use (IDU) is the major risk activity for HIV infection (Communicable Diseases Scotland, 1989a,b,c). The South East of Scotland suffered an epidemic of IDU which started in the early 1980's and peaked around 1983. This was coincident with an influx of relatively cheap heroin, the use of Edinburgh as a distribution point for the rest of Scotland and very high levels of equipment sharing as a consequence of a lack of needles and syringes. The users were young, mostly unemployed and the majority were living on council estates (Pearson *et al.*, 1985; Haw & Liddell, 1987; Brettle & Nelles, 1988). Unfortunately, HIV was introduced at the peak of heroin use resulting in very rapid spread amongst injecting drug users (Peutherer *et al.*, 1985; Robertson *et al.*, 1986; Brettle *et al.*, 1987; Urquhart *et al.*, 1987).

Whilst Edinburgh had a voluntary sector for dealing with injecting drug users, during the 1970's and early 1980's there had been a gradual reduction in the prescribing of substitute drugs by general practitioners and psychiatrists based on the assumption that spontaneous resolution of addiction would occur with a small overall mortality of around 1% per year (Ritson & Plant, 1977; Robertson & Bucknall, 1986; Waldorf & Biernachie, 1979; Wille, 1983). Thus, when the epidemic of IDU occurred, there was little or no medical provision for dealing with the problem.

The published models of health care for HIV and AIDS are based on the experience of clinics in San Francisco or London where the majority of patients affected have been homosexual or bisexual and such models of health care do not entirely apply to injection drug users (Gee, 1989; Jenner *et al.*, 1986). IDU itself creates considerable difficulties for health services notably in the area of missed appointments and patients lost to follow up (Brettle, *et al.*, 1992). The aims of an IDU-related service should be to initiate and then maintain contact, but this may require diverse initiatives such as methadone, psychological and social provisions as well as medical care. To date there has been little if any assessment of the success or failure of IDU-related HIV medical services in delivering care, the majority of papers proposing various theories of care, but rarely providing factual evidence of success or failure.

Since 1985, services for individuals with HIV or AIDS have been developed at the City Hospital in Edinburgh. The considerable psychosocial and physical problems associated with HIV-infected patients necessitated the development in Edinburgh of a multi-disciplinary team able both to manage patients and co-ordinate their care. This paper describes that team, its approach to the care of HIV infected drug users and the results of its out-patient service.

Patients and methods

A voluntary self referral clinic was established in the Edinburgh Regional Infectious Disease Unit (RIDU) to provide open access counselling and HIV antibody testing on October 16th, 1985 to coincide with the commencement of testing of all blood donations by the National Blood Transfusion Service (Brettle *et al.*, 1987). As an essential pre-requisite to providing voluntary HIV testing, medical clinics for seropositive patients were also established, initially within the general clinics. The service was initially staffed by a consultant and one part time medical officer but latterly also by research registrars, full time medical officers and other consultants.

The general RIDU clinics had been faced with large numbers of HIV-infected drug users with no management options for their addiction other than abstinence. There were very few general practitioners or psychiatrists, with notable exceptions, willing to prescribe oral opiate

substitutes and it was obvious that the previous philosophy of awaiting spontaneous resolution of addiction was no longer practicable with the advent of HIV. In 1986 it was also suggested that continued IDU was associated with an accelerated loss of CD4 lymphocytes in HIV-infected patients and, therefore, as an HIV management strategy, the prescribing of oral methadone was commenced (Des Jarlais *et al.*, 1987).

Patients were evaluated for their HIV problems and those found to be injecting drugs were offered a methadone maintenance programme. Methadone, initially in daily instalments of 'DTF' 1 mg/ml solution (an elixir which includes chloroform to induce vomiting if injected), was provided via a hospital prescription which could be taken to any dispensing pharmacist. The majority of initial prescriptions were, and still are, written for daily dispensing, but variations such as two or three times per week are also used. No other drugs of addiction such as dihydrocodeine, buprenorphine, prochloperazine or benzodiazepines are provided. Initially, the majority of patients were in receipt of hospital methadone prescriptions, but with time, more general practitioners have taken on long-term opiate substitute prescribing.

As a consequence of the lack of drug services in Edinburgh there was a rise in the number of uninfected injection drug users seeking treatment, until in June 1987 they accounted for over one-third of the referrals (Brettle *et al.*, 1992). Unfortunately, the response of the Health Board management to this problem was to restrict the service at the City Hospital to only HIV seropositives, rather than to increase the available resources. This created a two-tier system such that it was easier to obtain oral drugs if infected and resulted, not surprisingly, in critical comments from the ACDM (Anonymous, 1988). Eventually, this illogical situation was rectified with the creation of the Community Drug Project in April 1988 (Greenwood, 1990).

Patients are provided with other medication such as zidovudine, antibiotics, etc., as necessary. Initially, *Pneumocystis carinii* pneumonia (PCP) prophylaxis was organized using inhaled pentamidine via the district nurse service although latterly cotrimoxazole has been used more extensively. Generally, however, other than methadone and zidovudine, the majority of prescribing is done by general practitioners with advice from the hospital clinic.

As a consequence of disruption to the general clinics and the large number of missed appointments it was decided in November 1986 to provide IDU-related HIV medical care at a separate all day clinic (Brettle *et al.*, 1992). Provided the patients attend at some time on that day, they are seen by a doctor. This overcame the problem of patients arriving late for morning clinics and being sent away.

Patients are offered routine medical surveillance for their HIV infection, methadone maintenance therapy where necessary, as well as advice on their drug problems. As far as possible a number of other facilities such as counselling, contraceptive advice and supplies, inhaled pentamidine, dental care and refunding of bus fares are also provided on site. Paediatric follow-up is available in the community or via a combined family HIV clinic from the same out patient department.

The majority of IDU-related AIDS or HIV problems have, when necessary, been admitted to the RIDU. Patients are admitted via their general practitioner, the local accident and emergency departments or the HIV medical clinic to wards which also cater for Infectious Diseases and General Medicine. There is a dedicated HIV team, both medical, paramedical and nursing, but no other specialized drug dependence staff. Additional team members now include a dedicated psychiatrist and clinical psychologist as well as physiotherapists, occupational therapists, dietitian, counsellors, liason social workers, liason district nurses and community psychiatric nurses. The consultant staff provides medical continuity

of care for both in-and out-patients. Continuity of nursing care is achieved wherever possible by re-admitting patients to the same ward.

A retrospective analysis of out-patient records was undertaken from 1989 to 1990 to assess the effectiveness of this service. In addition to providing medical care, some assessment of risk behaviour modification was also made at each clinic visit by recording self-reported IDU behaviour. A retrospective review of the in-patient care of HIV seropositive patients at the City Hospital was undertaken from the start of the epidemic until 31st December 1990. Those patients who did not attend for more than 1 year were flagged with the Registrar General to provide ongoing information concerning date and cause of death. In order to re-arrange an appointment it is necessary for defaulting patients to contact the clinic since appointments are not routinely sent out by post. Because the phenomena of re-attendance after missed appointments is so common, patients were defined as lost to follow-up if they had not re-attended before the 31st December 1991 and were not known to have died.

A confidential prospective database containing an assessment of clinical staging, injection drug use, oral drug use and weight, as well as biochemical, haematological and immunological parameters, is maintained on all patients attending the City Hospital. The patients are identified on the database by hospital number only and the cross-link between hospital number and name is stored on a separate database file which is kept on a removable 'floppy disc'.

Results

Out-patient care

The use of combined medical and drug clinics between 1985 and 1990 initiated contact with 511 HIV positive individuals and 68 HIV negative individuals, 75% IDU-related. However, 64 of the HIV positive and three of the HIV negative individuals had died by the end of 1990. From 1986 to 1989 a significant reduction in the ratio of defaulted to total appointments booked, had occurred coincident with the introduction of methadone and an all day clinic (Brettle *et al.*, 1992). Between 1989 and 1990 the default rate rose again from 17 to 25%, but significant increase in defaults was not seen amongst patients attending the all day clinic ($\chi^2_{(3)} = 1.91$) only amongst patients booked for other clinics ($\chi^2_{(3)} = 121.3$, $p < 0.001$, Table 1).

There was, however, no significant change in the number of patients who missed medical appointments between 1989 and 1990 (Table 2). In 1989 65% and in 1990 60% of individuals missed appointments booked at the clinic. There were, in addition, 19 new patients in 1989 and 14 new patients in 1990 who were referred to the clinic but never attended. There was no male/female difference in the defaulting population (data not shown).

In 1989, 50% of the total number of missed appointments were accounted for by only 68 of the patients (26% of the defaulters or 15.5% of the total patients). Looked at another way, 39.5% missed no appointments and 45% missed only one or two appointments per year and only 34/436 (8%) of the patients failed to receive any laboratory monitoring during 1989 at the City Hospital. During 1990, 62% of the missed appointments were accounted for by 88 of the defaulting patients (34.5% of the defaulters or 19% of the total patients). Again 44% missed no appointments, 36% missed only one or two appointments in the year and only 25/454 (5.5%) of the patients failed to receive any laboratory monitoring during 1990 at the City Hospital.

Table 1. *HIV appointments during 1989 and 1990*

Time	Actual	DNA(%)	Total
All-day clinic			
Jan–Jun 89	818	164(17)	982
July–Dec 89	836	153(15)	989
Jan–Jun 90	889	182(17)	1071
July–Dec 90	864	186(18)	1050
Total	3407	685(17)	4092
	$\chi^2_{(3)} = 1.91$		
Other clinics			
Time	Actual	DNA(%)	Total
Jan–Jun 89	556	87(14)	643
July–Dec 89	551	166(23)	717
Jan–Jun 90	562	228(29)	790
July–Dec 90	564	345(38)	909
Total	2233	826(27)	3059
	$\chi^2_{(3)} = 121.29, p < 0.001.$		

DNA = Did not attend

An analysis of patients who missed appointments in both 1989 and 1990 is shown in Table 3. This analysis does not include a number of patients; any new patients who attended in 1990, those that attended in 1989, but had no visits or requests for appointments in 1990, those dying in 1989. Essentially, 45% of the patients who missed appointments were

Table 2. *Frequency tabulation of missed appointments during 1989–90*

	1989		1990	
Frequency of missed appointments per patient	No. of patients	No. of missed appointments	No. of patients	No. of missed appointments
0	173	0	200	0
1	121	121	98	98
2	74	148	68	136
3	36	108	31	93
4	15	60	26	104
5	6	30	14	70
6	8	48	7	42
7	2	14	6	42
8	1	8	3	24
9	0	0	0	0
10	0	0	0	0
11	0	0	0	0
12	0	0	1	12
Total no. defaulting patients	263		254	
Total	436	537	454	621
Mean no. of missed appointments defaulting patient		2.04		2.44
No. of visits where laboratory monitoring occured		1826		2556
Mean no. defaults lab monitoring		3.4		4.1

Table 3. *Cross-tabulation of patients missing appointments during 1989–90: frequency of missed appointments per patient 1990*

Frequency of missed appointments per patient 1989	0	1–2	> 3	Total(%)
0	69	44	21	134 (36)
1–2	77	66	33	176 (47)
> 3	9	22	32	63 (17)
Total	155	132	86	373 (100)
(%)	(41.5)	(35.5)	(23)	(100)

consistent in their behaviour, 29% improved their attendance behaviour and 26% worsened over the 2 years. Of patients who attended in both years, only 2.5% with three or more missed appointments in a year had no missed appointments in the other year and only 2% accounted for three or more missed appointments in both years. In addition, 58% of these patients in 1989 and 64% in 1990 missed appointments in the other year.

The number of individuals lost to follow-up during 1986–90 varied between 8 and 11% per year and did not change significantly over time (Table 4, $\chi^2_{(4)} = 1.21$). The cumulative lost-to-follow-up rate between 1986 and 1990 was 124/582 or 21%. This figure includes the lost-to-follow-up patients who died after defaulting from the clinic. Amongst the HIV-negative individuals, the overall lost-to-follow-up rate was worse at 51/68 or 75%, whilst for the HIV-infected individuals the overall lost-to-follow-up was actually 73/511 or only 14%. A total of 64 HIV-infected patients had died by the end of 1990, a rate of 64/511 or 12.5%. Amongst the HIV-negative individuals the rate was 3/68 or 4.4%. The deaths in the HIV negative patients were in fact all drug users and a comparison of death rates amongst drug users revealed 38/385 deaths or 10% in HIV infected drug users and 3/50 deaths or 6% in uninfected drug users.

In-patient care

Between the onset of the HIV epidemic in Edinburgh in early 1983 and the end of December 1990, 269 (53%) of the 511 HIV-infected patients had been admitted to the RIDU. The 269

Table 4. *Annual number of patients lost to follow up by year*

Year	No. patients lost(%)		Total pts seen in year
1986	10(7)		143
1987	28(11)		258
1988	30(9)		330
1989	34(8)		436
1990	41(9)		454
χ^2_4 =		1.21	
p		NS	

The number lost to follow-up are those patients not seen by 31/12/91 and not notified as having died by the Registrar General Scotland.

Table 5. *Drug users attending the City Hospital assessed as injecting more than 50% of the visits during the year or at least once during the year*

	More than 50% of the year		At least once during the year	
Year	HIV positive (%)	HIV negative (%)	HIV positive (%)	HIV negative (%)
1986	47/111(42)	8/11(73)	58/114(51)	10/13(77)
1987	51/159(32)	13/27(48)	94/174(54	21/29(72)
1988	50/228(22)	7/21(33)	96/235(41)	5/18(28)
1989	40/286(14)	3/13(23)	94/289(33)	6/15(40)
1990	20/307(7)	6/17(35)	67/295(23)	8/16(50)
$\chi^2_4 =$	93.75	7.6	60.9	12.99
p	< 0.001	$= 0.1$	< 0.001	< 0.05

patients (74% infected by IDU) had been admitted on 1135 occasions with the number of admissions for each individual ranging from 1 to 31. These 1135 admissions had utilized 13,676 bed days. Patients who had acquired their HIV via IDU accounted for 825 (73%) of the admissions and utilized 9524 (70%) of the bed days (11.5 days/admission and 3 admissions/patient). The details of admissions and bed days utilized will be the subject of another publication.

Risk behaviour

The self-reported injecting behaviour of drug users attending the clinics each year is documented in Table 5. Amongst HIV-infected patients the percentage reporting injecting at more than 50% of the visits during a year fell from 42% in 1986 to 6.5% in 1990 ($\chi^2_{(4)} = 93.75$, $p < 0.001$) and those reporting injecting at one visit during a year fell from 51% in 1986 to 23% in 1990 ($\chi^2_{(4)} = 60.9$, $p < 0.001$). Amongst the uninfected drug users the percentage reporting injecting at more than 50% of the visits during a year fell from 73% in 1986 to 35% in 1990 ($\chi^2_{(4)} = 7.6$) and those reporting injecting at one visit during a year fell from 72% in 1986 to 50% in 1990 ($\chi^2_{(4)} = 12.99$, $p < 0.05$).

The self-reported use of opiates is documented in Table 6. Amongst HIV infected patients the percentage reporting opiate use for more than 50% of the visits during a year rose from 54% in 1986 to a peak of 70% in 1989 ($\chi^2_{(4)} = 10.22$, $p < 0.05$) and those reporting opiate use at least once during the year rose from 57% in 1986 to a peak of 75% in 1989 ($\chi^2_{(4)} = 14.3$, $p = 0.006$). Amongst the uninfected drug users the percentage reporting using opiates for more than 50% of the visits during a year rose from 50% in 1986 to a peak of 100% in 1990 ($\chi^2_{(4)} = 9.63$, $p = 0.054$) and those reporting opiate use at least once per year rose from 50% in 1986 to a peak of 100% in 1989 ($\chi^2_{(4)} = 9.6$, $p = 0.05$).

Discussion

Traditionally, health care for drug users has been based on psychiatric models developed for the management of addiction and has not concentrated on the physical aspects of care. Models for the treatment of drug addiction have utilized a variety of different regimens including contracts, therapeutic communities, substitution therapy, etc. Whilst such regimens have been evaluated for the treatment of addiction this has not been the case for the management of IDU-related HIV. In addition, some HIV centres seem to operate double

Table 6. *Drug users attending the City Hospital assessed as using opiates more than 50% of the visits during the year and at least once during the year*

	More than 50% of the year		At least once during the year	
Year	HIV positive (%)	HIV negative (%)	HIV positive (%)	HIV negative (%)
1986	51/95(54)	3/6(50)	55/97(57)	3/6(50)
1987	95/144(66)	16/18(89)	101/150(67)	17/19(89)
1988	110/184(60)	5/9(56)	116/188(62)	5/9(56)
1989	164/233(70)	9/9(100)	178/238(75)	9/9(100)
1990	153/237(65)	7/9(78)	167/240(70)	7/9(78)
$\chi^2_4 =$	10.22	9.3	14.3	9.6
p	< 0.05	$= 0.054$	$= 0.006$	$= 0.05$

standards for drug users—often expecting unrealistic behaviour change, such as cure of addiction before offering treatment modalities like zidovudine. Similar constraints on the behaviour of other risk groups are not imposed before offering medical care.

A review of the systems developed in Edinburgh and at the Montefiore Medical Centre in the Bronx of substitute drug prescribing and HIV services delivered from the same site by the same doctors suggested that this was an effective model of care for injecting drug users (Brettle, 1990b). It would appear that a particular skill mix is required of psychosocial and physical care which is accentuated for HIV-infected drug users. The San Francisco and Amsterdam experiences of providing services at two distinct physical sites seemed to provide either a poor medical and/or a poor HIV service for drug users—possibly by not achieving the best skill mix (Brettle, 1990b). Whilst combined clinics appeared to be the most efficient service they had not been systematically evaluated. This current analysis of the Edinburgh service supports our contention that combined medical and drug services are able to deliver medical care to drug users.

As an example, the default rate amongst injecting drug users has been steadily reduced by a number of measures including the use of a dedicated all-day clinic, on site prescribing of substitute methadone for opiate addiction (Brettle *et al.*, 1992) and a multi-disciplinary approach to care. The subsequent rise in the number of missed appointments between 1989 and 1990 was only significant in those patients not utilizing the all day clinic. This rise may have occurred because more clinics are now available and are being utilized by the most chaotic patients.

Despite the fact that non attendance occurred in 24% of booked appointments in 1990 laboratory monitoring of HIV was still achieved in 95% of the defaulting patients. In fact, an analysis of the default pattern for 1989 and 1990 revealed that a relatively small numbers of the total patients (15–19%) accounted for between 50 and 60% of the missed appointments. In addition, around 60% of these patients missed appointments in both years, but only 2% of such patients consistently miss 3 or more appointments per year. This supports the idea that a particular subgroup of patients account for the most of the problem of missed appointments. In both years an average of 41% of the patients attending missed only 1–2 appointments per year which seems acceptable and 45% of the patients were consistent in their behaviour from year to year. The increase in 1990 may in part be explained by the worsening ill health of the cohort. Thus, a relatively inefficient system from the health service point of view does achieve laboratory monitoring of HIV in even the most difficult drug users.

The annual lost-to-follow-up rate for individuals of around 8–11% seems very acceptable

and has remained constant since the clinic opened. The phenomena of re-attendance, even after a number of years, explains the lower than expected cumulative lost-to-follow-up rate of 14%. Not surprisingly, it is lower than the 81% lost-to-follow-up rate in HIV negative patients since the clinic system is very much geared towards HIV-infected individuals. The lost-to-follow-up rate amongst HIV negative patients also, of course, reflects the establishment of an alternative substitute prescribing clinic (the CDPS) in Edinburgh. It does, however, suggest that clinics offering medical care for drug users can achieve reasonable follow-up provided they are adapted to the patient's needs. The flagging of defaulters with the Registrar General has allowed us to be very confident that the lost-to-follow-up rate is accurate and is not obscured by covert deaths.

Admissions for HIV-related medical care were as common for drug users as for other risk activities and reflect the total package of care being provided at the clinic. The bed days utilized by drug users were also not excessive suggesting that their admissions were not more prolonged. However, only 53% of the drug users attending the clinic had required an admission suggesting that the population is at an early stage of HIV infection. Conclusions concerning in patient treatment for progressive HIV-infected drug users cannot, therefore, be made from these data and will be the subject of a future paper.

An assessment of risk activity based on self-reported behaviour suggested that IDU declined between 1986 and 1990, and that this decline was more common in HIV-positive than HIV-negative drug users. The decline in IDU can only be attributed in part to the medical clinics, since there has also been a general campaign in Edinburgh to reduce IDU. During the same time period the use of oral opiates increased, suggesting a change of route of administration rather than abstinence.

In three areas an IDU-related HIV medical service delivering substitute drugs and HIV medical services at the same site has been demonstrated to be effective: the ability to initiate contact, the ability to maintain that contact and the ability to help modify high risk IDU. Other care systems, which separate addiction from HIV medical care, should perhaps also evaluate their results in order that medical care for HIV-infected drug users can be based on facts rather than dogmas.

Conclusions

Dedicated clinics offering both drug management and medical care are able to initiate and maintain contact with drug users, as well as reduce their high risk IDU behaviour. Although there was a large number of missed appointments, the majority of these were, in fact, related to less than 10% of the patient population. Whilst such a system is inefficient from the health services point of view, it may be necessary in order to maintain contact with the most difficult drug users.

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ORIGINAL ARTICLE

Inpatient health care utilization for patients with HIV and AIDS in the Edinburgh City Hospital

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Summary: A retrospective analysis of HIV-positive patients admitted to the City Hospital, Edinburgh by 31st December 1992, 7 years after the inception of the HIV clinic, revealed that 373 patients, 72% of them injection drug users (IDUs), had required 2069 admissions (5.5/admitted patient, 3.3/clinic patient or 0.5/clinic patient/year) and had utilized 21 934 bed days (59 bed days/admitted patient, 35 days/clinic patient or 5 bed days/clinic patient/year).

The average length of stay (ALOS) was significantly longer for AIDS than HIV (non-AIDS) admissions (14.0 vs 9.5, $P<0.0001$) as it was for admissions with a CD200 diagnosis (a CD4 count below 200 cells per mm^3 on two consecutive occasions) compared to those without (12.1 vs 10.0 days, $P=0.004$). There was no gender effect on ALOS but there was a significant effect of risk activity; homo/bisexuals had a significantly longer ALOS than drug users ($P<0.0001$). Homo/bisexual patients with AIDS or a CD200 diagnosis had longer ALOS than drug users (15.7 vs 13 days and 15.8 vs 10.8). By 1992 each member of the clinic was on average utilizing one admission per year and 11.6 bed days per year. The number of admissions in that year for patients without a CD200 or AIDS diagnosis was however low (0.5 and 0.75 admissions/patient/year) compared to patients with an AIDS or CD200 diagnosis (2.6 and 1.6 admissions/patient/year).

The annual number of occupied bed days/living patient was greatest for those with AIDS (60 vs 5 days) or with a CD200 diagnosis (23.5 vs 4.1 days). Females with AIDS used more annual bed days than males (64.2 vs 52.7 days) but not if analysed by CD200 diagnosis (22.0 vs 24.1). As far as risk activity was concerned drug users used more bed days per year than homo/bisexuals with AIDS (60 vs 52 days) or without AIDS (5.4 vs 4.4 days). However homo/bisexuals used more bed days than drug users with a CD200 diagnosis (39.8 vs 20.4 days) or without (7.0 vs 4.2 days) a CD200 diagnosis.

Thus in Edinburgh, both clinical and immunological staging, were predictive of resource utilization. Gender, however, was not predictive and the effect of risk activity was complex possibly because of differing socio-economic status. The extra hospital resources for drug use related HIV appears to be in the form of more frequent admissions at all stages of HIV disease rather than in an increased ALOS per admission.

Keywords: Health care resource utilization, gender, risk group, immunological staging, CD200 diagnosis, AIDS, average length of stay, admissions, annual bed days

INTRODUCTION

Models of health care developed for HIV/AIDS have been based largely on homo/bisexual patients and such services do not always apply to injection drug users (IDUs)[1,2]. Equally the health service resource utilization for IDUs such as number of admissions (NOA), average length of stay (ALOS), annual bed days etc, may be different to other risk groups. There has also been little published on the health care resource utilization for early HIV infection and/or the effect, if any, of drug use.

An epidemic of injection drug use began in Edinburgh around 1980, peaked in 1983–84 and was associated with the sharing of injecting equipment[3–6]. In 1985 and 1986 surveys found that between 38% and 52% of Edinburgh drug users had been infected with HIV[4,7,8]. This report details the

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health care utilization of patients attending the Regional Infectious Diseases Unit (RIDU) with respect to HIV/AIDS between 1985 and 1992.

METHOD

In October 1985, an open access HIV testing and counselling clinic together with HIV medical clinics was established at the RIDU[8,9]. A confidential prospective database containing an assessment of clinical staging, IDU, oral drug use, weight as well as biochemical, haematological and immunological parameters is maintained on all patients attending the RIDU. A retrospective review of the inpatient care of HIV infected patients at the City Hospital was undertaken from the start of the epidemic until 31st December 1989. Thereafter data on admissions were collected prospectively via an admissions database.

The clinical status of the patients is defined by the 1987 CDC definitions of AIDS and the immunological status is defined by a CD4 count of greater than or less than 200 cells/mm^3 during any calendar year of attendance[10,11]. The criterion for fulfilling a CD200 diagnosis is the date of the first of 2 consecutive CD4 counts <200 cells/mm^3. If an individual fulfilled the criterion before or during an admission, or had an AIDS diagnosis before or during an admission, the admission was classified as such. The average length of stay was calculated by subtracting the date of admission from the date of discharge. Analyses of variance were carried out on all data unless otherwise indicated and statistical tests were carried out utilizing SPSS/PC.

RESULTS

Between the onset of the HIV epidemic in Edinburgh in early 1983 and the end of the study on 31st December 1992, 624 known HIV seropositive patients had attended the out patient department at the RIDU. Of these, 436 (70%) were IDUs. By the end of the study period 373 (60%) of all out-patients had been admitted to the RIDU at some point and 154 had developed AIDS. The 373 patients had been admitted on 2069 occasions (5.5/admitted patient, 3.3/clinic patient or 0.5/clinic patient/year) of which 146 were one day admissions of day patients. The number of admissions for each individual ranged from 1 to 35. The total number of bed days utilized was 21 934 (59 bed days/admitted patient, 35.2 bed days/clinic patient or 5.0 bed days/clinic patient/year). There were 879 (42.5%) admissions attributable to 141 patients with a diagnosis of AIDS and these admissions accounted for 11 461 (52%) bed days.

The total number of admissions to the RIDU during 1989, were 2196; 336 or 15% of which were HIV related. The occupied bed days during this year were 14 860, 3651 or 25% of which were HIV related. The ALOS for HIV admissions was 10.9 days whilst for non-HIV admissions it was 5.8 days. By 1992 the total number of admissions was 1999; 423, or 21% of which were HIV-related. The ALOS for HIV admissions was 11.0 days whilst for non-HIV admissions it was 6.2 days.

Table 1. Transmission category (TC) and gender of all out patients, number admitted (IP) and mean age at admission

	Total	IDU	Het	Ho/Bi	Trans	Male	Female
OP	624	436	85	93	6	433	191
%		70.0%	13.6%	14.9%	1.0%	69.4%	30.6%
IP	373	267	35	66	3	267	106
%		71.6%	9.4%	17.7%	0.8%	71.6%	28.4%
Mean age	31.7	30.1	33.0	36.7	45.5	32.8	29.3
SD	7.2	5.4	10.7	8.6	5.1	7.5	5.8

Two hundred and fifty-one (40%) HIV positive patients were not admitted during the study period, 105 were admitted once, 51 were admitted twice, and 217 admitted three times or more (maximum number of admissions = 35).

Table 1 (and Figures 1 and 2) show the characteristics of the HIV positive population by risk activity; IDU, heterosexual (Het), homo/bisexual (Ho/Bi) and transfusion (Trans) as well as by gender and age at time of admission. Risk was undetermined for 5 individuals. Analyses of variance indicated significant differences between the ages of different transmission categories ($F=103.3$, $P<0.0001$) and gender ($F=117.8$, $P<0.0001$).

Admissions

Table 2 (Figures 3 and 4) shows the number of admissions (NOA) per year, the number of patients

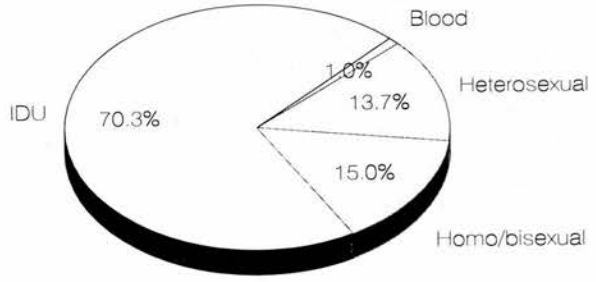

Figure 1. Transmission category or known risk activity of City Hospital Cohort

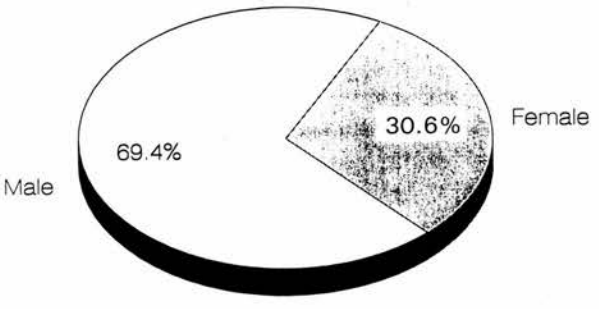

Figure 2. Gender of City Hospital Cohort

Table 2. Total number of admissions (A), number of people attending the clinic (B) and mean number of admissions per patient (C=A/B) by clinical (AIDS and Non-AIDS) and immunological staging (CD4 count of greater or less than 200 cells/mm³)

	AIDS			Non-AIDS			CD4≤200			CD4>200			Total			Deaths
	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	
<1987	6	4	1.5	63	134	0.47	5	11	0.5	64	127	0.50	69	138	0.50	5
1987	26	12	2.2	77	207	0.37	35	30	1.2	68	189	0.36	103	219	0.47	7
1988	64	26	2.5	131	273	0.48	85	69	1.2	110	230	0.48	195	299	0.65	9
1989	133	51	2.6	203	329	0.62	217	123	1.8	119	257	0.46	336	380	0.88	14
1990	284	73	3.7	257	340	0.76	389	161	2.4	140	252	0.56	529	413	1.30	29
1991	205	82	2.5	208	353	0.60	311	214	1.5	102	221	0.46	413	435	0.95	46
1992	173	66	2.6	251	335	0.75	322	199	1.6	102	202	0.50	424	401	1.06	39
Total	879			1190			1364			705			2069	624	3.32	149

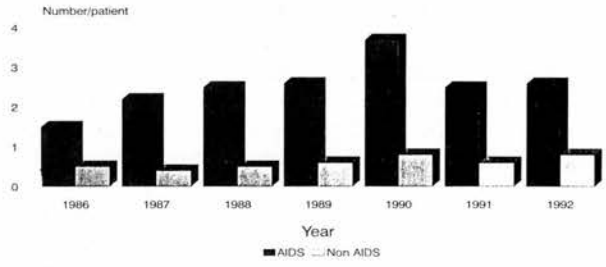

Figure 3. Mean number of admissions per patient by clinical staging (AIDS and Non-AIDS)

attending the clinic each year and the mean number of admissions per year per patient, by clinical and immunological category. These include the admissions to the ward which did not result in an overnight stay. The mean number of admissions per patient gradually increased over time, up to 1990 for all categories, but particularly for AIDS admissions. Over the time period the percentage of admissions for AIDS increased from 8.7% before 1987 to around 50% in 1990–91 and then decreased in 1992 to 41%. This was probably due to the large increase in deaths which occurred in 1990–1991. Similarly, those with a CD200 diagnosis increased from 7% before 1987 to about 75% from 1990 to 1992. The decrease in the total number of admissions after 1990 was contributed to by the opening of a separate facility for respite, convalescence and terminal care (Milestone House).

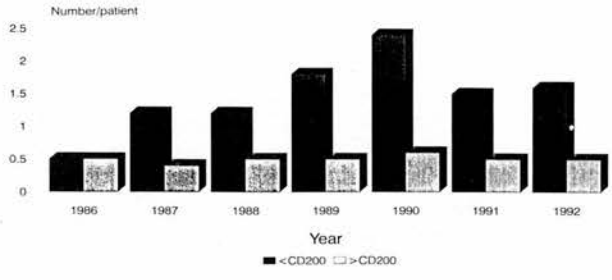

Figure 4. Mean number of admissions per patient by immunological staging (CD4 counts of greater or less than 200 cells/mm³)

Bed days

The number of bed days for HIV admissions steadily increased over time until 1991, when there was a decrease, for the reasons already given. The ALOS from 1986 to 1992 are shown in Table 3 (Figures 5 and 6). These exclude admissions where there was no overnight stay. The overall ALOS decreased from 1987 to 1991 (16 vs 10 days), but increased again in 1992 to 11.3 days. The ALOS of those with a CD200 diagnosis, however, continued to decrease over the study period although the ALOS for AIDS or HIV (non-AIDS) admissions also showed a nadir in 1991.

Over the study period 815 admissions occurred in 141 patients with a diagnosis of AIDS and accounted for 11 461 bed days with an ALOS of 14 days. By comparison there were 1108 HIV (non-AIDS) admissions of 292 patients, accounting for 10 473 bed days, with an ALOS of 9.5 days. Table 4 (Figures 7 and 8) shows the ALOS per patient admitted, by clinical and immunological category, risk activity and gender.

Analyses of variance were carried out examining the effect of risk, gender and AIDS or CD200 diagnosis on average length of stay. There were no significant interactions between AIDS or CD200 diagnosis with either risk activity or gender. There was a significant main effect of AIDS status ($F=23.1$, $P<0.0001$) and a weaker but significant main effect of CD200 diagnosis on ALOS ($F=4.7$, $P\leqslant 0.05$). There was a significant effect of risk activity ($F=3.8$, $P<0.05$) and individual comparisons using the test of Modified Least Significant Difference showed significantly longer lengths of stay for homosexual/bisexual men than for drug users. There was no significant effect of gender ($F=0.86$).

Annual bed day use

The average annual number of bed days utilized per living patient by clinical or immunological staging, risk activity and gender are shown in Table 5 (Figures 9 and 10). Drug users utilized more days than the heterosexuals or homo/bisexuals for AIDS and non-AIDS admissions (59.9 vs 44.7 vs 52.0 and 5.4 vs 3.3 vs 4.4 days) although not when analysed

Table 3. Average length of stay (ALOS) per admission by clinical (AIDS or Non-AIDS) and immunological staging (CD4 count of less than or greater 200 cells/mm³) as well as by year of admission

	AIDS			Non-AIDS			CD4≤200			CD4>200			Total		
	No	Mean	SD	No	Mean	SD	No	Mean	SD	No	Mean	SD	No	Mean	SD
<1987	6	34.8	26	63	14.1	15	5	30.4	33	64	14.8	15	69	15.9	17.1
1987	26	18.4	16	76	11.7	10	35	15.8	14	67	12.2	11	102	13.4	12.5
1988	62	11.8	15	128	10.2	10	83	11.9	14	107	9.8	10	190	10.7	12.2
1989	124	15.0	16	186	9.7	13	199	13.6	16	111	8.6	9	310	11.8	14.1
1990	233	14.8	20	214	8.4	14	324	12.0	17	123	11.0	20	447	11.7	17.9
1991	194	12.6	14	199	7.2	10	295	10.4	12	98	8.4	13	393	9.9	12.5
1992	170	13.5	15	242	9.7	13	313	12.4	16	99	7.7	6	412	11.3	14.4
Total	815	14.0	17	1108	9.5	13	1254	12.1	16	669	10.0	13	1923	11.4	14.8

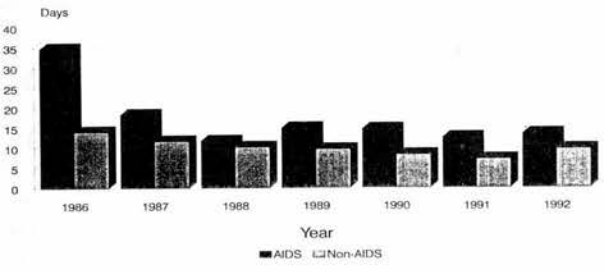

Figure 5. Average length of stay (ALOS) by clinical staging (AIDS and non-AIDS) and year of admission

by with or without a CD200 diagnosis (20.4 vs 23.6 vs 39.8 and 4.2 vs 1.6 vs 7.0 days). this is at least partly a reflection of the fact that homosexual men tended to become known to the clinic at a later stage than the drug users. The average time from first visit to the clinic to death or the end of the study for homosexual/bisexual men was 28 months with 40% of that time being with AIDS. This compared to 49 months for drug users with only 5.5% of that time with AIDS. Females utilized more annual bed days per year per patient than males for AIDS or HIV (non-AIDS) admissions (64.2 vs 52.7 and 5.4 vs 4.8) but not apparently when analysed by with or without a CD200 diagnosis (22.0 vs 24.1 and 4.5 vs 3.9).

First admissions

The clinical status of patients on their first admission was also investigated. Table 6 shows the AIDS and CD200 diagnosis of the transmission categories and genders on first admission. Significant differences were found on Chi square tests between the transmission categories (IDU, Het and Homo/BI) for AIDS versus HIV (non-AIDS) admissions ($\chi^2 = 93.9$, $P < 0.0001$), and also between sexes ($\chi^2 = 7.48$, $P < 0.01$). Differences were also found between transmission categories for CD200 diagnosis at first admission ($\chi^2 = 8.8$, $P < 0.05$), but not between the sexes ($\chi^2 = 1.95$). Further investigation showed that of 41 individuals whose first admission was the first time that they had been seen at RIDU 24 were homosexual men, (34% of all homo/bisexual men seen) 10 were drug users (2.6%) and 7 were heterosexual (12.7%). Drug users were more likely to be admitted prior to an AIDS or CD200 diagnosis than, particularly, homosexual men. Generally, females were more likely to be admitted at an earlier stage than males, though there was no gender difference, when homosexual men were excluded from the analysis.

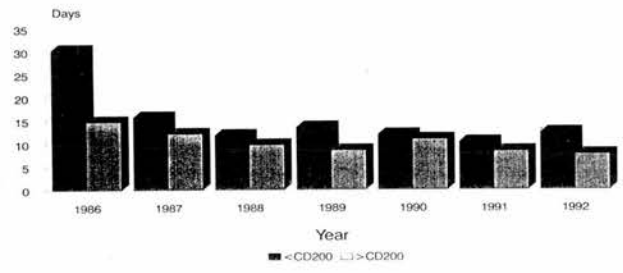

Figure 6. Average length of stay (ALOS) by immunological staging (CD4 count of less than or greater 200 cells/mm³) and year of admission

Sixty-eight of the admissions (3.3%) were as a direct result of injecting drugs (for instance injection injuries such as abscesses or cellulitis) and were unrelated to HIV infection or any other medical condition. A further 65 admissions (3.1%) were drug-related (usually detoxification or stabilization of drug use). The ALOS for both was 12 days; 22.75 days reducing to 7.2 days in 1992. The number of admissions each year was similar, with 20 admissions in 1988, 22 in 1990 and 28 in 1992.

DISCUSSION

In view of the dramatic onset in 1983 of the Edinburgh HIV epidemic in injection drug users[4,8], it is not surprising that the utilization of HIV inpatient services increased over time. The early stage of the Edinburgh drug-related HIV epidemic is demonstrated by the fact that 75% of drug users and 62% of homosexuals did not have a CD200 diagnosis at first admission, though there were other major differences between these transmission categories, as discussed below. The relatively early stage of the Edinburgh epidemic, in health care resource terms, is also exemplified by the fact that 40% of HIV positive patients in contact with the hospital did not require an admission, and only 35%

Table 4. Average length of stay by clinical (AIDS and Non-AIDS) and immunological staging (<or>CD200) for transmission category and gender

Risk Group	AIDS No	AIDS Mean	AIDS SD	Non-AIDS No	Non-AIDS Mean	Non-AIDS SD	CD4≤ No	CD4≤ Mean	CD4≤ SD	CD4>200 No	CD4>200 Mean	CD4>200 SD	Total No	Total Mean	Total SD
IDU	454	13.0	14.4	988	9.3	10.8	871	10.8	12.6	571	9.8	11.5	1442	10.4	12.2
Het	61	13.8	15.7	65	10.5	22.1	87	14.2	22.4	39	7.4	7.8	126	12.1	19.3
Ho/bi	298	15.7	19.9	43	13.6	27.5	284	15.8	20.1	57	13.7	25.2	341	15.4	21.0
Trans	0			10	5.0	4.3	9	3.9	2.7	1	15.0	0.0	10	5.0	4.3
Male	623	14.2	17.4	683	9.2	13.9	915	12.4	16.5	391	9.9	14.1	1306	11.6	15.9
Female	192	13.5	14.2	425	9.8	10.8	339	11.6	12.6	278	10.1	11.4	617	10.9	12.1
Totals	815	14.1	16.7	1108	9.5	12.8	1254	12.1	15.5	669	10.02	13.1			

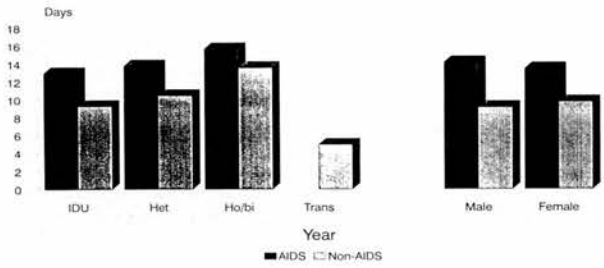

Figure 7. Average length of stay for AIDS and Non AIDS by transmission category and gender

had required 3 or more admissions. By the end of 1989 there were still only 51 patients with AIDS attending the clinic, less than 14% of all HIV positive patients attending in that year. This had risen to 154 (25%) by the end of 1992.

Clinical staging: AIDS and non-AIDS

Among the AIDS patients in this study, 141 out of the 154 (92%) had been admitted at some point and 92 (60%) had had 3 or more admissions. The ALOS for each AIDS admission in Edinburgh decreased from 35 days to 13.5 days whilst the number of admissions rose from 1.5 to 2.6 per AIDS patient. The reduction in ALOS is likely to be as a result of increased familiarity with the disease whilst the increase in the number of admissions is probably associated with increased survival. These results are comparable with a study of 863 patients with AIDS from Northern California in which the mean number of admissions was 3.3 and the ALOS was 17 days in 1983 but 10.7 days by 1987[12]. Considerable variations in the ALOS for AIDS have been reported between various geographical areas; the ALOS for 1983–1986 was 22.3 days for New York and 13.5 days for San Francisco whilst in 1988 it was 9.7 days for Washington State, 32 days for Boston and 18.5 days for New Jersey[13–16]. The number of admissions and the ALOS for AIDS are affected by local demography, health care systems, stages of the HIV epidemic, familiarity with the problems, anti-

Table 5. Average annual bed days per living patient for clinical (AIDS or Non-AIDS) or immunological staging (<or>CD200) by transmission category and gender

Risk group	AIDS	Non-AIDS	CD4<200	CD4>200	Total
IDU	59.9	5.4	20.4	4.2	8.4
Het	44.7	3.3	23.6	1.6	6.7
Ho/bi	52.0	4.4	39.8	7.0	23.5
Trans	0.0	2.1	2.2	1.7	2.0
Male	52.7	4.8	24.1	3.9	10.3
Female	64.2	5.4	22.0	4.5	8.3
Total	59.9	5.0	23.5	4.1	9.6

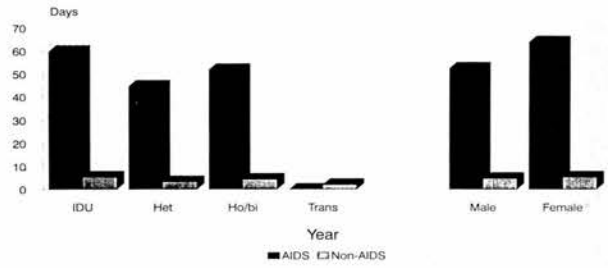

Figure 9. Average annual bed days per living patient for AIDS or Non-AIDS by transmission category and gender

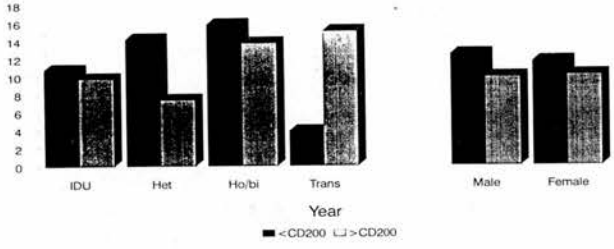

Figure 8. Average length of stay by CD200 status, transmission category and gender

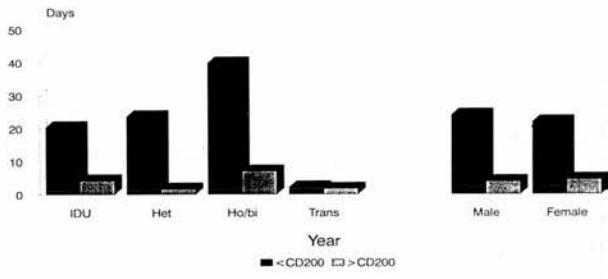

Figure 10. Average annual bed days per living patient for immunological staging (<or>CD200) by transmission category and gender

Table 6. Clinical and immunological status on first admission for transmission category and gender

Status	IDU		Het		Ho/bi		Trans		Male		Female	
	N	%	N	%	N	%	N	%	N	%	N	%
AIDS	16	8	6	38	37	70	0	0	51	26	8	10
Non-AIDS	190	92	10	62	16	30	2	100	149	74	69	90
CD4 < 200	51	25	3	19	20	38	0	0	56	28	18	23
CD4 > 200	155	75	13	81	33	62	2	100	144	72	59	77
Total	206	74	16	6	53	19	2	0.7	200	72	77	28

retroviral therapy and the use of newer therapies for opportunistic infections. There is also evidence of an increasing incidence of conditions such as mycobacterial infections, lymphoma etc. which are likely to require more protracted hospital stays[17].

The ALOS in Edinburgh for HIV (non-AIDS) admissions decreased from 14 days to 7 days in 1991 whilst the number of admissions per clinic patient clinic increased by a factor of 1.6 from 0.47 to 0.75 admissions per patient. It is unclear why the ALOS in 1992 was longer than in the preceding 3 years, but may reflect the fact that prophylaxis for opportunistic infections delays the onset of AIDS-defining illnesses, but does not prevent immunological decline as indicated by a CD200 diagnosis and the onset of serious non-AIDS ailments.

There were 1108 (57.6%) HIV (non-AIDS) admissions in 220 patients, accounting for 10 473 (48%) bed days. The fall in the proportion of HIV (non-AIDS) admissions to AIDS admissions from 1987 to 1990 reflects the development of the epidemic in IDUs. The proportion of bed days used by HIV (non-AIDS) patients also steadily decreased up to 1990.

In New Jersey the admission rate for HIV (non-AIDS) was 1.25/year/patient with an ALOS of 12.7 days whilst in the Montefiore Methadone cohort (1986–87) the admission rates were 0.22 and 0.27/patient/year[18,19]. AIDS accounted for only 14 and 16% of the Montefiore Methadone cohort admissions. Only 8% of the Edinburgh cohorts first admissions were for AIDS suggesting that the Edinburgh and Bronx cohorts are broadly comparable. The ALOS for HIV (non-AIDS) admissions for the whole of the USA was 17.1 days in 1985 and 14.1 days in 1988[20].

Immunological staging

CD200 diagnosis based on falling below a level of 200 CD4 cells/mm^3 was predictive of the number of admissions and the ALOS. There were nearly 3 times as many admissions for those with a CD200 diagnosis than for those without by 1992. There was a significant difference in ALOS between the 2 groups when looked at over the whole length of the study (12.1 vs 10.0). This was less marked than the difference between AIDS and non AIDS admissions, but has become longer over the past 12 months. It is probable that physicians were more likely to admit those with a CD200 diagnosis who were exhibiting some symptoms for investigation than those with a higher count with similar symptoms. Such admissions, where no opportunistic infection was found, would be of short duration compared with admissions of those who were known to have AIDS and this factor probably explains the relatively small difference in ALOS by CD200 diagnosis. These admissions could be considered as a form of 'prophylaxis' for opportunistic infections in a population with poor compliance for standard prophylactic treatment for pneumocystis pneumonia and who have a high incidence of bacterial pneumonia and chronic obstructive airways disease.

Both clinical and laboratory staging of immunodeficiency provide useful indications of health care resource utilization, but the fact that those who have a relatively healthy status with regard to their immunology and clinical status consume significant health care resources in terms of in patient care cannot be ignored. It is also important to note that, in Edinburgh by 1989, whilst HIV patients accounted for 15% of the admissions they occupied 21% of the bed days utilized in the Unit. This increased length of stay compared to other patients and the increased likelihood of admission with advancing immunodeficiency must be taken into account in health care planning terms.

Gender

There was no significant gender effect on ALOS whether analysed by AIDS or CD200 diagnosis but females were more likely than males to have their first admission prior to an AIDS diagnosis. This difference disappeared when drug users alone were examined suggesting that the result has more to do with times at which the different risk groups accessed health care rather than a gender difference. Women with AIDS used more bed days per year per living patient than men (64.2 vs 52.7) but the difference was not statistically significant.

Risk activity

Between 6–7% of both admissions and bed days in HIV positive patients could be identified as being solely related to the effects of drug use rather than to HIV infection. By comparison a similar survey

amongst the Montefiore Methadone programme revealed that 30–40% of the admissions in 1986–87 were drug related, suggesting perhaps that our cohort are less chaotic in terms of drug use than in the Bronx[14].

Drug users and those infected heterosexually had a shorter ALOS than homosexual men (15.4 vs 10.4 vs 12.1 days). This may be related to the finding that drug users were more likely to be admitted at an earlier stage in their illness than homosexual men; 8% of IDUs had AIDS on their first hospital admission compared with 70% of homosexuals. IDUs attend earlier in the illness, are more familiar with the clinic and may be more likely to attend at an early stage when ill. The reasons for this are unclear, but contributory factors may have been the early knowledge of HIV status in the IDU related HIV patients following massive publicity about the epidemic in drug users. It is clear from an earlier study that hospital admissions for drug users, prior to an AIDS diagnosis, can be largely accounted for by admissions with bacterial chest infections[21].

A more difficult question to answer is what effect concurrent drug use or risk activity has on health care resource utilization since the main risk groups are usually not comparable socio-economically. The effect of lower socio-economic status on non HIV admissions has been shown in the USA to increase ALOS by 3 to 30%[22]. In 1989 and 1992 AIDS patients attending RIDU on average utilized 15 and 13.5 bed days per admission, compared to 5.8 and 6.2 for non HIV patients. In Switzerland, where only 31% were drug users, AIDS patients utilized 23.3 days compared to 12.4 days per admission[23]. Two US studies have compared ALOS for AIDS for various risk groups; homosexuals (16.23 days), heterosexuals (21.54 days) and drug using heterosexuals (19.27 days)[14]. A further report[24] showed an ALOS for homosexuals (13.8 days), drug using homosexuals (11.1), heterosexuals (17.0 days) and drug using heterosexuals (19.4 days). In Switzerland by comparison no significant difference could be detected between the ALOS for homosexuals (18.5 days) or drug users (21 days) with AIDS[23].

In Edinburgh, when considering equivalent clinical or immunological stages, IDUs did not use excessive resources as judged by ALOS compared with other groups. Drug users were shown to make up 70% of the total population and, in any one year, they constituted from 70% to 84% of the cohort. Over all they constituted 72% of all those persons admitted and 69% of all days spent in hospital. However the average number of bed days used per living AIDS patient was greatest for drug users (60 days vs 52 days for homo/bisexuals). It seems that drug users overall do utilize more bed days per year than other risk groups although each admission tends to be shorter than other risk groups.

CONCLUSION

Thus in Edinburgh, both clinical and immunological staging, were predictive of resource utilization. Gender however was not predictive and the effect of risk activity was complex possibly because of differing socio-economic status. The extra hospital resources for drug use related HIV appears to be in the form of more frequent admissions at all stages of HIV disease rather than in an increased ALOS per admission.

Whilst the increased use of resources with AIDS or CD200 diagnosis is not unexpected it does underline the fact that the allocation of resources needs to be based on both clinical and laboratory measures of immunodeficiency since neither are sufficient to predict all the health care needs of a population.

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ORIGINAL ARTICLE

Injection drug use-related HIV healthcare—problems and management in Edinburgh

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Summary: The relatively high numbers of patients with IDU-related HIV in Scotland has resulted in considerable management difficulties not previously experienced by other medical units. Chronic physical ill health in drug users is becoming commoner with the advent of HIV and other centres are now experiencing the type of problems that the Regional Infectious Disease Unit (RIDU) in Edinburgh has faced over the last 10 years. Very little has been published concerning the difficulties of managing patients who use drugs and have a physical illness in medical units in the UK. This paper presents examples of common problems together with the RIDU's experience of management in the hope that it will help others to deliver effective and efficient physical and mental health care to patients with drug problems.

Keywords: Injection drug use, HIV, healthcare

INTRODUCTION

By the end of 1991, 35% of the AIDS cases and 50% of those infected with HIV in Scotland, were related to injection drug use (IDU)[1]. Some 52% of Scottish HIV reports originate from Lothian where 57% of HIV cases have involved drug use, the highest percentage in the UK for this particular risk group. The concentration of ill patients in Lothian is testified to by the fact that 50% of the reported cases of AIDS in Scotland and 67% of those with a CD4 count of less than 200 originate from Lothian[1].

The Regional Infectious Disease Unit (RIDU) has been managing IDU-related hepatitis problems since 1970 and IDU related HIV since 1985. The RIDU was designated as a Regional AIDS Centre in 1987 and refurbished in-patient and out-patient accommodation was opened in 1991. The majority of RIDU's established and refurbished accommodation was based on cubicles rather than open wards. Whilst this has been an advantage in terms of managing a diverse population with various infectious diseases it has also created its own problems in the management of the ward areas. Observation of behaviour is not as good as in an open ward and there is a continuing requirement for increased staffing levels with resultant increased costs.

Characteristics of IDU which affect the Health Service

The difficulties of engaging drug users for care of physical ill health should not be underestimated. IDU has a number of characteristics which are problematic for any health service; in the UK the activity itself remains illegal and may be associated with violence or unpredictable behaviour. The aggression associated with problem drug use is often related however to either drug excess (e.g. alcohol/opiates) or drug withdrawals (e.g. opiates or benzodiazepines). The illegality of recreational drug use (other than of alcohol and nicotine) ensures that it is difficult to deliver medical care for drug users whether HIV-infected or not since it is difficult to initiate or maintain contact. As an example the initial default rate at our own clinic was 60%[2]. Delivering medical care is doubly difficult when one considers that many of the individuals also come from socio-economically deprived areas where there is an associated lack of support in the community[3].

Illegal IDU is an expensive activity; it may be funded by theft, cheque book or credit card fraud, drug dealing on a minor or major basis, or via prostitution. The demographics of a drug using population vary with the exact geographical location but in Edinburgh around two-thirds of drug users are male and one-third are female[3]. Drug users are considered by many professionals to have a manipulative tendency in their dealings with individuals and society, possibly up to 70% of drug users may have a criminal record and an unknown number are considered to be 'working the system' i.e. committing Social Security fraud.

Engaging drug users is also difficult because of a 'crisis' type of life style with the need for daily planning to obtain the next supply of drugs. This is not particularly surprising if one considers the pharmacological facts that on average, an injecting heroin drug user requires 3–4 doses per day. Consequently their horizons may be limited to at the most the next 24 h. There is the phenomenon of day–night reversal which contributes to the difficulty

of attending early morning appointments. The numerous crises; social, financial legal etc. lead to the impression of a chaotic life style but in reality hospital appointments are low priority for a healthy drug user by comparison to the many other problems they may have to consider. As a group, drug users are not particularly health conscious by comparison for instance to gay men and this makes consideration of their possible health risks over the next 1–2 years' time a difficult concept to put over. Consequently without a *modified* health care system which understands and considers these problems, drug users have a tendency to record a high default rate in terms of attendance, possibly as high as a 60% default rate for outpatients[2].

It is important for those attempting to deliver health care also to be aware of the consequences of IDU-related HIV for the individual. As ill health develops all patients with HIV suffer a loss of income as a result of possibly both physical and mental deterioration. The disease process obviously also occurs in those engaged in illegal activities and this process may mean that they are far more likely to be apprehended in pursuit of criminal activities. Effectively this phenomenon could be described as 'criminal unemployment' and creates considerable difficulties for those funding an illegal drug habit. Consequently as HIV progresses there may be an increased dependency on the State. This dependency often manifests itself via numerous demands on the health service to prescribe substitute drugs as an attempt to offset a deficiency of illegal funds. This increasing pressure to replace lost income may result in additional difficulties for the NHS; increased theft in and around hospitals, drug dealing in hospital settings, blatant requests for medical help in making fraudulent social security claims (spurious travel expenses, non-existent weight loss, enhanced physical disability), requests for inappropriate hospitalization or manipulated emergency admissions which allow an individual to actually save money which would otherwise have been spent on food, heating etc.

The physical weakness and mental slowing which may accompany IDU related HIV also result in other problems for the drug user such as victimization, harassment and/or exploitation. This may in part be related to a prior position of superiority in the drug culture and a desire on the part of others in the community to repay past wrongs or previous harassment. Alternatively it may simply be related to the exploitation of weaker individuals. The net result however is a gradual inability to cope in the community. When this is combined with a very real difficulty in accepting the discipline of a hospital regime the scene is set for frequent precipitous admissions and discharges. The unwillingness or inability to adapt to changed circumstances results in 'revolving door' type admissions to hospital with considerable frustration for patients, relatives and staff[4]. In our experience increasing family anxiety, frequent hospital admissions and self discharges, increasing use of illegal drugs and harassment often herald the onset of serious HIV encephalopathy or frank dementia[4].

As far as the hospital is concerned IDU-related HIV admissions are often complicated by difficult behavioural problems or incidents; unexplained absences of patients from wards, disruptive visitors, frequent self discharges with re-attendance, self medication and/or with drug dealing in the wards by both patients and visitors and perhaps most importantly for the ward routine, the problem of day/night reversal (sleeping the day away and being awake all night) as a result of drug use. The wards and other hospital areas dealing with drug users may also be faced with the difficulties of theft, frequent noise disturbance, victimization and/or threats towards other patients, manipulation of staff or other patients, attention-seeking behaviour, aggression or assaults both verbal and/or physical on staff and other patients. For those working with drug users, there are also the added pressures that arise from peers; other hospital staff (nurses, doctors, etc.) expressing considerable displeasure over the behaviour of IDU-related HIV patients within the hospital and towards other patients.

Health service staff are naturally alarmed by the prospect of patients carrying offensive weapons such as knives and even on rare occasions guns. It is often not appreciated, however, that the patients are usually more frightened of each other rather than of the staff. In our experience the carrying of offensive weapons in Edinburgh by drug users is usually as a precaution against attack by their peers, rather than as a means of resolving disputes with health service staff. Many sworn enemies such as rival drug dealers may be brought together by HIV and the need to visit the hospital. The staff of course, may be initially entirely unaware of these ongoing difficulties or rivalries and they need an increased awareness of the possibility of highly dangerous relationships between peers. In managing HIV patients it is often also necessary to manage the problems of a patient's visitors as well as the problems of the patient.

Health care service for IDU

In view of all these difficulties it is not surprising therefore that whilst the health care system can cope with small numbers of drug users it has problems delivering a service for large numbers of drug users without disadvantaging its other patients. Even more difficulties occur when one is trying to manage a chronic illness that requires regular attendance over many years. Traditionally health care for drug users has been based on psychiatric models of care often involving the use of verbal or written contracts developed for the management of addiction. The breaking of the contract is followed by immediate discharge back into the community or cessation of the service.

This attractive approach is, however, very much less suited to a situation which necessitates delivering

physical aspects of care sometimes for a life-threatening condition. Our experience has been that whilst such individual contracts may be of help in managing the addiction they are rarely of help in managing the disturbed behaviour in physically ill patients. More important has been the adoption of a general contract of behaviour for the ward. This is effectively a set of rules of behaviour based on health and safety and respect for other individuals who are also ill.

Health care workers themselves are, not surprisingly, concerned and stressed over the difficult behaviour associated with drug use particularly the verbal or physical aggression, disruptive behaviour, theft, the carrying of offensive weapons, drug dealing, self medication, day/night reversal etc. Since much of the aggression and the carrying of offensive weapons is connected with the problems of the drug culture and fear of their peers rather than a wish to harm health care workers, *an understanding of the reasons* for their behaviour helps in managing it in the wards. Whilst as a group, injection drug users exhibit poor utilization of existing services, it is important to remember that some of this chaotic and violent behaviour is as much a characteristic of their community as their drug use[5].

Health care service for IDU-related HIV

Despite the fact that IDU-related HIV is becoming more common there are still relatively few units in the UK with a large enough clinical workload to be able to provide advice on the management of problems associated with IDU-related HIV. There are a number of methods of delivering care for HIV-infected drug users[6]. In San Francisco and Amsterdam the initial services offered HIV care at one site and drug problem services at a separate site[6]. Attendance in such situations is generally poor[6]. Reliance on physical restraint and coercion which superficially might have its attractions is problematic in view of the possibility of deliberate infection of staff by patients[7]. In addition the system is also interested in decreasing harm for both IDU and sexual behaviour by health education and a coercive system is unlikely to succeed.

RIDU Edinburgh

The method of organizing care for HIV patients which we have adopted in Edinburgh has been described previously[2,6,8]; essentially it relies on attracting individuals to the health care system via the facilities and services on offer. It is hoped that by using this method the chance of deliberate infection occurring for the staff is reduced. The difficulties faced by the RIDU in Edinburgh of having a unique population attending the Unit have necessitated a number of changes or alterations in the organization of health care system. The HIV-related service began in 1985 with the establishment of a voluntary self referral clinic at the RIDU to provide open access counselling and HIV antibody testing coincident with the commencement of testing of all blood donations by the National Blood Transfusion Service[9]. As an essential prerequisite to providing voluntary HIV testing, medical clinics for seropositive patients were also established, initially within the general medical clinics.

The general RIDU clinics had been faced with large numbers of HIV-infected drug users with no management options for their addiction other than abstinence. There were very few general practitioners or psychiatrists, with notable exceptions, willing to prescribe oral opiate substitutes in 1985 and it was obvious that the previous philosophy of awaiting spontaneous resolution of addiction was no longer practicable with the advent of HIV. In 1986 it was also suggested that continued IDU was associated with an accelerated loss of CD4 lymphocytes in HIV-infected patients and therefore, as an HIV management strategy, the prescribing of oral methadone was commenced[10].

Patients were evaluated for their HIV problems and those found to be injecting drugs were offered a methadone maintenance programme. Methadone, initially in daily instalments of 'DTF' 1 mg/ml solution (an elixir which includes chloroform to induce vomiting if injected), was provided via a hospital prescription which could be taken to any dispensing pharmacist. The majority of initial prescriptions were, and still are, written for daily dispensing but variations such as 2 or 3 times per week are also used. No other drugs of addiction such as dihydrocodeine, buprenorphine, prochlorperazine or benzodiazepines are provided on an outpatient basis although all prescribed drugs are provided on an inpatient basis. Initially the majority of patients were in receipt of hospital methadone prescriptions, but with time, more general practitioners have taken on long-term opiate substitute prescribing. As a consequence of the lack of drug services in Edinburgh there was a rise in the number of uninfected injection drug users seeking treatment, until in June 1987 they accounted for over one-third of the referrals[2]. The management's response to this increased demand was to limit the service delivered by RIDU to those infected with HIV.

Eventually this anomalous and disastrous situation was rectified with the creation of the Community Drug Project in April 1988 to cater for individuals of unknown HIV status[11]. Patients attending RIDU are provided with other medication such as zidovudine, antibiotics etc. as necessary. Initially *Pneumocystis carinii* pneumonia (PCP) prophylaxis was organized using inhaled pentamidine via the district nurse service although latterly co-trimoxazole has been used more extensively. Generally, however, other than methadone and zidovudine, the majority of prescribing is done by general practitioners with advice from the hospital clinic.

As a consequence of disruption to the general clinics and the large number of missed appointments a policy of stratification of clinics for 'chaotic'

and 'non-chaotic' days as well as offering both drug and medical services at the same site was adopted[2,8].

Patients are offered routine medical surveillance for their HIV infection, methadone maintenance therapy where necessary, as well as advice on their drug problems. As far as possible a number of other facilities such as counselling, contraceptive advice and supplies, inhaled pentamidine, dental care and refunding of bus fares are also provided on site. Paediatric follow up is available in the community or via a combined family HIV clinic from the same out patient department.

The majority of IDU-related AIDS or HIV problems have, when necessary, been admitted to the RIDU. Patients are admitted via their general practitioner, the local accident and emergency departments or the HIV medical clinic to wards which also cater for Infectious Diseases and General Medicine. There was a dedicated HIV team, both medical, paramedical and nursing, but initially no other specialized drug dependence staff. Additional team members now include a dedicated psychiatrist and clinical psychologist as well as physiotherapists, occupational therapists, dietitian, counsellors, liaison social workers, liaison district nurses and community psychiatric nurses. The consultant staff provide the medical continuity of care for both in- and out-patients. Continuity of nursing care is achieved wherever possible by re-admitting patients to the same ward.

As a consequence of the problems of drug use higher staffing levels are required to contain and cope with the problems of this difficult population which stretch from 'bad behaviour' to violent aggression and frank psychosis. We have noticed that more of the most difficult problems tend to occur at high levels of occupancy whether this is in the outpatient department or the wards.

Only 11 of 15 beds in the refurbished ward which deals with mainly HIV patients rather than infectious diseases, were cubicles. The pressure for cubicles for medical reasons has necessitated the use of cubicles from adjacent wards. In addition, in order to spread out the different patient populations attending the RIDU and reduce or avoid problems there has been an additional need to utilize more than one ward area. Consequently the patients have been spread over 3 wards rather than one, in an attempt to reduce behaviour problems. This of course requires more resources and increases the cost of care. Similar problems exist for the outpatient department and in order to spread out the different patient populations attending the RIDU, as detailed above, and to reduce behavioural problems more clinics are organized to spread out the patients' attendance over the week. This obviously requires a higher staffing level than if fewer mixed clinics were utilized.

Continuity of care from both nurses and doctors has, however, been one of our most effective means of reducing problems and incidents. Prior knowledge of the patient by the caring team can easily avoid problems. For the refurbished ward dealing with mainly HIV patients this concept has been extended to rostering and all the nursing staff rotate from day to night duty.

Using combined medical and drug clinics, RIDU had initiated contact with 511 HIV positive individuals by the end of 1990, 75% IDU-related. There had been a significant reduction in the number of missed appointments (60% to 16%, $P<0.001$) following the introduction of methadone and an all day clinic[2]. An analysis of the patients missing appointments during 1989–90 revealed; that 36–45% of patients attending each year missed only one or 2 appointments, that the majority of missed appointments each year were accounted for by less than 20% of the patients, around 60% of these patients missed appointments in both years and that only 2% of patients attending both years consistently missed 3 or more appointments per year[8]. Laboratory monitoring of HIV, that is at least one sampling episode in a year, was achieved in 92–95% of the patients attending each year[8]. The annual number of patients lost to follow-up varied between 7–11% per year but did not change significantly over time, whilst the cumulative number of HIV-infected individuals lost to follow-up after 5 years was only 14%[8].

In addition, maintaining contact with the patients over long periods was associated with harm reduction measures being adopted[8]. Amongst HIV-infected patients the percentage reporting injecting drugs at more than 50% of the clinic visits during a year fell from 42% in 1986 to 6.5% in 1990 ($P<0.001$) and those reporting injecting at one visit during a year fell from 51% in 1986 to 23% in 1990 ($P<0.001$)[8]. By comparison the percentage reporting opiate use for more than 50% of the visits during a year rose from 54% in 1986 to a peak of 70% in 1989 ($P<0.05$) and those reporting opiate use at least once during the year rose from 57% in 1986 to a peak of 75% in 1989 ($P=0.006$)[8].

The inpatient medical care of drug users has also been reasonably successful. A retrospective analysis of HIV-positive patients admitted to the RIDU by 31st December 1992, revealed that 373 patients, 75% of them injection drug users (IDUs), had required admission[12]. Homo/bisexual patients with AIDS had rather longer average length of stay (ALOS) than drug users (15.7 vs. 13 days) but drug users used more bed days per year than homo/bisexuals with AIDS (60 vs. 52 days). The extra hospital resources for drug use related-HIV appeared to be in the form of more frequent admissions at all stages of HIV disease rather than in an increased ALOS per admission[12].

Thus combined medical and drug clinics together with a multi-disciplinary team approach to medical care was successful in delivering health care to HIV-infected injection drug users. However, as a consequence of the need to maintain contact for long periods the health care service has had to tolerate more difficult and problematic behaviour from the patients.

THE PROBLEMS OF IDU-RELATED HIV HEALTH CARE IN RIDU, EDINBURGH

There have been a variety of problems associated with IDU-related HIV medical care and some specific examples of the various problems the RIDU has had to cope with are set out below.

Risk of infection and isolation requirements

There are no student nurses attached to the refurbished inpatient ward for HIV and there are reduced student numbers on the other RIDU wards because of the problem of untrained or unskilled individuals having to deal with the problem of HIV. As an example, the usual nursing establishment for a medical ward in the City Hospital is around 21 whole time equivalents (WTE) but one-third of these are student nurses. By comparison because of HIV the student numbers in the RIDU vary from 0% in the refurbished inpatient ward for HIV (Ward 14) to around 10% in the other wards (personal communication H Coutts and S Parker, Ward 14 City Hospital, Edinburgh).

A large number of patients in the RIDU require isolation in cubicles because of infectious conditions such as salmonella, tuberculosis (TB), or infective diarrhoea. Cubicles are also required because of the nature of the patient population i.e. mixed sexes (one-third are female) and mixed risk groups (20% homosexuals and 70% drug users).

The staffing required for isolation cubicles is higher than for open or 'Nightingale' wards. On an isolation ward nurses are not immediately available for problems such as answering the telephone etc. as a result of the frequent requirement to undertake hand washing before leaving the cubicle. The nursing establishment for an infection ward is consequently greater than for a general ward. In 1993 the ratio of the number of nursing staff of all grades to the number of beds was 0.79 for a mainly non-cubicle medical ward (respiratory medicine) in the City Hospital, between 1.06–1.11 for our general infectious disease wards where 55% of the beds are single cubicles, and 1.7 for our refurbished ward where 73% of the beds are single cubicles (personal communication H Coutts and S Parker, Ward 14 City Hospital, Edinburgh). Ideally 2 nurses are required for each cubicle on a ward.

Escort duty

Every patient leaving the RIDU for any investigation is accompanied by a trained nurse. This was instituted because other areas of the health service were extremely reluctant to cope with our patients, and difficult incidents occurred. Other departments were also concerned over the spillage of body fluids such as vomitus, blood from disconnected intravenous lines etc. A review of the financial year 1992–3 revealed an average of 2.12 WTE nurses out of the RIDU/month covering escort duties. This is equivalent to 0.53 WTE out of the RIDU/day. The grade of staff varied from an average of 7 h month of a G grade sister to 33.3 h of an E grade nurse/month (personal communication H Coutts and S Parker, Ward 14 City Hospital, Edinburgh).

Patient dependency

The physical care of the patients with HIV, especially IDU-related HIV, varies from mildly ill to high dependency (just short of an intensive therapy unit). The mixture of serious physical ill health combined with serious mental ill health is rarely found in any other area of medicine and as yet there is no dependency scale that easily reflects the problems. This lack of an appropriate indicator for care levels has led to difficulties in justifying resources. Whilst there is a dedicated HIV team, both medical and paramedical and psychosocial, there are no other specialized substance abuse staff as might be available in other centres.

The dependency of our patients is both physical and psychological. On a physical scale it can vary from just short of assisted ventilation because of respiratory failure, to the walking well with numerous psychological problems. On the psychological scale the patients can be entirely well or have agitated psychotic states with physical assault on staff (one of the episodes described below).

A 6-month survey of inpatients during 1992 revealed that on average 35.5% of the patients in the RIDU wards each day had HIV infection; 89% of the patients in the wards each day required total care (attention every 2 h) whilst 0.9% of the patients in the ward each day required constant care (one nurse in constant attention). In addition 7% of the HIV patients in the ward each day or nearly one patient/day in the ward each day required increased supervision as a result of medical or drug related drowsiness or because of psychiatric disturbance (personal communication H Coutts and S Parker, Ward 14 City Hospital, Edinburgh).

A survey of dependency utilizing the Patient Assessment Information System (PAIS) scoring system which only accurately reflects acute nursing intervention (and omits the psychological needs) was undertaken on 12 randomly chosen HIV and ID discharges[13]. This revealed a requirement for 81.81 h of nursing on one day with only 47.5 h available for high risk patients and 52.5 h for ID patients with only 32 h available on that day (personal communication H Coutts and S Parker).

Psychiatric problems

HIV-related disease may present with a number of psychiatric problems including frank psychosis. However, the differential diagnosis is extensive and includes toxic confusional states from drugs or infections, space-occupying lesions or HIV related dementia. Admission to the RIDU is commonly

requested in HIV-positive patients in order to exclude the diagnosis of an organic psychosis. There is a very reasonable concern that HIV patients may have an increased likelihood of an organic psychosis which will be more difficult to diagnose in a psychiatric hospital.

During a 12-month period (1992) 4 psychotic patients were admitted to the RIDU to exclude organic psychosis rather than be admitted to the local psychiatric hospital. The time the patients remained in the Unit varied from a few days to over a month and not surprisingly this put considerable strain on the nursing staff. During one of these admissions a member of the ancillary staff was assaulted by a psychotic patient (attempted strangulation).

Security incidents

Over a 12-month period (from August 1992) our busiest ward for HIV experienced 22 reported security incidents. These consisted of 2 physical assaults on staff members by patients, one episode of self-harm (slashed wrists) by a patient, 11 episodes of verbal aggression towards staff threatening physical assault, 5 episodes of serious self medication requiring medical attention, one episode of theft of a patient's valuables, one episode of the fire alarm being set off by patient's children, and one episode of theft of ward equipment (later returned after lengthy discussions!).

During the same time period the outpatient department suffered 12 serious security incidents consisting of, 3 episodes of theft of equipment, 4 episodes of verbal assault threatening physical assault, one episode of physical assault on a consultant (RPB), one episode of a fight between 2 patients which resulted in facial lacerations, one episode of damage to a consulting room as a result of a patient being asked to observe the no smoking policy and at least 2 episodes of unconsciousness requiring several hours of constant care in the day bed area as a result of excess alcohol and drugs. In every year since 1985 we have had to deal with the problem of concealed offensive weapons such as guns and knives. However, the peak of incidents in the outpatient department occurred in 1989 when there were 40 security incidents or 3.3 events per month. There are obviously many more incidents each week not serious enough to require reporting or the attention of the police, which are safely avoided or defused by the staff but which take considerable time to manage.

Interestingly there has been a steady decline in the number of security incidents following the opening of our refurbished outpatient department. In my opinion much of the improvement in behaviour relates to the improved design of the department (3 small and separate waiting areas rather than one large common waiting area).

Self medication

Continued use of non-prescribed drugs administered either orally or by injection cannot be totally eliminated in a Unit whatever the level of supervision. Unlike Drug Detoxification Units, restricted visiting and body searches are not possible for visitors nor for patients who are seriously ill. This results in episodes of excess sedation requiring at the very least constant care or infusions with antidotes and/or the risks of fire from smoking (see below).

Fire incidents

Since the majority of the patients smoke heavily and prefer excessive amounts of sedative drugs, there is a constant danger of fires started by careless cigarettes. Much of the day and night is spent re-enforcing the ward's rules with regard to smoking. For instance, repeatedly requesting patients not to smoke in bed or when drowsy. Over a 20-month period (10/91–5/93) there were 34 fire incidents in the City Hospital involving the attendance of the local Fire Brigade. Of these 15/34 or 44% of the fire incidents occurred in the RIDU area. Ten or 66% of the RIDU fire incidents were related to patients smoking. Of the 7 ward evacuations that occurred as a result of fire incidents in the hospital 6 or 86% of the evacuations occurred in the RIDU area. Four or 57% of the RIDU evacuations were as a consequence of smoking.

Unfortunately, since the patients' addiction to cigarettes is probably greater than or at least equal to opiates, in my opinion it is impossible to enforce a total no smoking policy for the inpatient areas. Smoking is restricted to patients (as opposed to their visitors) and only in their rooms but problems still arise. Not surprisingly the enforcement of such a policy and coping with the fires requires considerable staff especially since 66% of the events occurred out of office hours.

MANAGEMENT STRATEGIES ADOPTED BY RIDU EDINBURGH

In dealing with the diverse problems that I have outlined above a number of strategies have been adopted which others might find of use in this area.

- Violent activities, assaults etc. are managed by calling the police. Patients are informed that illegal drug taking is just as illegal in hospital as out. It is pointed out that other patients may complain to the police via a local drugs' hot line if they observe illegal drug dealings or taking on the wards. By comparison request for information from the Police concerning addresses, times of attendance, etc. for crimes committed off site are not acknowledged.
- There is fairly tight control of prescribed drugs early on in disease process with accompanying harm reduction messages. The message concerning prescribing is that its function is to

provide a safety net for the physical discomfort of addiction rather than to provide a free buzz or 'stone'.

- The healthcare system attempts gradually to increase the level of contact between hospital and patient over time. This gradual introduction of the patient to the 'system' has allowed the hospital to get used to the behaviour of patients using drugs and for them to get used to hospitals' routines. This is one form of re-socialization for the individual with problem drug use.
- The healthcare system aims to provide a supportive and caring environment but with firm discipline over misbehaviour and illegal activities. Perhaps most importantly wherever possible the rules are based on health and safety principles rather than moral or legal overtones. For instance injecting in the hospital is forbidden because of the dangers to staff. Similarly, being stoned is discouraged because of the increased risks of hypostatic pneumonia or fire hazards from concomitant smoking. The harm reduction messages are aimed at improving a patient's well-being.
- Wherever possible the regime for outpatient appointments remains flexible (anytime on a set day) in order to allow for missed appointments. However, the patients are made aware of the need for some structure in the system by making the patient aware of the hospital's limitations. Temporary reductions in methadone dosage (5 ml) have been employed to persuade individuals to attend for their regular hospital appointments and avoid the problems of presenting to the outpatient department when there are no doctors available to prescribe controlled drugs.
- The law relating to the prescribing of drugs such as methadone is explained in verbal and written format in order to remind patients of the fact that by law prescriptions cannot be altered by telephone. This includes the dose, date and timing of instalments.
- Wherever possible we attempt to avoid confrontation over situations that cannot be resolved. This has often meant adapting the regime or removing the patient from the environment that they find difficult. On occasions this may require us either to allow the patient to self discharge or if necessary to discharge the patient from the Unit. Equally the transfer of patients between wards has also been utilized in difficult situations. However, the patients are always offered an outpatient follow-up appointment if they leave the hospital or are discharged. If at all possible treatment in the community will be arranged to try to avoid long spells in hospital which the patients find trying and boring. Such long hospital admissions are difficult for the patients since they have to change their usual routines whether this is remaining in bed all day and being awake all night, simply reducing the amount of drugs consumed each day or handing over control of their drugs to the nursing staff. Increased drug taking in hospital or difficult behaviour is often a symptom of boredom and much can be done to avoid this, for instance by providing satellite TV or computer games.
- A major part of the treatment plan is the co-ordination of substitute prescribing with other carers. For instance, telephoning a patient's GP to check on the doses of prescribed drugs, the cancellation of current controlled drug prescriptions on admission, (to avoid double prescribing via hospital admissions). If necessary this may require confronting patients with evidence of double prescribing and a discussion of why this is detrimental from a health point of view. Spurious admissions 2–3 days before the end of a prescription may be the first indication that the patient's drug habit has increased and that a more frequent dispensing regimen is required until stability ensues. Alternatively it may also reveal an unhealthy black-market drug habit which needs to be addressed. Careful prescribing on discharge is also required to avoid similar problems in community. This may require actually arranging appointments with GPs and prescribing up until that date to avoid the possibility of inadvertent double prescribing by the GP and the hospital.
- Whilst in the ward illegal drug use which is harmful to the patient or other patients usually requires careful discussion in order to arrive at a compromise over the amount of drugs prescribed and the amount of drugs used illegally. Generally this compromise is achieved by suggesting that the dose of prescribed drugs will be reduced until a satisfactory level of consciousness is achieved that reduces the fire risk and the necessity of increased nursing observation. Such reductions eventually result in increased cost for the patient in terms of the need to purchase black market supplies of drugs. Usually a sensible compromise can be arrived at.
- Patients who require to be inpatients often have their illegal or extra drug use covered in order to allow time for investigations or treatment. However the patients are warned that this does not imply any sort of contract or obligation for increased doses on discharge. If the admission is prolonged then an offer of detoxification to the doses prescribed would be made.
- Patients presenting with obvious withdrawal symptoms from alcohol or opiates with a physical illness requiring an admission would be covered with extra doses of opiates or short courses of benzodiazepines (diazepam or chlordiazepoxide). Similarly agitation as a result of

prior stimulant use would also be covered for inpatients. The prime aim would be to reduce the chance of agitation and disturbed behaviour in the wards.

- A major problem for patients has been the fear of pain often relating to the surgical intervention. In general the most successful regimen employed has been either a subcutaneous infusion of opiate over and above maintenance drugs or the use of oral slow release morphine preparations. Unfortunately the design of most infusion pumps allows the patient to boost the pump and without any limit this can lead to problems of opiate excess. In these situations a switch to oral morphine slow release has usually solved the problem. The actual doses employed vary with each patient and in general, provided observation reveals that the patients are not excessively sedated, from a health and safety point of view there is no upper limit on the doses employed to relieve pain. For instance, the maximum daily dose employed to date in a non-drug user with KS requiring palliative care has been 7.5 g. At present we have an IDU-related HIV patient on a total of 3.5 g of opiate for pain secondary to MAI.
- Not surprisingly there is considerable concern amongst the staff over the level of prescribing of sedative drugs. However it is important to note that euthanasia (the deliberate hastening of death by a doctor) or assisted suicide is not practised as an overt or covert policy of the medical staff. The nursing staff need to have confidence in the medical management policy relating to sedative and pain control prescribing. The major difficulty is that a number of patients, particularly drug users, request high levels of sedation prior to death and this may cause concern amongst a number of staff, medical and nursing as well as relatives. Staff or relatives often find it difficult to accept that the medical staff should accede to patients' requests for what appears to be excessive sedation.
- In the case of pain relief the medical staff commonly increase drugs to relieve pain either at the request of the patient or at the request of nursing staff or relatives if the patient is observed to be distressed. A similar set of principles are required for the relief of psychological distress in connection with requests by patients for increased sedative medication. It is important to acknowledge that patients requiring palliative care have a right to request increased doses of sedative drugs in the case of psychological distress. Failure to deal with this psychological distress adequately often leads to management problems and in the wards between patient and nurse, nurse and doctor or even nurse and nurse. One symptom of this psychological distress is an increased use of illegal drugs on top of prescribed drugs in an attempt to achieve the desired level of sedation. This uncontrolled or unregulated prescribing often results in care problems such as fire hazards with smoking whilst heavily sedated or overdose requiring increased nursing care. Not surprisingly there is a major concern amongst the nursing profession that in such situations the dispensing of prescribed drugs may result in the untimely death of a patient and possible legal or disciplinary action.
- The relief of psychological distress is thus as important a facet of the management of a patient who is terminally ill, as adequate pain relief. Many patients do not wish to discuss death and dying and in fact if prompted will request medication to relieve them of the distress of contemplating their approaching death. The management of such distress and requests for relief is right and proper. In some patients this distress may be relieved by counselling but in others increased levels of sedation are appropriate. The major concern is differentiating the well patient with HIV who simply wishes to use more drugs (stoned) from the patient for whom active therapy is not appropriate and requires relief of distress. All of us have problems defining exactly when a patient becomes 'terminally' ill with HIV. However, once a decision has been made that the patient requires palliative care the nursing staff, relatives and medical staff all find it much easier to accept that relief of psychological distress is appropriate.
- It therefore seems appropriate to give consideration for such sedative therapy for those requiring palliative therapy. Relief of severe psychological distress is a perfectly acceptable part of palliative therapy and must not be ignored. In our collective experience when patients near to death have been given adequate pain relief and/or psychological relief use of illegal drugs has ceased. This has often required quite alarming doses of opiates as a result of past use of opiates, but in all cases that could be recalled the large doses were observed to be safe in hospital.

CONCLUSIONS

The range of problems which occur with IDU-related HIV are not only extensive but also very different to those usually faced by the health service. The RIDU in Edinburgh has had to adapt in order to manage drug users with a chronic illness. This adaptation has required new skills on the part of the staff and the gradual reduction in problems and incidents suggests that not only are the staff adapting but possibly the patients are also adapting to our health care system. The essential aim is over time to increase a patient's awareness of their responsibilities for their own health as well as to the health care system. Despite this improvement, the

RIDU is still having to cope with a considerable amount of disturbed behaviour, probably more so than other Units managing HIV in the UK. As IDU-related HIV appears in other areas of the UK these with the associated disturbed behaviour. Hopefully our experience of how we have adapted and responded to the behavioural problems will be of some help.

Some may question why a health care system should have to cope with this sort of behaviour and there seems no doubt that if the patients were not infectious and capable of infecting other individuals, including health care staff, it is unlikely that funds would continue to be made available for the current level of service which is extremely expensive (in the region of around £3 million per year for the inpatient and outpatient facilities). HIV/AIDS funds are now being reduced in line with the reductions in the public sector borrowing requirement. It also appears that the epidemic may be about to plateau.

However, caution is required in this area of healthcare since any suggestion of a lack of caring by society may result in a backlash with the possibility of increased levels of aggression towards the health service. Lower levels of staffing, the use of cheaper methods of staffing such as temporary ('bank') staff, a higher turnover of staff with reduced continuity of care and/or higher occupancy levels of difficult patients will lead to an increase of violent behaviour with increased risks for staff of deliberate or accidental inoculation of HIV.

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The Edinburgh City Hospital cohort: analysis of enrolment, progression and mortality by baseline covariates

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Summary

We describe baseline characteristics, enrolment, progression and mortality of the Edinburgh City Hospital HIV cohort. There were 431 men and 191 (31%) women; 439 (71%) infected via injection drug use (IDU); 92 (15%) via homosexual intercourse; 84 (13%) via heterosexual intercourse and 7 from blood products. Median annual rate of CD4 cell loss was 49 (90% range: 15–146); Both homosexual men and patients aged >40 years at enrolment lost CD4 cells significantly more quickly. In multifactorial analysis controlled for baseline CD4 count and IgA, there was no gender effect, but young patients (<25 years) progressed significantly more slowly to AIDS (RR 0.4, $p=0.00$). Homosexual men progressed significantly more quickly than IDUs, with adjusted relative risks (RR) of 2.9 ($p=0.00$), 2.5 ($p=0.01$) and 1.5 ($p=0.1$) for progression to CDC stage IV, AIDS and death, respectively. The three-year survival rate post-AIDS was 25% (SE 4.3) and there was no gender effect on survival. There was, however, an age effect whereby individuals diagnosed with AIDS in their 40s or later showed poorer survival (RR 1.9, $p=0.04$). Zidovudine treatment after an AIDS diagnosis significantly lengthened post-AIDS survival (RR 0.5, $p=0.08$).

Introduction

In common with several other European cities, Edinburgh experienced an injection drug use (IDU)-related HIV epidemic in the early 1980s. It started in early 1983, and spread rapidly through a young group of needle-sharing drug users in the city housing estates.[1–4] The HIV epidemic was recognized in 1985, and hospital-based medical services were established in that year specifically to address the IDU risk.[1,5,6] Injection drug users (IDUs), not surprisingly, form the core of the Edinburgh City Hospital prevalent cohort, and their homogeneity with respect to time of infection, age and risk activity makes them a valuable cohort for studying effects of other cofactors such as gender on HIV disease progression. Patients had the advantage of reasonably easy access to a health-care system. This paper describes the prevalent cohort, its pattern of enrolment, overall progression to defined clinical and immunological endpoints and survival from those endpoints. The effects on progression and survival of gender, risk activity, age and enrolment year were also investigated.

Methods

Patients

A voluntary self-referral clinic was established in the Edinburgh Regional Infectious Disease Unit (RIDU), City Hospital, Edinburgh in October 1985 to provide open-access counselling and HIV antibody testing.[3] As an essential pre-requisite to providing voluntary HIV testing, medical clinics for patients found to be

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HIV-seropositive were also established in the Out-Patient Department of the RIDU.[5,6]

All HIV-positive patients visiting the RIDU self-referral clinic between its inauguration in October 1985 and December 1992 (plus a small number of HIV-positive patients seen in 1984 and 1985 before the opening of the clinic) were included in the present cohort. A confidential prospective database containing an assessment of clinical staging, IDU, oral drug use and weight, as well as biochemical, haematological and immunological parameters, is maintained on all patients attending the RIDU. Those patients who did not attend for more than one year were flagged with the Registrar General to provide information about date and cause of death.

Using combined on-site medical and drug-prescribing clinics, with a multi-disciplinary team approach to medical care, we have been able to initiate and maintain contact with HIV-infected drug users. In addition to delivering health care, we have also noted a reduction in both self-reported and observed high-risk injection drug use. A more complete description of the methods and results of this approach has been reported elsewhere.[5,6] Regular attenders were scheduled to be seen every 3–6 months, whilst irregular attenders had laboratory monitoring performed on an opportunistic basis.

Laboratory methods

Lymphocyte surface markers, including CD4 count, were performed throughout by flow cytometry on whole-blood analysis. Blood samples were stained by directly conjugated monoclonal antibody pairs using CD16/CD45 to confirm a lymphocyte gate (Becton Dickenson Leukogate) and CD4/CD8 to identify T-cell subpopulations (Becton Dickenson). Data analysis used Simulset software following flow cytometry on a Facscan analyser (Becton Dickenson). Absolute CD4 counts were derived from the total white-cell count performed by the Department of Haematology, Royal Infirmary, Edinburgh (Sysmex) and lymphocyte and CD4 percentages obtained by flow cytometry. Since 1989, the HIV Immunology Laboratory has regularly participated in the MRC/NEQAS National Quality Assurance Scheme for T lymphocyte numbers and has consistently demonstrated acceptable performance.

Prior to June 1990, serum IgA quantification was by a nephelometric method using polyclonal specific antisera (Scottish Antibody Production Unit, Carluke). After that time, a commercial radial immunodiffusion method was used (Binding Site, Birmingham). The two methods were cross-validated at the time of technique transfer.

Statistical methods

Enrolment patterns were investigated by regressing root CD4 count at enrolment vs. descriptive cofactors (age, gender, risk activity, year of enrolment). Enrolment CD4 count, a surrogate for duration of infection, was the first CD4 count in the initial 365 days of follow-up, regardless of the clinical stage of

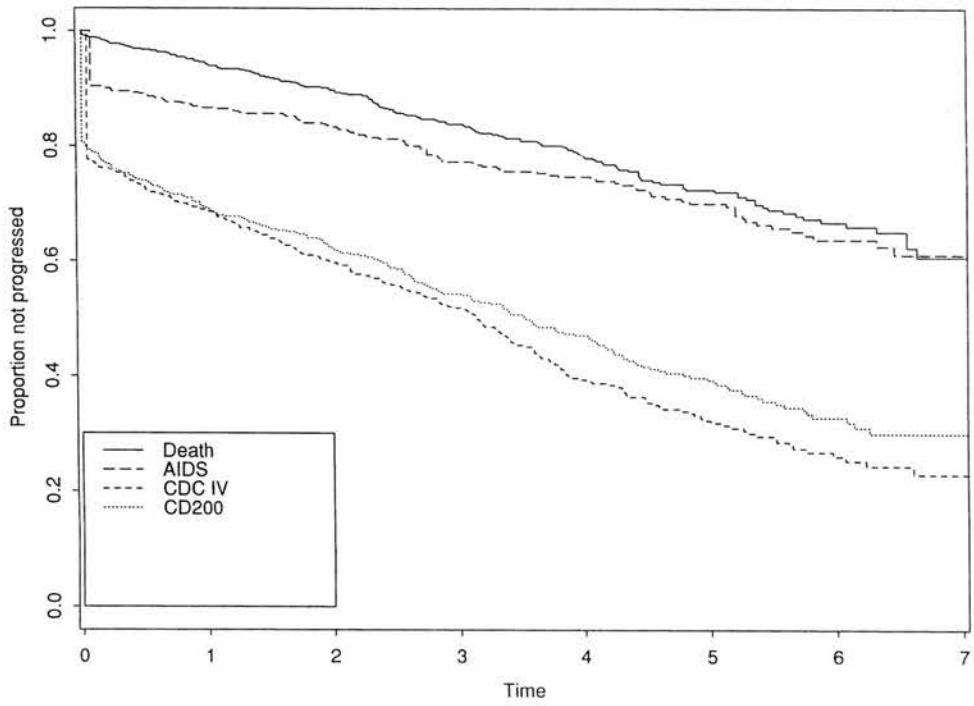

Figure 1. Progression from enrolment to CD200, CDC stage IV, AIDS and death.

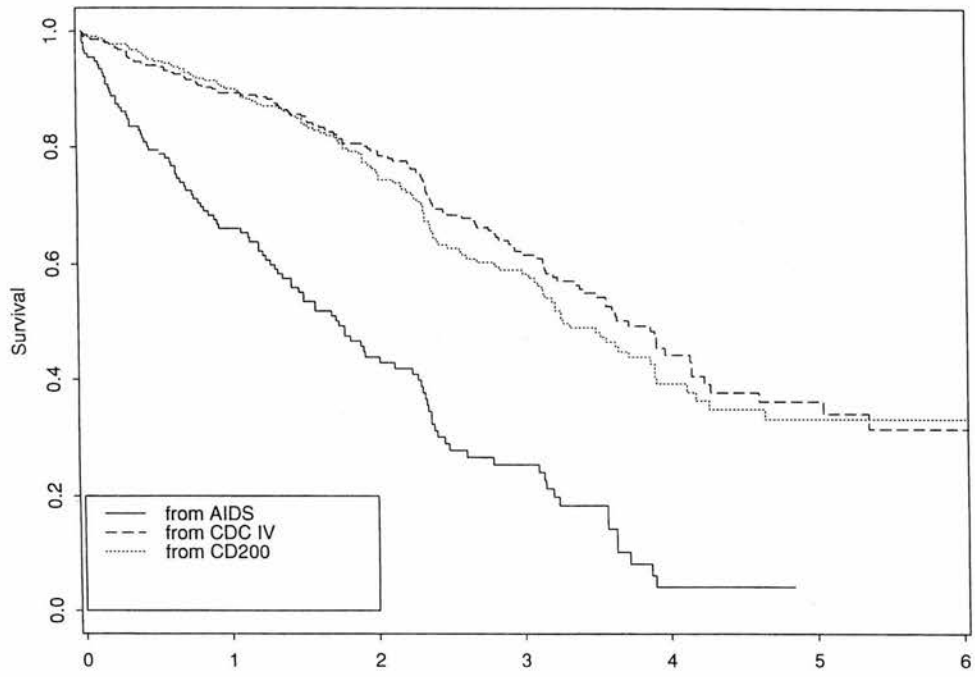

Figure 2. Kaplan-Meier survival curves from CD200, CDC stage IV and AIDS.

the patient; the root transformation was used to symmetrize and normalize errors in the regression model.

Progression rates to CDC stage IV and AIDS (1987 definition) and to CD200 diagnosis (defined by the earlier of two consecutive CD4 counts below 200 or an AIDS diagnosis, whichever occurred first) were calculated using the Kaplan-Meier method. Patients not reaching these endpoints were censored in two ways according to whether they were deemed 'active' or 'inactive' participants in the study at 31 December 1992. Because of a number of missed appointments, and significant temporary dropout from the study, an active participant was defined as a patient who had been seen within the last year of the study and was censored at the close of the study; an inactive patient was one who had not been seen for a year or longer and was censored at the last clinic visit. This strategy was designed to induce independent censoring by (1) making some adjustment for 'walking-well' patients whose dropout was linked to continuing good health whilst (2) allowing for the presence of genuine lost-to-follow-ups in whom status post-dropout could not be ascertained. It is likely to be the correct approach for progression to clinical endpoints.

On the other hand, because flagging with the Registrar General provides good ascertainment of deaths, post-dropout a different policy was adopted for survival. Active participants were again censored at 31 December 1992; inactive participants were censored at 30 June 1992, because of a possible six-month lag in death reports from the Registrar General reaching the City Hospital. Mortality rates were calculated from enrolment and also from AIDS, CDC stage IV and CD200 diagnoses, again by the Kaplan-Meier method. Deaths from all causes, including drugs overdose, were included.

The effect of cofactors (age, gender, risk activity, year of enrolment) on progression was analysed using the Cox proportional hazards model; end-points of AIDS, CDC stage IV and mortality from all causes were considered. Eligible patients in these analyses were patients who enrolled free of the end-point-defining condition in question, and who had marker values within 365 of enrolment and before experiencing the end-point. To control for differential enrolment patterns between risk groups, and thus to minimize the bias of onset confounding,[7] baseline CD4 counts and IgA measurements were included as surrogates for duration of infection in proportional hazards regressions.

Changing administration of zidovudine over the years of its availability to the cohort was investigated by an analysis of disease stage at the uptake of treatment. Four stages were defined: patients with AIDS; AIDS-free patients with CD4 counts <200; AIDS-free patients with counts 200–500; AIDS-free patients with counts >500. In each calendar year of follow-up, a patient living in that year was assigned to stage according to lowest CD4 count in that year and AIDS status. Patients in each category were then further divided according to whether (i) they had commenced zidovudine in a previous year; (ii) commenced the drug in that year; or (iii) not yet taken zidovudine. Thus a three-way cross-tabulation

of the patients by year, disease stage and zidovudine treatment was obtained.

The effects of cofactors on survival from AIDS, CDC stage IV and CD200 diagnosis were investigated, and the advantages of pre- and post-diagnosis zidovudine were considered by use of a time-dependent switch in proportional hazards regression.

Finally, for patients with ten or more serial CD4 determinations a rate of root CD4 loss was estimated from linear regressions of CD4 count on the root scale against time. Dependence of rate of loss of root CD4 count on cofactors was then explored.

Results

Cohort summary

Between October 1985 and 31 December 1992, 622 patients were enrolled in the cohort. Of these, 191 (31%) were women, 439 (71%) were infected via IDU, 92 (15%) via homosexual intercourse, 84 (13%) via heterosexual intercourse alone, and seven (1%) via blood products. Average age of patients at enrolment was 28.6 (SD 7.3) years with 563 patients (91%) aged between 20 and 40. However, there were significant age differences between exposure categories: IDUs had a mean age of 27.1 (SE 0.26) years at enrolment, but homosexual men were older, with a mean age of 34.8 (SE 0.92) years. During 1984–85, 30 patients were enrolled, whilst from 1986 to 1992 the patients enrolled each year numbered 104, 114, 104, 110, 63, 63 and 34.

Follow-up summary

Up to 31 December 1992, the number of clinic visits at which laboratory monitoring was undertaken was 10 940 with an mean of 17.6 (SD 14.5) visits per patient. With follow-up defined as the time between first and last clinic visits, 63% had >2 years of follow-up, 50% had >3 years and 23% had >5 years; at least five clinic visits were made by 76% of the cohort, 61% made at least ten clinic visits and 35% made at least 20 visits.

Against this background, a drop-out phenomenon also took place: cohort members became 'lost-to-follow-up' (in the sense that they were not seen at the clinic for long periods), and a subset later reappeared at the clinic. 112 patients had not been seen for a year at 31 December 1992 (and were believed still alive).

Diagnoses and mortality

A 1987 diagnosis of AIDS was made on 154 individuals during the period of study. Moreover, 349 received an AIDS or CDC stage IV diagnosis, and 316 were CD200 cases. Some 38% of AIDS diagnoses (59 patients) and CD200 diagnoses (120 patients) as well as 40% of CDC stage IV diagnoses were made at the enrolment visit. However, over the years 1987 to 1992, proportionally fewer diagnoses were made at enrolment (data not shown).

The AIDS defining conditions for the above 154 patients were; 83 (54%) *Pneumocystis carinii* pneumonia, 21 (14%) oesophageal *Candida*, 10 (6.5%) Kaposi's sarcoma, 5 (3%) atypical mycobacteriosis, 5 (3%) AIDS dementia complex, 4 (2.5%) cerebral toxoplasmosis, 3 (2%) disseminated tuberculosis, 3 (2%) lymphoma, 13 (8%) more than one opportunistic infection, and 7 (5%) other opportunistic infections such as infections with cytomegalovirus, herpes simplex virus and progressive multifocal leucoencephalopathy.

One hundred and forty-nine patients died during follow-up; 97 (65%) of the deaths were considered to be AIDS deaths and a further 19 (13%) resulted from medical conditions which occurred before the patient formally satisfied an AIDS diagnosis. A number of pre-AIDS deaths (21, 14%) were caused by drugs overdose and undetermined cause (12, 8%).

Zidovudine therapy

Zidovudine treatment was commenced in 379 patients (61%), although 17 subsequently came off the drug within 100 days, and 48 came off the drug within a year. In total, 95 patients (25% of those commencing) have elected to stop taking zidovudine. The proportion of eligible patients taking the drug in each of the three most advanced disease stages (CD200–499 and non-AIDS, CD4 <200 and non-AIDS, AIDS) increased steadily over the years 1987 to 1992. Many patients in the first two of these bands commenced the drug in 1990–92 (Table 1).

Enrolment pattern

An enrolment CD4 count was available for 563 patients in the cohort. Regression analysis showed gender, risk group, age and enrolment year effects on initial presentation at the clinic (Table 2).

Women enrolled earlier in their HIV disease than men (root CD4 counts were 2.3 higher for females: female IDUs aged 25–29 years who enrolled in 1987 would have had a first CD4 count of $(21.4+2.3+0-0.7)^2=23^2=529$, compared to expected first CD4 count of 428 for male counterparts). Homosexuals enrolled at very significantly lower first CD4 count than IDUs (root CD4 differential of -4.2, SE 0.9). Enrolment CD4 count was higher in younger patients (baseline age-group: 25–29 years) and enrolments in recent years were at a much more advanced CD4 count (root CD4

Table 1 Use of zidovudine 1987–1992

Disease stage	AZT status	1987		1988		1989		1990		1991		1992	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
*CD4 500+	Already on AZT	0		0		0		0		0		0	
	Newly on AZT	0		0		0		1	3	0		0	
	Not yet on AZT	57	100	52	100	33	100	31	97	16	100	5	100
	Total	57		52		33		32		16		5	
*CD4 200–499	Already on AZT	0		3	2	5	3	14	8	34	22	57	42
	Newly on AZT	2	2	2	2	16	9	33	20	35	22	11	8
	Not yet on AZT	93	98	128	96	156	88	121	72	87	56	69	50
	Total	95		133		177		168		156		137	
*CD4 <200	Already on AZT	0		9	13	21	20	37	29	80	48	120	68
	Newly on AZT	11	31	21	30	27	25	53	42	53	32	21	12
	Not yet on AZT	25	69	41	57	58	55	36	29	34	20	36	20
	Total	36		71		106		126		167		177	
AIDS	Already on AZT	0		7	32	23	49	41	69	35	67	35	73
	Newly on AZT	2	20	12	55	21	45	14	24	9	17	3	6
	Not yet on AZT	8	80	3	13	3	6	4	7	8	16	10	21
	Total	10		22		47		59		52		48	

Only patients alive in each year are included in the counts.
* Immunological staging for non-AIDS cases only.

differential of −4.6 and −7.2 for patients enrolled in 1989 and 1991–92 compared to pre-1987, for example).

Progression from enrolment

Progression rates to AIDS, CDC stage IV and CD200 at 5 years after enrolment (Table 3) were 30% (SE 2.3), 68% (SE 2.4) and 54% (SE 2.6); death rate was 28% (SE 2.2). Progression and mortality rates in the IDUs alone were somewhat lower (see Table 3) at 5 years at progression 21% (2.4), 64% (2.8) and 55% (2.9), and mortality 22% (2.3).

We included 367 patients in the analyses of progression (controlled for baseline CD4 and IgA) to CDC stage IV, of whom 177 were diagnosed with the endpoint; the AIDS analysis included 375 patients, of whom 49 progressed to AIDS; the analysis of mortality included 506 patients, of whom 126 died. There was no apparent gender effect.

Significant risk group effects (see Table 4) emerged however, with homosexual men progressing more quickly than IDUs after allowance for age, enrolment CD4 and IgA). Relative risks were 2.9 ($p<0.001$), 2.5 ($p=0.01$) and 1.5 ($p=0.1$) for progression from enrolment to CDC stage IV, AIDS and death, respectively. Heterosexuals progressed more slowly than IDUs, with relative risks of 0.5 ($p=0.02$), 0.4 ($p=0.14$) and 0.4 ($p=0.05$) for the three endpoints. Pronounced age effects were not generally evident, once baseline CD4 count and IgA were taken into account. Calendar year effects were apparent in analysis of mortality but not otherwise. Enrolments in recent years seem to have died significantly more quickly.

Survival from diagnoses

Three-year survival rates (Table 5) post AIDS, CDC stage IV and CD200 were 25% (SE 4.3), 61% (SE 3.3) and 58% (SE 3.5), respectively. Equivalent rates in the IDUs alone were somewhat higher at 34% (SE 6.3), 70% (SE 3.7) and 64% (SE 4.2).

No gender effect (Table 6) on survival from any of the three diagnoses was found. Homosexuals experienced higher mortality after the two earlier diagnoses with relative risks of 1.8 ($p=0.02$) for CDC stage IV and 1.6 ($p=0.05$) for CD200. Heterosexuals showed poorer survival from CDC IV (RR 2.2, $p=0.02$); however there were no risk group differences in survival from AIDS.

An age effect was found, with patients having any diagnosis in their 40s showing poorer survival; relative risks of 1.6 ($p=0.09$), 1.9 ($p=0.03$) and 1.9 ($p=0.04$) for survival from CD200, CDC IV and AIDS, respectively. No statistically significant effect of year of diagnosis was found.

For patients treated with zidovudine after an AIDS diagnosis, survival post-AIDS was marginally significantly lengthened (RR 0.5, $p=0.08$). However, for patients treated with zidovudine after CD200 and CDC IV diagnoses, survival post-diagnosis was signi-

Table 2 Regression of enrolment CD4 count (on square-root scale) on cofactors

Cofactor	*n*	Coefficient	SE	t-statistic
Intercept	NA	21.4	0.9	NA
Female	172	2.3	0.7	**3.2**
Homosexual exposure	81	−4.2	0.9	**−4.6**
Heterosexual exposure	76	−1.2	0.9	−1.3
Age <25	171	1.4	0.8	1.9
Aged in 30s	168	−0.5	0.7	−0.7
Aged in 40s	39	−2.6	1.3	**−2.0**
Enrolled 87	107	−0.7	1.0	−0.7
Enrolled 88	102	−2.9	1.0	**−2.9**
Enrolled 89	106	−4.6	1.0	**−4.6**
Enrolled 90	61	−5.4	1.2	**−4.6**
Enrolled 91–92	92	−7.2	1.1	**−6.6**

$n=563$; R-square = 0.26; F statistic = 17.8 on 11 551 df: very highly significant. Statistically significant t statistics are shown in bold; 5% critical value 2.0, 1% critical value 2.6, 0.1% critical value 3.3.
Baseline: male IDU aged 25–29 years when enrolled pre 1987.
Examples for calculation of enrolment CD4 values: enrolment CD4 count for a female, IDU, aged 25–29 years who enrolled in 1987 = [21.4 (intercept coefficient) + 2.3 (gender coefficient) + 0.0 (risk group baseline) + 0.0 (age group baseline) − 0.7 (enrolled 87 coefficient)]^2 = 23^2 = 529; enrolment CD4 count for a homosexual man in his 30s who enrolled in 1990 = [21.4 (intercept coefficient) + 0.0 (gender baseline) − 4.2 (risk group coefficient) − 0.5 (age group coefficient) − 5.4 (enrolled 90 coefficient)]^2 = 11.3^2 = 128.

ficantly shorter, which probably shows merely an administration bias towards sicker patients in the use of zidovudine (Table 1). Also, patients treated with zidovudine before CD200 showed higher mortality post CD200 than untreated patients.

Rates of CD4 loss

There were 361 patients with ten or more CD4 determinations from which to calculate rates of CD4 decline. The mean rate of cell loss per year was 58; the median was 49; the 90% range was −15–146. When slopes were calculated by regression on the root scale, the mean rate of loss per year was 2.1; the median was 1.6; the 90% range was −0.4–5.5. Regression of these slopes against cofactors showed significantly faster decline in homosexuals and in patients aged in their 40s at enrolment (Table 7). It also showed significantly shallower slopes in enrolments in the most recent calendar years 1989–1992.

Discussion

Methodological issues

There are important methodological considerations in documenting progression in a prevalent cohort. Clinical enrolment is not a meaningful event in the natural history of the disease, but is an event which occurs after some unknown prior duration of infection which differs from individual to individual. This means that it is difficult to make useful comparison of progression rates from enrolment between cohorts, and it is also difficult to assess cofactor effects on progression within a cohort, because cofactors may themselves be associated with different durations of infection prior to enrolment. This latter problem is known as 'onset confounding' and is the most serious of three potential biases in the assessment of cofactors in prevalent cohorts described by Brookmeyer and Gail.[7]

Using only baseline immunological markers (CD4 count and IgA) and cofactors, we attempted to extract as much progression information as possible from a prevalent cohort. We did this by first seeking to understand the enrolment pattern in the cohort through regression of enrolment CD4 count (on the square root scale) against cofactors. This analysis confirmed our suspicion that there were differences between typical enrolment times in different sections of the cohort. Thus we found, for instance, that homosexual men enrolled late in their HIV disease compared to IDUs, consistent with our knowledge that the cohort was initially formed from a targeted group of IDUs who were known to be at risk and were enrolled shortly after the Edinburgh epidemic first became apparent. We also found that women enrolled at significantly higher CD4 counts than their male counterparts, and that average first CD4 count steadily declined over the enrolment period.

Having verified that enrolment differences existed in the cohort, we attempted to control for this in an analysis of cofactor effects on progression through the use of baseline CD4 count and IgA as surrogates for duration of infection. These two are well known to be powerful markers of disease progression.[8,9] While this method may not be the most desirable way of showing cofactor effects on disease progression, it is one way of using the large volume of baseline information we had at our disposal to obtain indications of the phenomena which are occurring. It also has wide applications for other prevalent cohorts. Full verification of these results, for example the lack of gender effects, requires an analysis of progression from seroconversion and this will be published in a separate paper.

Analysis of survival post-diagnosis of AIDS, CDC IV and CD200 is less affected by prevalent cohort

Table 3 Progression and mortality rates from enrolment for whole cohort and IDUs only

Endpoint	Year	Risk set		Cumulative cases		Cumulative rate (%)		SE %	
		All	IDUs	All	IDUs	All	IDUs	All	IDUs
Death	1	554	409	35	18	6	4	0.9	1.0
	2	468	372	60	29	10	7	1.3	1.2
	3	394	318	89	48	16	12	1.6	1.6
	4	285	241	112	65	22	17	1.9	2.0
	5	210	183	131	78	27	22	2.1	2.3
	6	107	101	143	88	33	28	2.6	2.8
AIDS	1	443	357	80	20	13	5	1.4	1.0
	2	364	303	95	29	17	7	1.6	1.3
	3	304	257	120	48	23	14	1.9	1.8
	4	237	210	129	53	25	15	2.0	2.0
	5	160	144	141	64	30	21	2.3	2.4
	6	90	85	152	74	36	28	2.8	3.1
CDC IV	1	361	295	188	97	31	23	1.9	2.0
	2	277	226	233	135	40	33	2.1	2.4
	3	211	180	267	162	48	42	2.2	2.6
	4	132	115	313	202	61	56	2.3	2.8
	5	77	69	334	220	68	64	2.4	2.8
	6	36	35	345	231	74	71	2.5	3.0
CD200	1	358	296	183	91	31	22	1.9	2.0
	2	281	234	218	119	38	30	2.1	2.3
	3	226	192	251	144	46	38	2.2	2.5
	4	158	139	278	168	53	46	2.3	2.7
	5	96	87	300	188	61	55	2.5	2.9
	6	55	53	313	201	67	63	2.7	3.1

Table 4 Regression effects on progression from enrolment to CDC stage IV, AIDS and death

Group	CDC stage IV ($n=367$)				AIDS ($n=435$)				Death ($n=506$)			
	n	Cases	RR*	CI	*n*	Cases	RR*	CI	*n*	Cases	RR*	CI
Female	134	61	1.0	0.7–1.5	145	15	0.7	0.4–1.3	159	23	0.8	0.5–1.3
Male	233	116	1	Baseline	290	59	1	Baseline	347	99	1	Baseline
Homosexual	20	16	**2.9**	1.7–5.0	36	17	**2.5**	1.3–4.8	71	36	**1.5**	0.9–2.4
Heterosexual	52	12	**0.5**	0.2–0.9	59	3	0.4	0.1–1.4	68	4	**0.4**	0.1–1.0
Other risk	295	149	1	Baseline	340	54	1	Baseline	367	82	1	Baseline
Age <25 (young)	134	64	1.0	0.7–1.4	148	11	**0.4**	0.2–0.7	161	26	0.7	0.5–1.2
Age 35+ (old)	53	21	0.8	0.5–1.3	69	16	0.9	0.5–1.6	90	29	1.1	0.7–1.7
Age 25–35	180	92	1	Baseline	218	47	1	Baseline	255	67	1	Baseline
Enrolled 90–92	67	18	1.5	0.8–2.6	100	14	1.9	0.8–4.2	122	20	**2.0**	1.0–4.0
Enrolled 88–89	133	60	1.0	0.7–1.5	157	22	0.8	0.5–1.5	194	55	1.4	0.9–2.3
Enrolled 84–87	167	99	1	Baseline	178	38	1	Baseline	190	47	1	Baseline

* Relative risk adjusted for other cofactors plus baseline CD4 count and IgA.
Bold figures indicate significant and marginally significant associations ($p<0.1$) with progression.

biases and results are likely to be generalizable, particularly in view of the careful censoring scheme we have applied to minimise the effect of patient loss-to-follow-up.[10] We have not attempted to make exhaustive analysis of zidovudine effects on progression. Rather we have chosen to document the usage of the drug in the cohort and to look at possible effects on post-diagnosis survival. In this paper we have also undertaken a brief and preliminary investigation of immunological progression. Although some estimates of slope are erratic, due to the volatile nature of the CD4 count,[11] the results of this approach are in agreement with the analysis of clinical progression in their suggestion that the homo-

Table 5 Survival from AIDS, CDC4 and CD200

Survival from	Year	Risk set		Cumulative deaths (all causes)		Cumulative rate (%)		SE %	
		All	IDUs	All	IDUs	All	IDUs	All	IDUs
AIDS	1	89	43	50	27	66	63	3.9	5.7
	2	48	23	77	40	44	42	4.4	6.1
	3	21	9	94	47	25	34	4.3	6.3
CDC IV	1	269	187	35	19	89	91	1.7	1.9
	2	187	142	61	32	79	84	2.4	2.6
	3	101	79	96	51	61	70	3.3	3.7
	4	38	40	118	65	44	54	4.0	4.7
CD200	1	253	171	30	12	90	94	1.7	1.7
	2	155	112	62	29	76	83	2.7	2.9
	3	87	64	94	50	58	64	3.5	4.2
	4	35	30	117	64	39	48	4.1	5.1

sexual men progress much more quickly than IDUs. We have restricted our presentation and use of covariate information to statistical methods that are readily implemented in routine statistical software.

The Edinburgh cohort

The Edinburgh cohort of HIV-infected patients has a number of notable features; a known start to the IDU-related HIV epidemic,[4,12] detection of the epidemic within 2 years,[1] a high proportion of women, and a relatively stable population. In addition, despite being largely composed of patients who acquired the infection via IDU, there has been good clinical and immunological follow-up, with a relatively low drop-out rate for this risk group.[5,6] Some of the long gaps in clinical follow-up can be attributed to imprisonment or living away from Edinburgh in order to avoid the drug scene. The system of flagging defaulters with the Registrar General has provided us with reasonably accurate mortality rates. Since the epidemic was detected within 2 years of its onset, it is likely that very few symptomatic patients have died without coming to our attention.[1,3,13,14]

Zidovudine therapy was commenced in 61% of the patients in this cohort, and may have had some effect on outcome. The use of zidovudine at our centre was for the most part non-randomized (only 50 patients participated in Concorde[15]) and was a clinical decision made in the light of then currently available evidence of efficacy.

For Edinburgh patients treated with zidovudine after an AIDS diagnosis, survival post-AIDS was lengthened (RR 0.5, $p=0.08$) as recently reported Europe-wide.[16] However, for patients treated with zidovudine after CD200 and CDC IV diagnoses, survival post-diagnosis was significantly shorter. Possible explanations include an administration bias toward the sicker patients in the use of zidovudine.

Enrolment pattern and progression from enrolment

Few convincing cofactors for progression have been confirmed, apart from age[17–23] and HLA phenotype.[24–31] Moreover, it is dangerous to compare progression rates from prevalent cohorts (injection drug users, women) unless their maturity (from the outset of the epidemic) and access to pre-AIDS prophylaxis and treatment are known (see above). In the Edinburgh cohort, enrolment CD4 counts, adjusted for risk activity, age and enrolment year, suggested that women enrolled at higher CD4 counts than men (root CD4 differential of 2.3, SE 0.7); and homosexuals much later than injecting drug users (root CD4 differential of -4.2, SE 0.9). Enrolment CD4 count was also higher in the early calendar years of recruitment (for example root CD4 differential from pre-1987 to enrolment year in 1991–92 of -7.1, SE 1.1) so that the recent pattern is predominantly but not exclusively (see below), of late presentations of infections that were acquired 8 or 9 years previously in 1983–84.

Prevalent cohorts often do not distinguish between patients enrolling with AIDS or symptomatic disease and those developing disease under observation. Whilst one may assume that individuals with AIDS will present quickly to a health service, this may not be the case for patients with CDC stage IV disease. In Edinburgh, a large percentage of those enrolling in the early years were symptomatic: 56% of enrolled patients in 1987 had symptomatic disease at enrolment but only 33% by 1991. Increased patient propensity for HIV testing, more aggressive contact

Table 6 Regression effects on survival from CD4200, CDC stage IV and AIDS

Group	CD200 ($n=316$, deaths = 121)				CDC IV ($n=349$, deaths = 126)				AIDS ($n=154$, deaths = 106)			
	n	Deaths	RR*	CI	*n*	Deaths	RR*	CI	*n*	Deaths	RR*	CI
Female	78	21	0.8	0.4–1.3	93	23	0.8	0.5–1.4	29	17	0.9	0.5–1.7
Male	238	100	1	Baseline	256	103	1	Baseline	125	89	1	Baseline
Homosexual	70	43	**1.8**	1.1–2.8	77	43	**1.6**	1.0–2.5	59	43	1.0	0.6–1.7
Heterosexual	38	11	1.6	0.8–3.2	34	11	**2.2**	1.1–4.4	18	10	1.0	0.5–2.2
Other risk	208	67	1	Baseline	238	72	1	Baseline	77	53	1	Baseline
Age in 40s at diagnosis	40	23	**1.6**	0.9–2.7	35	20	**1.9**	1.1–3.3	26	22	**1.9**	1.0–3.4
Age in 30s at diagnosis	126	45	1.1	0.7–1.6	124	47	1.3	0.9–2.0	67	44	1.2	0.8–1.9
Age <30 at diagnosis	150	53	1	Baseline	190	59	1	Baseline	61	40	1	Baseline
Diagnosed 91–92	109	10	0.7	0.3–1.5	114	13	1.0	0.5–1.9	55	24	1.0	0.5–1.9
Diagnosed 89–90	125	58	1.1	0.8–1.7	138	49	0.9	0.6–1.4	65	49	0.8	0.5–1.5
Diagnosed 84–88	82	53	1	Baseline	97	64	1	Baseline	34	33	1	Baseline
AZT before diagnosis	87	28	**2.3**	1.2–4.4	87	21	1.7	0.9–3.3	77	56	1.2	0.6–2.4
AZT after diagnosis	177	78	**1.7**	1.0–3.1	197	86	**1.7**	1.0–2.8	55	37	**0.5**	0.3–1.1
No AZT	52	15	1	Baseline	65	19	1	Baseline	22	13	1	Baseline
Enrol at diagnosis	87	28	1.4	0.9–2.1	138	67	1.3	0.9–2.0	59	38	**0.5**	0.3–0.8
Enrol before diagnosis	229	93	1	Baseline	211	59	1	Baseline	95	68	1	Baseline

* Relative risks adjusted for other cofactors.
Bold figures indicate significant and marginally significant associations ($p<0.1$) with survival.

Table 7 Regression of slope of root CD4 decay on cofactors

Cofactor	*n*	Coefficient	SE	t-statistic
Intercept	NA	2.14	0.29	NA
Female	126	0.02	0.25	0.1
Homosexual exposure	48	2.17	0.37	**5.9**
Heterosexual exposure	34	−0.21	0.41	−0.5
Age <25	126	−0.07	0.28	−0.3
Age in 30s	100	−0.09	0.29	−0.3
Age in 40s	21	1.31	0.52	**2.5**
Enrolled 87	87	−0.10	0.31	−0.3
Enrolled 88	66	−0.23	0.34	−0.7
Enrolled 89	67	−0.71	0.34	**−2.1**
Enrolled 90	27	−1.11	0.47	**−2.4**
Enrolled 91–92	17	−2.03	0.58	**−3.5**

$n=361$; R-square = 0.17; F statistic = 6.47 on 11 349 df; highly significant. Statistically significant t statistics are shown in bold; 5% critical value 2.0, 1% critical value 2.6, 0.1% critical value 3.3.

Baseline: male IDU aged 25–29 years when enrolled pre 1987.

Examples for calculation of annual decay in root CD4 [or slope]: for a female, IDU, aged 25–29 years who enrolled in 1987 = [2.14 (intercept coefficient) + 0.02 (gender coefficient) + 0.0 (risk group baseline) + 0.0 (age group baseline) − 0.7 (enrolled 87 coefficient)] = 2.06. From Table 2, her expected root CD4 [CD4 count] count at enrolment was 23.0 [529] and would be expected to be 23 − 2.06 or 20.94 [438] at the first anniversary of her enrolment in 1988, 20.94 − 2.06 or 18.88 [356] at the second anniversary of enrolment in 1989, 23 − (3 × 2.06) or 16.82 [283] at the third anniversary of enrolment in 1990 and 14.76 [218] in 1991. Thus the slope of CD4 cell loss in this case would be 529 − 218 = 311 or 77.8 cells per year.

tracing procedures for drug users and dedicated combined medical/drug clinics might explain this effect, together with some new infections.

By the 6th year *after* enrolment in the Edinburgh City Hospital cohort, 74% of the patients initially well had become symptomatic and nearly 36% had developed actual AIDS (Table 3). Progression for injection drug-users was not worse than for the group as a whole with 71% being symptomatic by the 6th year, and 28% having already progressed to AIDS, as confirmed by proportional hazards regression which indeed showed higher adjusted relative risk for homosexually acquired HIV disease. That homosexual transmission of HIV may result in faster progression than injection drug-user transmission has been suggested by the MAP workshop comparison of differently HIV-exposed incident cohorts.[32] Survival after an immunological endpoint (CD200) or a clinical endpoint (CDC stage IV) was better for those <25 years of age.

Survival from AIDS

Without treatment, in general, around half of patients with AIDS survive one year but only a fifth for three years.[33] Edinburgh's one and three year post-AIDS survival rates were 66% and 25%. The only cofactor effect on post-AIDS survival was older age at AIDS diagnosis. For instance, relative to patients aged 25 or younger, patients aged 26–35 had an adjusted relative risk of 2.2 (90% CI, 1.5–3.3) and patients aged over 35 had a risk of 4.1 (CI, 2.6–6.6) for post-AIDS death. It had been generally assumed that the survival for injection drug users with AIDS was shorter than for other risk groups but several studies[33–35] besides our own counter this presumption. In Edinburgh, where tuberculosis is an uncommon AIDS diagnosis, the major AIDS-defining condition in IDUs was *Pneumocystis carinii* pneumonia.

As with IDUs, the initial impression based on data from the USA was that women had a poorer survival from AIDS than men.[34,36,37] Women with HIV generally present late for medical care in the USA[33,36,38] with, for example, two-thirds of women with HIV being detected by neonatal screening not receiving medical care[39] or 39% with a CD4 count of <200 cell/mm^3.[41] Those studies with good access to health care, however, have shown women to have equivalent if not better survival,[33,35,36,40–43] and a significant difference in survival for men and women in San Francisco disappeared when anti-retroviral drug use was controlled for, which also suggests that socio-economic factors, delays in diagnosis, poor utilization of, or poor access, to medical services are more important than gender.[42]

Our experience, which may not even reflect the rest of the UK, is that women in Edinburgh present early for treatment. Possible reasons are the close integration of obstetric, paediatric and HIV services in Edinburgh, a service free at the point of delivery and the mothers' concerns over their ability to care for their children. The Edinburgh cohort is made up of a substantial number of women of comparable age and risk activity to men. They may, however, have seroconverted later on average but only by some two months.[12] The prevalent cohort does not show a gender effect for progression from enrolment to symptomatic disease (CDC stage IV or AIDS), from symptomatic disease to death, nor in immunological progression (rate of loss of CD4 count).

Although we and others have failed to demonstrate a major difference between the sexes in the rate of progression from HIV to AIDS, there is concern over whether AIDS accurately reflects the natural history of HIV in women, since the initial definition was

after all based largely on homosexual men. To date in Edinburgh, we have not found a different spectrum of HIV disease for women. For instance, in a retrospective survey of 612 HIV-related admissions there was no excess of female admissions except for detoxification, investigation of episodes of loss of consciousness and urinary tract infections.[44] In addition, the lack of an excess mortality for HIV-infected women compared with men in Edinburgh does not support the argument that the AIDS definition as applied in the UK is a poor reflection of the overall time course of female HIV disease.

Rates of CD4 loss

The mean rate of cell loss per year was 58; the median was 49 and the 90% range was −15–146 showing that a number of patients appeared to be gaining CD4 in the period for which measurements were available. The regression of these slopes against cofactors showed significantly faster immune decay in homosexuals and in patients aged in their 40s at enrolment. It also showed significantly shallower slopes in enrolments in the most recent calendar years 1989–92. This may be because individuals with the fast trajectories came in before 1989, whilst those enrolling more recently may be on slower trajectories and consequently be at a later immunological point than the earlier enrolments as the enrolment analysis seemed to suggest. Alternatively, there may have been an ascertainment bias in the selection of patients from recent years for inclusion in this analysis whereby patients who obtained ten CD4 counts quickly (and were thus included) were patients receiving zidovudine and being closely monitored; such patients might show shallow slopes in response to treatment.

Non-AIDS-related deaths

There is evidence that, amongst drug users especially, mortality data collected on AIDS patients greatly under-represents the toll of serious HIV disease. In New York, Stoneburner reported that amongst narcotic drug users there had been a rapid increase in both AIDS and non-AIDS-related deaths such that by 1986, for every AIDS-related death in a drug user, there was one other as a consequence of conditions such as tuberculosis, endocarditis and bacterial pneumonia.[45] Similar data have been reported from Europe.[46,47] More recently this effect was again reported from drug users prospectively followed via a Methadone maintenance programme where only 57% of the deaths were attributed to AIDS.[48]

The Edinburgh City Hospital cohort data also support this phenomenon but to a lesser degree than noted in the USA or Europe with 37% of our deaths being non-AIDS-related. The majority of non-AIDS deaths after the development of AIDS was related to hepatitis, and in fact hepatitis accounts for 18% of our drug-user deaths. By contrast, in New York the major cause of non-AIDS death was bacterial pneumonia or sepsis, and no excess of deaths for liver disease was noted in comparison to HIV-negative drug users on the same programme.[48] The absence of a substantial number of deaths in our cohort attributed to bacterial pneumonia or sepsis may be as a consequence of access to primary health care and earlier use of antibiotics.

Paradoxically, the excessive non-AIDS-related mortality for drug users results in little difference between drug users and homosexuals in overall survival despite a lower progression rate in drug users and shorter survival for homosexuals after AIDS. Overall survival for HIV as opposed to progression rates may well be the same for the two risk groups, suggesting perhaps that the majority of non-AIDS deaths in drug users are HIV-related rather than drug-related.

Conclusions

It is dangerous to compare progression rates from prevalent cohorts unless their maturity is known. Analysis of enrolment CD4 count gives insight into cohort maturity. Also baseline CD4 counts (at least) should be taken into account when investigating how cofactors influence progression rates and mortality in prevalent cohorts. Serial CD4 counts were used for a separate purpose: to estimate individual rates of immunological progression, which were then related to cofactors. Apart from earlier enrolment, no gender effects were apparent. Homosexual men in Edinburgh enrolled later in their HIV disease than IDUs, and had faster immunological and clinical progression of their HIV disease. Older age was also associated with faster immunological progression and with poorer survival post-AIDS.

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