THE EARLY YEARS OF THE EDINBURGH HIV EPIDEMIC

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DEDICATION

For my parents

SUMMARY

Published studies on morbidity and mortality associated with HIV infection have focused on patients with AIDS or advanced HIV disease and on "opportunistic diseases". But morbidity and mortality can be increased even in the very early years of HIV infection. The aim of this thesis is to document the early natural history of HIV infection.

A medical clinic for the care of HIV infected patients was established in Edinburgh in October 1985. By November 1989, 409 patients had attended this clinic and most were under regular follow up. Most patients were injection drug users (IDUs) accounting for 78% attenders, 12% were homosexual men, 7% were infected heterosexually, 1% from blood products and in 2% there were no documented risk factors. Most of the IDUs acquired HIV infection between September 1983 and June 1984 and are a unique cohort for prospective natural history studies. The other clinic attenders provide a valuable comparison group.

The first four years of the clinic were chosen as the cut off point for early natural history, being six years after the introduction of HIV into the IDU population of Edinburgh. Morbidity was assessed by hospital admissions. All hospital admissions by HIV positive patients in Edinburgh were analysed. These included admissions to the designated HIV unit and to all other general and psychiatric hospitals in Edinburgh. All deaths before November 1989 were analysed, whether they occurred in hospital or at home and all post mortem results were obtained.

By November 1989, 910 admissions were recorded. Although 612 of these were to the designated HIV unit, 298 were to other hospitals in Edinburgh. IDUs accounted for 702 (77%) admissions, homosexual men for 136 (15%), patients with heterosexually acquired HIV infection for 62 (7%)

and recipients of blood products for 10 (1%). The most frequent admissions were for conditions directly related to drug use. These comprised overdose, trauma, injection injuries and detoxification and accounted for 220 admissions. From comparisons with published data this number is in excess of what would be expected in a historical cohort of HIV negative IDUs. Most days in hospital were used by patients with respiratory conditions (187 admissions). These were the single commonest reason for admission to the designated HIV unit. The majority (97) were for bacterial chest infections (BCIs) and only 48 were with *Pneumocystis carinii* pneumonia (PCP). Of these 48 admissions, seven had a concomitant BCI. Differentiating BCIs and PCP clinically was difficult, as was the diagnosis of PCP in IDUs. A clinical algorithm was therefore drawn up for the management and investigation of IDUs presenting with respiratory symptoms and a separate study of the use of induced sputum techniques was conducted. This latter study confirmed the value of these techniques, obviating the need for bronchoscopy, the usual "gold standard".

Most of the patients admitted did not have AIDS (only 32% admissions to the designated HIV unit had AIDS), and most had disease classed as "asymptomatic" by the 1987 CDC staging system (40% of admissions to the designated HIV unit had CDC disease stage 2 or 3).

A total of 189 admissions were with bacterial infections. Most of these were chest and urinary tract infections and pelvic inflammatory disease. IDUs and women were disproportionately represented amongst these admissions and most of these admissions were in patients with CDC stage 2 or 3 disease. A further study was carried out to assess the prevalence of bacteriuria amongst hospitalised patients. From this, the prevalence of asymptomatic bacteriuria was 13% in women and 3% in men, considerably higher than expected from studies of HIV negative patients without urinary tract abnormalities. Among samples from symptomatic patients, bacteriuria was found in 43% women and 6% men.

Unlike other cohorts of IDUs there was only one admission with tuberculosis. This is most likely to be due to the low prevalence of tuberculous infection in the UK. A study of the records of tuberculin testing and BCG vaccinations given in the schools programme confirmed this to be the case. From 310 records matched of patients attending the HIV clinic who had records available from the Edinburgh schools BCG programme, 243 had been given BCG. Only nineteen chidren (6%) had evidence of previous tuberculous infection and none of these had reactivated by 1994.

Thirty four deaths were recorded before November 1989, of which 19 were due to AIDS, two to liver disease and 13 were ascribed to drug use. Post mortem examination revealed that one of the deaths in the latter category was due to a florid meningoencephalitis. Despite the prevalence of bacterial infections, no deaths were attributable to this. Multiple pathology was detected in all patients dying of AIDS, with unexpected findings in eight of the nine patients who had post mortem examinations.

These findings demonstrate a high level of morbidity and mortality even in the early years of HIV infection. Most previously published studies have focused on homosexual men and patients with advanced HIV disease and AIDS. This thesis has the advantage of documenting disease in patients hitherto not the focus of research, namely women, IDUs and patients with early stage HIV infection. It also provides a complete picture of an epidemic in one city, having studied all hospital admissions and deaths. The preponderance of bacterial infections as a cause of morbidity is important for prevention and prophylaxis. The documentation of health care utilisation is vital for planning of future resources.

CHAPTER ONE

INTRODUCTION

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INTRODUCTION

1. General introduction
2. The epidemic among injection drug users
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General Introduction

The first intimation of the twentieth century pandemic which has been described as the greatest new public health challenge this century,[1] was in the Morbidity and Mortality Weekly Report of 5 June 1981 where five cases of *Pneumocystis carinii* pneumonia (PCP) in homosexual men were described.[2] Following this the Centers for Disease Control (CDC) in Atlanta began active surveillance. The condition was named the acquired immunodeficiency syndrome (AIDS) and the causative virus, a retrovirus, now termed the human immunodeficiency virus (HIV) was identified in 1983. Antibody testing for HIV became available in 1985. By the end of December 1990, 307,379 AIDS cases had been reported by 157 countries to the World Health Organisation and an estimated 10 million people were HIV infected worldwide.[3] The United Kingdom accounted for 4098 of the AIDS cases.

The virus is transmitted by sexual intercourse with an infected person, by inoculation of infected blood whether by transfusion or by sharing of infected needles, and by vertical transmission from mother to child. The virus specifically infects and destroys CD4 helper inducer lymphocytes and the resulting immunological depression places the patient at risk of neoplasms and infections which are not normally seen with an intact immune system. These infections are termed opportunistic infections (OIs) and there are certain characteristic infections typical of HIV induced immunosupression. A CDC classification for the clinical definition of AIDS and HIV infection was introduced in 1986 and revised in 1987 and 1992.[4-6] Other classification systems have been formulated but the CDC system is the most widely used and the 1987 version is the one used in this thesis. The CDC classification divides HIV infection into four stages (figure 1.1). Stage 1 is primary HIV infection which in some cases is associated with a

glandular fever type seroconversion illness. Stage 2 is asymptomatic HIV infection and stage 3 describes persistent generalised lymphadenopathy. Stage 4 is indicative of symptomatic HIV infection and includes all AIDS conditions. Stage 4a was originally termed AIDS-related complex (ARC) and describes constitutional symptoms, stage 4b describes neurological conditions, stage 4c2 is for "minor" OIs and stage 4e incorporates a variety of other conditions including any which the physician feels is indicative of symptomatic HIV infection and which is not otherwise itemised. Some neurological conditions in stage 4b and some conditions in 4e are AIDS defining. Stages 4c1 and 4d are AIDS defining. Stage 4c1 describes major OIs such as PCP and 4d describes opportunistic tumours such as Kaposi's sarcoma and lymphoma. Generally most patients will progress through the four stages although they may present for medical care at any point. The time from initial HIV infection to AIDS (progression) and then to death (survival) is as yet unknown and varies between individuals.[7-9] An approximate figure is that 50% of patients will progress to AIDS within ten years of seroconversion.[10]

Numerous studies are in progress to try to identify the rate of progression of HIV disease and any factors, known as cofactors, which may influence this. Most good studies come from centres caring for large numbers of AIDS patients such as New York or San Francisco and these centres are able to produce statistically significant and meaningful results because of the large numbers of patients involved. But despite well documented cohorts these studies are often limited by the lack of accurate seroconversion data, particularly in cohorts of homosexual men who may not have required medical care (and therefore had no blood taken) prior to developing symptomatic HIV disease. Seroconversion data are best found from cohorts of patients infected through blood products, particularly haemophiliac groups who were often followed prospectively before HIV infection and in whom not only the exact date of infection but some idea of the amount of the

infecting inoculum (by number of units of factor VIII infused) is known. But rates of progression may vary between risk groups and accurate data taken from one cohort cannot necessarily be extrapolated for use in others. Two well studied cohorts are the Royal Free Hospital haemophiliac cohort from London and the Edinburgh haemophiliac cohort.[11,12] These two cohorts have particular relevance for comparison with the City Hospital, Edinburgh cohort because they involve primarily Caucasian heterosexual British men who all receive their medical care within the National Health Service system. In the Royal Free cohort, 112 HIV positive haemophiliacs have been followed prospectively since December 1979. The earliest serum found to be HIV positive was on 12 December 1979 and their last seroconversion was estimated to be in July 1985.[11] This cohort has found age, duration of HIV infection and previous cytomegalovirus infection to be important cofactors for progression.[11,13-16] The year of AIDS diagnosis also has an important effect on survival, mainly as a result of antiretroviral treatment with zidovudine (since 1987) and PCP prophylaxis with inhaled pentamidine (since 1988).[14,17-19] The importance of the Edinburgh haemophiliac cohort lies in the fact that 32 patients with haemophila A who were exposed to the same batch of HIV contaminated factor VIII concentrate are being prospectively studied; 18 patients seroconverted to become HIV positive, and the 14 who did not remain under observation as a control group.[12] Studies of this cohort have identified that the extent of host immune reactivity, which may be genetically determined, can affect progression.[20] Studies of HIV infected blood transfusion recipients have identified the clinical state of the blood donor, and age as important predictors of disease progression.[21,22] Worldwide, older age has been found to be the most important cofactor.[23-26] Controversy continues about the importance of previous cytomegalovirus infection,[27-29] duration of HIV infection,[8,30] continued injection drug use,[31-33] and the occurrence of an HIV seroconversion illness.[34,35]

The large American cohorts, in addition to identifying cofactors for progression, have identified clinical and laboratory markers as predictors of disease progression - important for identifying those patients who might gain most from early antiretroviral or other therapy. The initial cohort studies are from San Francisco where many homosexual men were taking part in studies of the incidence, prevalence and prophylaxis of hepatitis B infection before the advent of HIV.[30] The important MACS (Multi Center AIDS Cohort Study) study has recruited homosexual men in order to study the epidemiology of HIV infection.[36] The San Francisco cohort has identified ß2 microglobulin, packed cell volume, HIV p24 antigenaemia and the proportion and number of CD4 lymphocytes as independent and important laboratory predictors of clinical progression.[37] Other laboratory markers for progression include neopterin,[12,38] but controversy continues over the importance of elevated immunoglobulins A and G[12,39] and thrombocytopenia.[9,40] Some markers such as ß2 microglobulin are only of use in selected risk groups.[40] CD4 lymphocyte counts and percentages, although still not yet available in many centres as routine laboratory tests, are now widely used as a marker for starting treatment and as surrogate end-points for clinical trials.[41-43] The major limitation of CD4 counts is in their variability - due to laboratory factors, prolonged transit time to the laboratory, time of day at which the sample was taken and the influence of intercurrent infections. CD4 counts in immunocompetent people can vary by as much as 1000 cells/mm^3 and the normal range is usually between 500 and 1500 cells/mm^3.[44] Serial CD4 counts provide a very valuable guide to clinical care. CD4 counts have been shown to fall by about 80 cells per year in HIV infected individuals.[45,46] Certain opportunistic infections have been shown to occur below particular CD4 cut-off points.[47] For instance, PCP is unlikely to develop at CD4 counts above 200 cells/mm^3,[48,49] and it is therefore now recommended that a CD4 count of 200 cells/mm^3 be used as a guide for institution of primary PCP prophylaxis.[50] The AIDS Clinical Trials Group (ACTG) in America base much of their stratification within clinical trials on

CD4 counts. For instance, in their trial ACTG 019 of asymptomatic HIV infected patients randomly assigned to placebo, zidovudine 500mg per day or zidovudine 1500mg per day the results were analysed in three groups; namely patients with CD4 counts above 500 cells/mm^3, those with CD4 counts between 200 and 500cells/mm^3 and those with CD4 counts below 200 cells/mm^3.[51]

The antiretroviral drug zidovudine became available in Britain in 1987 and has been shown to prolong survival in patients with AIDS and symptomatic HIV infection.[52-54] Controversy still exists over the benefit of using it in patients who are asymptomatic and whose CD4 counts are above 200 cells/mm^3.[51,55-57] Its use is limited by its toxic effects of severe anaemia and leucopenia, myopathy, headaches and nausea and vomiting.[58,59] At the time of writing, zidovudine is the only licensed antiretroviral drug in Britain but trials are on-going of other drugs including didanosine (ddI), dideoxycytidine (ddC), soluble CD4, immunoglobulin, diethylcarbamazine, interferon and vaccine therapy either singly or in combination.

The epidemic among injection drug users

The first evidence of HIV infection in injection drug users (IDUs) came from three cases of AIDS in children in New York in 1977.[60] These babies had not received blood transfusions but were born to mothers known to be IDUs. The earliest known case of AIDS in an adult IDU occurred in 1979 in a man who was also known to be homosexual. The first five known cases of AIDS among heterosexual IDUs occurred in 1980.[60] Since then IDU has been implicated in thousands of HIV reports worldwide. By the end of 1990 over 60,000 AIDS cases had been reported in IDUs from more than 25 countries.[61] By 1981 HIV was widespread among injectors in New York and

Italy.[62,63] It had spread to South America by 1983, to Australia by 1985 and to Asia by 1987.[61] In some cities the incidence was more striking than in others. In New York, seroprevalence increased from less than 20% in 1978 to over 50% in 1983.[60] This was followed by reports from Edinburgh of seroprevalence of 51% among IDUs by 1985[64] and from Bangkok where seroprevalence increased from less than 10% in 1986 to over 40% in 1987.[61] By contrast some IDU communities continue to show low rates of infection. In Britain there are some striking regional differences. Glasgow, 70 km from Edinburgh, had a seroprevalence rate of less than 4.5% in 1985[65] and a report from the following year from South London showed a seroprevalence of less than 1%.[66] Data from Merseyside from 1991 continue to show a zero-rate of locally acquired HIV infection.[67]

Studies comparing risk behaviour between IDU communities with low and high rates of HIV infection have been done[68] but the most elegant studies to determine risk factors for acquisition of HIV infection by IDU have been among participants in methadone maintenance programmes (MMPs). Marmor reported on a 1987 study of 308 IDUs recruited from methadone maintenance or drug detoxification programmes in Manhattan, New York City, of whom 50.7% were HIV positive.[69] The most significant risk factors for HIV acquisition were the frequency of drug injection and the proportion of injections in "shooting galleries" (places in which drugs bought elsewhere can be injected either with rented or with personally owned needles and syringes). Schoenbaum studied 452 patients enrolled in a methadone treatment programme in the Bronx, New York. Almost 4.2% were HIV positive and similar risk factors were identified.[70] The most significant were the frequency of drug injection (cocaine in particular) and the percentage of injections with used or shared needles. In addition, the presence of HIV infection was independently associated with being black or Hispanic or of low income. The number of heterosexual sex partners who used intravenous drugs was associated with HIV infection in women. These risk factors have

been confirmed in numerous other studies.[64,71] Duration of drug use has been associated in some studies with acquisition of HIV infection but refuted in others.[64,72]

Following the identification of risk factors for HIV infection, many countries have assessed their attempts at risk reduction among IDUs.[73] The most widely accepted method of risk reduction has been with oral methadone substitution, either as maintenance therapy or in a detoxification programme.[74] Programmes which have received the most scientific review include the Dutch system and the New York programmes. The Dutch system of low threshold methadone ("methadone by bus") has led to a stabilisation of the number of drug addicts at 20,000 (0.15% of the population) and a stable seroprevalence of HIV infection at 30%.[75,76] In the New York system the programmes are more restrictive, but many results have shown a marked decrease in acquisition of HIV infection once IDUs have entered a methadone maintenance programme.[69,77,78] Needle and syringe exchange schemes are generally not legally available in the United States but have been evaluated in the Netherlands and the United Kingdom where they have been found to be effective.[79,80] "Cleaner injecting" and bleach programmes are, however, available in the United States.[78] In Merseyside where, as quoted above, the incidence and prevalence of HIV infection is 0%, ampoules and reefers of heroin are prescribed to IDUs.[67] Paramount in any risk reduction programme is education of those at risk.[61,76]

The natural history of HIV infection in IDUs has many important differences compared with other risk groups. Much of this is related to the morbidity and mortality of IDU itself, unrelated to HIV infection. Before the HIV epidemic there were few resources available in most countries for IDUs and very little published research on the effects of drug use. In a 1967 review of the major medical complications of drug addiction Louria estimated that 1% of IDUs in New York City per year died as a result of overdose.[81] Endocarditis, pulmonary emboli, pulmonary fibrosis and

granulomatosis, lung abscess, pneumonia, hepatitis, tetanus and malaria were other medical conditions which gave rise to substantial morbidity and mortality.[81,82] In a British study published the following year Bewley noted that there had been a steady increase in the number of addicts notified to the Home Office and that British heroin addicts had a mortality rate of 28 times that of the general population and twice the reported rate of heroin addicts in New York.[83] A subsequent Home Office study of 1499 deaths among IDUs in Britain for the years 1967-81 estimated the mortality of drug addicts at 16 times that of the age and sex matched population - described as "the elusive natural history of addiction".[84] More recent studies since the onset of the epidemic have identified overdose, violence, endocarditis, cirrhosis and septicaemia as causes of excess mortality in IDUs without AIDS.[85,86] Although in these studies the patients did not have AIDS, HIV infection without AIDS could affect the natural history of these diseases. In many studies the mortality rates due to violence and overdose amongst IDUs have stayed stable since the onset of the AIDS epidemic.[85,87] Excess morbidity in HIV negative IDUs has been demonstrated particularly for tuberculosis and bacterial pneumonia.[88,89] In Selwyn's study of 144 HIV positive and 289 HIV negative IDUs in a New York methadone maintenance programme, the cumulative yearly incidence of pneumococcal pneumonia in seronegative IDUs was over eight times that of the general US population.[89] Other complications of drug use which result in increased morbidity in IDUs are thrombophlebitis and soft tissue infection, bone and joint infection, rhabdomyolysis associated with temazepam injection, deep venous thrombosis, candida endophthalmitis and sexually transmitted diseases resulting from prostitution.[90-92] Some complications, such as benzodiazepine withdrawal seizures or temazepam injection skin necrosis, are particularly common in areas such as Scotland where new drug users are likely to be "polydrug" abusers of pharmaceutical drugs such as temazepam, buprenorphine, dihydrocodeine, cyclizine and dipipanone.[93-95]

Apart from the above non-HIV related complications of drug use (which have mainly stayed at a steady state during the AIDS epidemic) the natural history of HIV infection itself is different among IDUs.[87] AIDS defining illnesses differ among risk groups (such as the preponderance of Kaposi's sarcoma among homosexual men) and oesophageal candidosis, cryptococcosis and PCP are more frequent AIDS defining diagnoses in IDUs when compared with other risk groups.[96] To concentrate on AIDS defining diagnoses as evidence of differing natural history of HIV infection in IDUs would miss the wider spectrum of HIV related diseases. In a New York analysis of 7884 deaths in IDUs between 1978 and 1986, Stoneburner found that deaths due to pneumonia, endocarditis and tuberculosis were markedly increased.[87] In a further analysis of selected case records he surmised that HIV was implicated in 44% of these pneumonia deaths, 32% of the endocarditis deaths and 69% of the tuberculosis deaths. Selwyn demonstrated an increase in mortality from bacterial pneumonia and sepsis from 3.6/1000 in 1984 to 13.6/1000 in 1987 amongst IDUs in MMPs in New York.[85] The HIV status of these IDUs was not known but the dates are co-incident with the AIDS epidemic. Morbidity, which can be more difficult to define than mortality, has also increased amongst IDUs for diseases such as tuberculosis and bacterial pneumonia. Hospitalisations for pulmonary tuberculosis (not an AIDS defining illness by the 1987 CDC definition) have increased amongst HIV positive IDUs in New York.[85,88] In his study comparing 144 HIV positive with 289 HIV negative IDUs, Selwyn found that seropositive subjects (none of whom had developed AIDS) were five times more likely to develop bacterial pneumonia than the seronegative group.[89] Similar studies have confirmed these findings.[97] Incidence, severity and mortality of endocarditis have been reported to be increased in HIV positive IDUs compared with negatives.[98,99]

Partly as a result of different disease manifestations within the natural history of HIV infection, progression to AIDS and survival with AIDS are

known to differ between risk groups.[10] The situation with regard to IDUs is further complicated in that IDUs as a group comprise a larger percentage of women, tend to be younger and, in United States studies, are more likely to be non-Caucasian than some other risk groups. Many studies when ascribing differing rates of HIV disease progression and differences in survival have failed to take account of these variables. Also, in studies so far reported, cohorts of haemophiliac patients and homosexual men have been studied for longer and more completely than IDU cohorts and therefore are not directly comparable.[10] As an example, a reasonably large study of 526 New York AIDS patients, 47% of whom were IDUs, reported that although the initial AIDS defining diagnosis was the most powerful predictor of survival, the combination of male sex and IDU, black race and younger age were associated with more favourable survival.[100] Compare this with a study of 5833 New York AIDS patients, 28% of whom were IDUs.[101] This study also found that the manifestations of disease at AIDS diagnosis to be the most powerful predictor of survival but that survival was somewhat worse for those infected via IDU and that it was particularly poor for black female IDUs. With regard to studies reporting on risk of progression to AIDS among IDUs, much attention has focused on the risks of continued drug injecting. Many, although not all, studies have found an association between continued IDU and progression.[32,78] Markers for disease progression also differ in IDUs compared with other groups and in particular, serum ß2 microglobulin is of very little predictive value.[40,102]

Another aspect which has particular relevance to American studies on IDUs (particularly progression and survival) is access to health care.[103] Studies from the methadone maintenance programmes, mainly from New York, usually compare HIV negative and positive IDUs and have made an important contribution to our knowledge of the epidemic in IDUs.[88,89] However they cannot be directly compared with equally important progression studies of homosexual white men from San Francisco.[37]

European studies have to a certain extent redressed this balance with as much research, particularly in Italy and Spain, concentrating on IDUs as on other patient groups. In Britain all patients have equal rights to health care although some patients may have more difficulty in accessing it than others. In Edinburgh most of the patients are indigenous Caucasians who access health care equally. With a cohort comprised mainly of IDUs with known seroconversion dates and a comparison group of heterosexually and homosexually infected Caucasians, studies of this group will help to answer some of the above problems and questions about rates of progression, survival and early natural history of HIV infection.

The Edinburgh epidemic

Edinburgh is a small city of 300,000 inhabitants most of whom are indigenous Caucasians. In 1985 there were an estimated 2,000 injection drug users in the city.[104] Drugs in Edinburgh were primarily taken by injection and the dominant drug used was heroin which, usually brought in via the port of Leith, was in plentiful supply in the early 1980s.[64] Because of an acute shortage of needles and syringes in Edinburgh from 1982 onwards (the local legal retailer closed and there was subsequent unofficial prohibition by pharmacists) injecting equipment began to be widely shared.[105] The situation became very similar to the "shooting galleries" of New York[69,70] when up to 20 people would share injecting equipment in quick succession. Equipment was not cleaned between users unless the syringe was rinsed with tap-water. The practice of "washout" - when blood was drawn back into the syringe in order to flush out any remaining heroin - was routine and must have increased the contamination of the syringe. In a study of 78 IDUs in Edinburgh, 49 (63%) shared needles at least weekly and 33 (42%) reported daily sharing.[68]

The first intimation of the HIV epidemic among IDUs in Edinburgh was published in a letter to the Lancet in November 1985.[106] A commercial anti-HIV assay had recently become available following which several workers from different countries documented seroprevalence rates among IDUs varying from 1.5% in England[107] to 48% in Spain.[72] One hundred and six serum samples from IDUs attending the Royal Infirmary of Edinburgh were tested of which 40 (38%) were found to be positive. At that time no clinical data were available but samples found to be HIV positive were much more likely also to have evidence of past hepatitis B infection (90% vs 62%). Following this discovery, further serological studies were made, including retrospective testing of stored sera from IDUs. This was possible because of the interest taken in IDUs by a group of general practitioners, and because of an outbreak of hepatitis B amongst IDUs in Edinburgh in 1982.[64] This outbreak was attributed at the time to the increase in the sharing of needles and syringes as described above. During and following the hepatitis B outbreak, all IDUs who attended the West Granton Medical Group (a general medical practice serving a population of 18,000 patients in a deprived area of Edinburgh where drug use is common) had blood taken for hepatitis B markers as a routine, and any unused sera was stored by the virology laboratory. In 1985, sera from 164 IDUs were tested for HIV and 83 (51%) were found to be positive. Because of the availability of stored sera, samples which were found to be positive had previous samples tested successively until a negative result was found, thereby identifying the period during which seroconversion occurred. In some cases a very accurate time of seroconversion was obtained - the time between the last negative and the first positive specimens being less than a month. No positive results were obtained before September 1983 which is when HIV was probably introduced to the drug using population in Edinburgh. This study was not anonymous and samples were linked with clinical information. There was a statistically significant correlation between the frequency of needle sharing and seropositivity. There was no sex difference between the seropositive

and seronegative groups (60 men and 23 women were seropositive) but the seropositive patients were significantly younger and had used heroin for a shorter time (average 4.6 years). Follow up of this cohort in 1988 found 94 of 146 (64%) patients tested to be HIV positive.[93] Because many of the group who injected from 1982 onwards have not been tested, the seroprevalence of HIV amongst this group could be as high as 80%. It is this study, the availability of sera stored from 1982 onwards and the resultant accurate seroconversion dates which make this cohort of IDUs a unique and valuable cohort to study the natural history of HIV infection.

Interestingly, on the same day that Robertson's study was published in the British Medical Journal,[64] an HIV seroprevalence study of IDUs in Glasgow was published in the Lancet.[65] The Glasgow drug using population in 1983 was estimated at a minimum of 5,000[108] and provides a valuable comparison with Edinburgh. Twenty seven of 606 (4.5%) samples from Glasgow IDUs tested in 1985 were HIV positive. Analysis of clinical information available revealed that in 20 of these samples the patient had a home base in or had recently moved away from Edinburgh and only three of the IDUs were based in the west of Scotland (i.e. around Glasgow). But 70% of that study population had evidence of hepatitis B infection. Comparisons of self reported habits between IDUs in Edinburgh, Glasgow and London revealed more sharing of injecting equipment in Edinburgh.[66,68,109]

A voluntary self-referral clinic was established in the Edinburgh Regional Infectious Diseases Unit at the City Hospital to provide open access for counselling and HIV antibody testing.[110] The clinic was opened on 16 October 1985 to coincide with the start of HIV testing of all blood donations by the National Blood Transfusion service. Apart from self-referrals, patients could be referred by social workers, general practitioners, other hospitals or drug self help agencies. A medical officer was present whenever the clinic was open although the clinic was not medical. All patients with positive HIV antibody tests were offered full medical screening and follow-

up in the infectious diseases clinic (held in the same department). The aim of the clinic was to present a non-medical but confidential counselling image. Within the first year 441 new patients had been counselled at 980 clinic attendances.[111] IDUs accounted for 191 patients (119 men and 72 women) among whom the seropositivity rate was 52%. One hundred and fourteen (26%) attenders were HIV positive of whom 100 (88%) were IDUs. This reinforced the importance of the HIV epidemic among IDUs in Edinburgh. Whereas in Robertson's study[64] all patients came from one general practice in the north of Edinburgh, patients attending the City Hospital counselling clinic were referred from all over Edinburgh. Of 441 patients attending, 78% were from within the city of Edinburgh, 12.5% were from the rest of Lothian region, 6% were from other parts of Scotland and 0.5% were from England. Additionally, 44 (23%) Edinburgh based IDUs had shared needles in 48 other locations (including two in Amsterdam, one in Rotterdam, one in Paris, 15 in London and nine in Glasgow) and of these, 52% were HIV positive.

Following the detection of the HIV epidemic in Edinburgh, the need for the counselling clinic and for expansion of medical services, extra medical clinics were established within the Infectious Diseases Unit[110,112] and patients requiring in-patient medical care were admitted to the infectious diseases wards. Alternative sites for HIV testing, counselling and in-patient care exist in Edinburgh including the genito-urinary medicine clinic, the blood transfusion service and through general practitioners and general medical hospital units. The counselling clinic was set up as an alternative to these with one specific aim of attracting IDUs who can be a particularly difficult group to access and to treat. Whilst most homosexual men attend the genitourinary medicine clinics, the infectious diseases unit had been caring for and had experience in dealing with IDUs for some years because of complications associated with injection drug use including hepatitis B, endocarditis and abscesses.

All attenders at the City hospital HIV clinic have been prospectively followed since October 1985. This group comprises HIV positive IDUs, homosexual men, heterosexually infected HIV patients and some HIV negative IDUs (usually partners of HIV positive IDUs). Records of every patient's every outpatient attendance since October 1985 have been entered on a database computer file. Data collected include weight, height, age at first injection, number of years injected, whether drugs have been injected since the last out-patient attendance (and if so, which and how often), drug substitution therapy prescribed, antiretroviral (including trial drug) treatment and prophylaxis against opportunistic infections. Blood tests recorded include HIV seroconversion dates, lymphocyte surface markers, HIV antigen levels, full blood counts, liver function tests and serology for syphilis, hepatitis B, C, D, toxoplasma and cytomegalovirus. Accurate seroconversion data are available on the IDUs, most of whom seroconverted between September 1983 and mid 1984. Data are entered following a protocol by research assistants and all medical case notes are kept permanently in the clinic and are available for reference should any discrepancies be found in the database.

By November 1989, four years after the inception of the City Hospital clinic and six years after the introduction of HIV into the Edinburgh injecting population, 409 HIV positive patients had attended the City Hospital medical clinic - 319 (78 %) were IDUs, 50 (12%) were homosexual or bisexual men, 28 (7%) were infected via heterosexual intercourse, four (1%) via blood products and in eight (2%) there were no documented risk factors.

This thesis will be analysing only those HIV positive patients in Edinburgh who have attended the City Hospital clinic. The aim of the thesis is to document the early natural history of HIV infection. Observation and clinical management of these HIV positive patients in the early years of their infection revealed that they were suffering considerable morbidity. Morbidity and mortality in patients without advanced disease had not

previously received much attention in the literature as most studies had focused on patients with AIDS or CDC stage 4 disease. Evaluation of this morbidity documents a wider spectrum of HIV related disease. An evaluation of the associated health care utilisation is necessary for further allocation of health care resources both within Edinburgh and elsewhere.

Figure 1.1

1987 CDC classification of HIV disease[5]

Stage 1: Seroconversion illness

Stage 2: Asymptomatic infection

Stage 3: Persistent generalised lymphadenopathy

Stage 4: Symptomatic disease, comprising

- 4a: constitutional disease
- 4b: neurological disease
- 4c1: severe opportunistic infections **
- 4c2: lesser infections *
- 4d: tumours
- 4e: other diseases attributable to HIV or indicative of a defect in cell mediated immunity

** includes the following:

- candida of oesophagus or respiratory system
- extrapulmonary cryptococcosis
- chronic cryptosporidiosis
- chronic isosporiasis
- cytomegalovirus other than liver, spleen or lymphatic
- chronic mucocutaneous/visceral herpes simplex
- disseminated histoplasmosis
- atypical or extrapulmonary tuberculosis
- *Pneumocystis carinii* infection
- cerebral toxoplasmosis > 1 year age
- disseminated coccidioidomycosis
- extraintestinal strongyloidiasis
- progressive multifocal leucoencephalopathy
- recurrent non-typhoidal salmonella septicaemia

* includes the following:

- persistent or recurrent oral candida
- oral hairy leucoplakia
- nocardiosis
- pulmonary tuberculosis
- multidermatomal herpes zoster

From: Centers for Disease Control. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. MMWR 1987; **36** (suppl 1S):3S-15S.

CHAPTER TWO

EDINBURGH HOSPITAL ADMISSIONS BY HIV POSITIVE PATIENTS

BEFORE NOVEMBER 1989

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Introduction

The data routinely collected on the HIV positive patients attending the City Hospital clinic are used to describe the Edinburgh cohort with particular reference to the natural history of HIV infection. Because data are on all patients attending and because markers of disease progression (CD4 count, HIV antigenaemia, CDC staging) and of drug use are prospectively recorded the data have been used to evaluate co-factors for disease progression.[31,40] The use of health care resources has also been audited from study of the out-patient records.[112] But no data were routinely collected on hospital admissions by this group of patients. Any data on in-patients would be complementary to the out-patient data since they would describe a more complete picture of the natural history of HIV infection in each patient. Data on admissions would provide a more accurate picture of disease progression. A study was therefore performed of all admissions by HIV positive patients to the Regional Infectious Diseases Unit (RIDU) at the City Hospital, the designated centre for in patient care of HIV positive patients.

Although most HIV positive patients who attend the City Hospital clinic are likely to have any medical admissions to the City Hospital (or if referred elsewhere to have the admission referred or supervised by the City Hospital) a study of City Hospital admissions alone might not be representative of all admissions and of the early years of the Edinburgh HIV epidemic. Particular categories of admissions which would be likely to be admitted to hospitals other than the City include self-poisoning, injection injuries and any gynaecological admissions. Edinburgh has three main teaching/general hospitals (the Western General, the Eastern General and the Royal Infirmary of Edinburgh) and one central Accident and Emergency Unit at the Royal Infirmary. All three hospitals have acute general surgical wards (of which there are none at the City Hospital). All admissions in Edinburgh with self-

poisoning are referred direct to the Regional Poisons Unit at the Royal Infirmary. The Western General Hospital houses the Institute of Neurological Sciences and has a large gastro-enterology department. Gynaecological admissions in Edinburgh are referred to the Royal Infirmary or the Wetern General Hospital. All psychiatric admissions in Edinburgh are to the Royal Edinburgh Hospital (general acute psychiatry), the Royal Victoria Hospital (psychogeriatrics) or Gogarburn hospital (mental handicap). Admissions by HIV positive patients who had attended the City Hospital as an out patient but who were admitted to other hospitals in Edinburgh were included in the study. Excluded from the study were children under the age of 16 and any HIV positive patient who had not been admitted to, or had not attended the clinic at the City Hospital.

There are three main centres of HIV care in Edinburgh - the City Hospital RIDU, the Genitourinary Medicine Department at the Royal Infirmary and the Haematology Department at the Royal Infirmary. Most patients whose out patient care is at the Genitourinary Medicine Department but who require in patient care are referred to the City Hospital for admission. Most of these patients are homosexual men. The Haematology Department provides in patient and out patient care for haemophiliac patients and some other patients infected through blood products. Their admissions were not included in this study. Patients admitted to hospital but who did not attend a clinic on a regular basis or who learnt of their HIV positivity during that admission would generally be referred to the City Hospital RIDU, as the designated HIV unit, for on going care. This study therefore analyses most Edinburgh admissions by HIV positive patients apart from the small group of haemophiliac men. The study period chosen was from October 1985 until 31st October 1989. The City Hospital HIV outpatient clinic was established in October 1985, hence the starting date of the study. The aim of the study was to describe admissions within the early years of the Edinburgh HIV epidemic and therefore the cut off point was four years after the inception of

the City Hospital clinic and six years after the introduction of HIV into the drug using community in Edinburgh.

Methods

A database file of all inpatient admissions was retrospectively compiled. Two medical research fellows (LW, FC) reviewed the medical case notes of all HIV positive patients attending the City Hospital clinic. All case notes in which a City Hospital admission was recorded were examined further and data extracted according to a protocol. These data comprised hospital identification number, date of birth, sex of the patient, risk factor for acquisition of HIV infection, date of admission to and discharge from hospital, CDC status on admission, CD4 lymphocyte count on admission, whether or not the patient was prescribed zidovudine or didanosine, date of death and primary and secondary causes of admission. A code for medical diagnoses was drawn up and each admission diagnosis was ascribed a code. The data were entered on to a database file (database III plus) and each record of the file contained one hospital admission. Each patient, therefore, had a varying number of records depending on the number of times he had been admitted to the City Hospital (range 1 - 22). The only variable with missing values was the CD4 lymphocyte count. Since October 1989 these data have been collected prospectively on a weekly update basis.

A separate database of admissions of HIV positive patients who had attended the City Hospital but who had been admitted to other hospitals was drawn up. The psychiatric admissions were obtained by a slightly different method from the general admissions. The methods for the general admissions are described first. Relevant admission diagnostic classifications were identified in the International Classification for Diseases handbook

(ICD-9). These comprised: AIDS, deficiency of cell-mediated immunity, HTLV-III, carrier or suspected carrier of other specified infectious organism, contact with or exposure to other viral disease, drug dependence, addiction and withdrawal, homosexuality, poisoning and gynaecological admissions. The Scottish Health Services Hospital Diagnostic and Operations Index for the years 1985 until October 1989 inclusive was searched for admissions in the above categories to each of the three main teaching hospitals. Admissions under each category were matched by name and date of birth with City Hospital indexes (although the City Hospital database files do not actually contain names). The gynaecological admissions were found to be so numerous that they were only matched if the admission diagnosis had some mention of HIV or AIDS. This was not the case for the categories of drug dependence, addiction and withdrawal or poisoning. In these categories all the admissions were searched and patients who had attended the City Hospital HIV clinic were identified by name and date of birth. Therefore, in the category of admissions related directly to drug use, patients who had not identified themselves as being HIV positive to the other hospitals, or who had not known themselves to be HIV positive at the time of admission, or in whom the Scottish Health Services Hospital Diagnostic and Operations Index did not contain details of HIV positivity, were still included in the study. Admissions not in the drug related categories (eg bacterial chest infections) would however be missed unless there was mention of HIV infection on the Scottish Health Services Hospital Diagnostic and Operations Index.

Medical records for HIV positive patients known to the City Hospital but admitted to one of the three other hospitals before November 1989 were requested (ie excluding HIV positive patients who were admitted to other hospitals but who were not known to the City Hospital). This database was drawn up from the requested records in exactly the same way as described above. Data on CDC staging, CD4 count on admission and antiretroviral therapy were recorded so infrequently in these medical records that these

categories were not included in the second database. Data recorded on the second database therefore included identifying number, date of birth, sex, risk group, date of admission and discharge from hospital, first three diagnoses with coding and the hospital of admission. Both databases were searched for duplicates which were then removed eg. an inpatient from the City Hospital might have been referred to and admitted to another hospital for a specialised investigation or procedure (eg CT scan or laparotomy) and would therefore have appeared on both databases.

All psychiatric case records are kept in a central records office (Lothian Psychiatric Register). The hospital unit numbers were obtained from the central computer for all patients discharged with a diagnosis of HIV infection, AIDS, drug misuse or homosexuality (as per the general admissions study methods) and who were admitted between 1st November 1985 and 1st November 1989. The case records were taken for all 160 of these admissions, and, where the patient was HIV positive (whether or not this was known at the time) details were taken of admission and discharge dates, psychiatric diagnoses, whether or not the HIV status was known at the time of discharge, CD4 count and CDC stage. Admissions before 1985 in these case records were also included. These psychiatric admissions were all included in the second database.

The study period was from October 1985 until November 1989. A few admissions to the City Hospital were recorded before October 1985 and, where available, these admissions were included in the figures of the first year. The first year of the study therefore refers to the 12 months from October 1985 to the end of October 1986, the second year from November 1986 to October 1987, the third year from November 1987 to October 1988 and the last year of the study from November 1988 to 31st October 1989.

Both admission databases were analysed primarily by admission diagnosis codes (chapter two) and thereafter by risk group, sex, CDC staging, CD4

count, presence or absence of AIDS, year of admission and hospital of admission, of AIDS patients and of readmissions (chapter three). The 1987 system of CDC staging was used.[5]

Analysis was mainly in the form of descriptive epidemiology. Statistics were calculated using the software package "Epi Info version 5.01b" for chi squared tests. Yates correction was used for two by two tables with a total of less than 100. Fisher's exact test was used when the expected value of any cell in the two by two table was less than five. Statistical significance was set at the 0.01 probability level. Confidence limits for odds ratios were calculated at the 95% level.

Ethical permission was obtained from the Lothian Health Board Ethics of Medical Research Sub-Committee for Medicine and Clinical Oncology (application MCO/57/92) and from the Sub-Committee for Psychiatry and Clinical Psychology (application 93/42). Permission was also obtained from the Information and Statistics Division, Common Services Agency and the clinical directors and principal medical records officers of all the hospitals concerned.

Results

Synopsis

A total of 910 admissions were recorded; 612 to the City Hospital and 298 to the other hospitals. The 612 admissions to the City Hospital were made by 208 patients and the 298 admissions to the other hospitals by 121 patients. A total of 8738 bed days were occupied and mean length of admission was 9.6 days. IDUs accounted for 702 (77%) admissions, homosexual men for 136 (15%), heterosexual patients for 62 (7%) and

recipients of blood products for 10 (figure 2.1). By comparison over the same period, i.e. before November 1989, 409 patients had attended the City Hospital clinic; 78% were IDUs, 12% were homosexual, 7% heterosexual, in 2% no risk factors were found and in 1% the patient was a recipient of blood products (figure 2.2).

The most frequent admissions were for conditions directly related to drug use (figure 2.3). These comprised overdose, trauma, injection injuries and detoxification and accounted for 220 admissions. The largest amount of bed days were used for respiratory conditions which was the second most common reason for admission (187 admissions). One hundred and one admissions were for genitourinary and gynaecological conditions, 98 for gastrointestinal and hepatic conditions, 91 for neurological, 38 for psychiatric and 35 for haematological conditions. Forty seven admissions were for day treatments, 45 for investigation and 48 for a variety of other conditions. A total of 2195 bed days were used for respiratory conditions, 1403 for drug related conditions, 1192 for neurological, 984 for gastrointestinal and 531 for genitourinary and gynaecological conditions and 442 bed days were for admissions for investigation.

Drug related admissions

Overdose

Drug related events were by far the most common reason for patients from the City Hospital cohort to be admitted to other hospitals. Injection injuries, trauma and overdose accounted for 48% (144) of all the admissions to other hospitals in Edinburgh. Most (100) of these were due to overdose. Only two

patients with overdose were admitted to the City Hospital. One was a patient with AIDS who had been attending the City Hospital frequently and the other was a homosexual man who took an overdose of 100 zidovudine capsules - this was uncomplicated and the admission lasted only two days. A further two admissions with overdose were to the Western General Hospital and the rest were to the Regional Poisons Unit in the Royal Infirmary. Fifty five admissions were in male IDUs, 41 in female IDUs and four were in women (two patients only) with heterosexually acquired infection. The average age was 24. Despite the large number of admissions, only 155 bed days were occupied by overdoses. The patient stayed overnight in 85 admissions, seven admissions lasted two days, three lasted three days, one took four days, two took seven days, one took nine days and one lasted 20 days. Twenty nine of the overdoses were with a mixed concoction of drugs and the predominant drugs in every case were opiates (heroin, methadone, dihydrocodeine, dipipanone, dextromoramide) and benzodiazepines (diazepam, triazolam, temazepam). In only two cases (in the same patient) were non-heroin drugs specified as being taken intravenously. Other drugs taken were paracetamol (7), chlormethiazole (3), thioridazine (2), carbamazepine (2), cyclizine (1), temgesic (1), procyclidine (1), mefenamic acid (1), clonidine (1), amitryptiline (1) and prednisolone (1). The two admissions in non-IDUs were for overdose of triazolam in one, and the other patient who was admitted three times took paracetamol and diazepam on one occasion each and a mixture of chlorpromazine and "speed" on the other. Only six admissions were "complicated" - by aspiration pneumonia in four cases, opiate induced pulmonary oedema in one and respiratory and renal failure in one. One patient with aspiration pneumonia died on the second day of admission with overdose of unknown substances - this was his fourth overdose admission. The patient with opiate induced pulmonary oedema had five overdose admissions in the space of six months. The first of these was a 20 day admission following an overdose of paracetamol and unknown substances which resulted in respiratory and renal

failure requiring dialysis and eight days of ventilation. The frequent number of readmissions is reflected in the fact that only 43 patients were admitted with overdose - 23 patients were admitted once, ten patients twice, six were admitted on three occasions, two on four, one on five occasions and one female IDU was admitted 26 times within the study period. Her admissions were usually overnight (the longest stay was four days) and she took a large variety of substances - paracetamol on five occasions, caffeine (Proplus tablets) on two and thereafter mainly hypnotics and opiates.

Injection injuries

Of the remaining 44 admissions for drug related causes to other hospitals, 20 were directly related to recent injection drug use. Seven of these were for incision and drainage of abscesses (five buttock, one thigh, one arm) and accounted for 41 bed days (range 1 - 27, mode 1). Four men were admitted with cellulitis requiring antibiotics. Seven admissions were because of acute ischaemia. Buprenorphine (Temgesic) was implicated in two cases, one of which resulted in ischaemic necrosis of the thigh. Diconal (a mixture of dipipanone and cyclizine) was implicated in another man in whom injection into the femoral artery (whilst in prison) resulted in a hindquarter amputation, acute renal failure and osteomyelitis. He was in the Royal Infirmary for 31 days before being transferred to the City Hospital for 113 days convalescence. One man required partial amputation of three digits of his left hand in March 1989 and in July was readmitted with acute ischaemia of his left hand after injection into his brachial artery. These seven admissions accounted for 53 bed days.

Twenty nine admissions (356 bed days) were recorded to the City Hospital with injection related injuries. Nine were with abscesses accounting for 184 bed days (range 2 - 27 days per admission), all in patients with CDC disease

stage 2 or 3. One patient had thrombophlebitis and two patients had cellulitis. In 13 cases the injury was not specified.

Detoxification

Fourteen admissions to the Royal Edinburgh Hospital were for detoxification and these are documented in the section on psychiatric admissions. No admissions were recorded to any of the other hospitals for drug withdrawal. Twenty nine City Hospital admissions in 21 patients had a primary discharge diagnosis of detoxification. In this category of admission women outnumbered men (15 women, 14 men). Average length of admission was 13.5 days (total 392 days). Only three patients had CDC stage 4 disease. Assessing the outcome of these admissons was difficult. Three admissions were deemed successful, including a 38 day stay by a pregnant woman. Six admissions (in five patients) were successful at the time but the patients subsequently relapsed. Twelve admissions were thought to be unsuccessful at the time. Average length of stay was not significantly different between the successful and unsuccessful admissions (16.4 and 15.4 days respectively). Three admissions were for alcohol detoxification. Perhaps more significantly, nine patients admitted for other reasons had a second discharge diagnosis of detoxification. Five of these were in patients admitted with bacterial chest infections. The average length of stay in these five was 14.8 days, considerably longer than the mean for chest infections as a whole.

Other drug and alcohol related admissions

There were six admissions in four patients with staphylococcal endocarditis. All were before 1986 in patients who had CDC stage 2 disease. Average length of admission was 47 days (range 24 to 66). One

woman spent six days in the Royal Infirmary before transfer to the City Hospital.

A further seven admissions (37 days) to the City Hospital were directly related to alcohol abuse. Two of these patients were homosexual men, one was a heterosexual woman and the rest were drug users. The diagnosis in two was of acute intoxification and in the other five it was chronic alcohol abuse in whom in three cases admission was also precipitated by abdominal pain, altered bowel habit and a recent rape.

Trauma

Trauma accounted for 28 admissions and 157 bed days. Seven of these were specified as being stab wounds (three required laparotomy with eventual suturing of the liver in one and stomach in one, and one patient required scrotal exploration). Seven were for fractures (malar, orbital floor, mandible, nose, tibia and fibula). Four were for slashed wrists (and one of the overdose admissions had a concurrent diagnosis of slashed wrists). One episode of trauma resulted in a black eye requiring a five day hospital admission in a patient known to have HIV-related thrombocytopenia. One patient fell out of a window sustaining injuries which required laparotomy, ventilation and tracheostomy and a ten day hospital admission. This last injury may not have been entirely drug related but did occur in a drug user. Eight of the trauma admissions were to the Western General Hospital, five were to the City and the remainder were to the Royal Infirmary.

Respiratory admissions

A total of 187 admissions (21% of all admissions) were for investigation and treatment of respiratory disorders. One hundred and eighty of these were to the City Hospital and constituted the single most common reason for admission to the City (29% of admissions). These cases were therefore studied in more detail. Because the same amount of detail was not available on the seven respiratory admissions to the other hospitals they are summarised first. One homosexual man was admitted for 19 days to another hospital with *Pneumocystis carinii* pneumonia (PCP). The other admissions were all in IDUs. Two of these IDUs had unspecified bacterial chest infections, one had severe staphylococcal pneumonia and pyohaemothorax requiring 17 days in hospital, one had atypical chest pain and one patient with PCP was transferred from the City Hospital to the Western General for ventilation but died shortly after transfer (see below). In a further eight admissions to other hospitals, a secondary diagnosis of respiratory disease was made. These patients were all IDUs and in six of the admissions the primary diagnosis was of overdose. Three were cases of aspiration pneumonia, one patient had respiratory failure requiring eight days of ventilation, one had opiate induced pulmonary oedema and one had an unspecified chest infection. The other two admissions were in one woman who developed chest infections during admissions for cholecystectomy and pelvic inflammatory disease.

Of the 180 respiratory admissions to the City Hospital, 97 (ie 16% of all City admissions) were due to bacterial chest infections (BCIs), 48 (8% of City admissions) were due to PCP and 35 (6% of City admissions) to other chest related disorders (figure 2.4). The number of these admissions rose steadily over the four years studied with 12 recorded in the first year (eight BCIs, one PCP, three other chest conditions), 25 in the second year (12,

eight and five BCIs, PCP and other chest disorders respectively), 51 in the third year (31, 12 and eight) and 92 in the fourth (46, 27 and 19).

Pneumocystis carinii pneumonia

Pneumocystis carinii pneumonia (PCP) was diagnosed in 42 patients and accounted for 48 admissions (25 in homosexual men, 16 in IDUs and seven in heterosexually HIV infected patients; 36 men and 12 women). Two female patients had three episodes of PCP and two male patients had two episodes. Average age was 33 (range 22-57). Two women were pregnant at the time of diagnosis of PCP. One pregnancy was terminated. The other woman gave birth four weeks later to an initially healthy female child. Although the mother remained well for over one year her child died of PCP at six months of age.[113] Two IDUs (5%) died, both during their first presentation with HIV disease and both with other concomitant HIV related illnesses (CMV pneumonitis in one and cerebral lymphoma in the other). Average length of hospital stay was 23 days (range 2 - 102 days) and PCP accounted for a total of 1065 bed days.

Diagnostic techniques for PCP changed over the four year period. Initially diagnosis was made by cytological examination of silver staining of bronchoalveolar lavage fluid. Bronchoscopy was then mainly replaced by sputum induction and in 1989 silver staining was replaced by monoclonal antibody techniques. In 17 cases the diagnosis was made on the basis of clinical features and response to treatment. A definite diagnosis was made in 31 cases, 12 by silver staining and 19 by immunofluorescent antibody techniques. Specimens were of induced sputum in 21 cases, bronchoalveolar lavage in nine and open-lung biopsy in one. In one patient bronchoalveolar lavage samples were negative but a positive result was obtained two weeks later from an induced sputum sample.

Treatment was with co-trimoxazole in 34 cases, pentamidine in five and with both in six. One patient was initially treated with cotrimoxazole and the treatment course was completed with clindamycin and primaquine. In five patients antibiotic treatment was supplemented with oral steroids.

In seven (five IDUs, one homosexual man and one African heterosexual woman) of the 48 cases of PCP (15%), a concomitant BCI was diagnosed. Thrity two patients (73%) had a $pO_2 < 10$ kPa, of whom nine (20%) had a $pO_2 < 7$kPa but only six (14%) had a $pCO_2 > 5.5$ kPa. Chest X ray was abnormal in 75% and surprisingly that percentage remained static over the four years studied despite increased physician awareness and earlier attempts at diagnosis with improved diagnostic techniques.

Chest infections due to other opportunistic organisms

These included three admissions for atypical mycobacterial infections (*Mycobacterium kansasii* and *M. avium intracellulare*) and one for pulmonary tuberculosis. One patient was in hospital for 106 days with presumed candidal pneumonia. He was treated empirically for both tuberculosis and PCP but a clinical improvement was not seen until anticandidal therapy was started.

Bacterial chest infections

Ninety-seven admissions (42 female and 55 male) were recorded for BCIs. Bacteria were identified in 72 cases (74%), including *Haemophilus influenzae* in 29 and *Streptococcus pneumoniae* (16 different serotypes) in 22.

No patients died but the associated morbidity was significant. BCIs accounted for 948 bed days with an average duration of hospitalisation of ten

days (range 1 - 43, median 8). All patients were symptomatic and 50% had radiological pneumonia. Blood gas analysis was performed in 59 admissions: 42 (71%) had a pO_2 < 10 kPa and 27 (46%) had a pCO_2 > 5.5 kPa. Peak flow measurements were carried out on 59 admissions and 14 (24%) had readings of <300l/min. Lung function tests were performed on recovery in 64 admissions, and of these, 52% were found to have a ventilatory defect and 45% had reduced carbon monoxide transfer factor.

Most of these patients did not have AIDS or "symptomatic" HIV disease. There were 50 admissions in patients with CDC disease stage 2 and 3, 13 with 4a, one with 4b, 16 with 4c1, 14 with 4c2, two with 4d, and one with 4e. The 50 admissions in patients who did not have "symptomatic" HIV disease accounted for 458 bed days (48% of total bed days used for BCIs).

Of all patients admitted with BCIs, 98% smoked cigarettes and most also smoked marijuana. At the time of admission 80% were receiving opiates and 80% benzodiazepines.

Ninety (93%) of the 97 admissions due to BCIs were in IDUs (figure 2.5) compared with 71% of those attending the City Hospital HIV clinic having drug-related disease ($x^2_{(1)} = 25.5$, $p < 0.0001$). In this study, IDUs were five times more likely than the other HIV positive patients to be admitted with a BCI (95% confidence limit 2.75 - 9.520).

Differentiating BCIs from PCP was often difficult, particularly since several infections could occur concurrently. Symptoms of weight loss, fever and breathlessness were more marked in PCP whereas cough productive of sputum was more characteristic of BCIs. The average CD4 positive lymphocyte count at diagnosis of PCP was 56 cells/mm^3 (range 0 - 240) compared with an average for BCIs of 296 cells/mm^3 (range 0 - 1040). White cell count was low or normal in PCP compared with BCIs where 29% of patients were found to have either a raised neutrophil count or one which had doubled ($p < 0.02$, $x^2 = 5.72$ with Yates correction). In many

neutropenic patients, although the neutrophil count had doubled, it was still below normal. Comparison with previous neutrophil counts was therefore an important part of assessment. Because of the difficulty in differentiating PCP and BCIs clinically an algorithm was drawn up and a study conducted to assess the value of induced sputum techniques in the diagnosis of PCP in IDUs (see chapter four).

Other respiratory disorders

Two patients were admitted with Influenza A and five admissions were found to be due to upper respiratory tract infections. In addition, ten admissions were for investigations of breathlessness, ten for exacerbations of chronic obstructive pulmonary disease and asthma and one for a pneumothorax.

Genito-urinary and gynaecological admissions

Genito-urinary (GU) diagnoses accounted for 101 admissions and 531 bed days. The most common diagnosis in this category was pelvic inflammatory disease for which there were 26 admissions. Fourteen of these were in IDUs and 12 were in heterosexual women. The average age of these women was 24 years. Many of these women were admitted on a number of occasions (one was admitted six times and two women had five admissions each) so that only ten women accounted for the 26 admissions. Four of these admissions were to the City Hospital, the rest to the other hospitals in Edinburgh. Pelvic inflammatory disease accounted for 100 days in hospital, admissions ranging from one to 21 days (mode = 1 day). Organisms were specified in only three cases - *Mycoplasma hominis* in one and *Neisseria gonorrhoeae* in two.

Ten admissions (25 bed days) were for termination of pregnancy. One woman was admitted for two terminations and all but one of the women were IDUs. Three admissions to the City Hospital were because of a primary diagnosis of pregnancy. One of these admissions was elective and lasted 38 days because of a successful detoxification. The other two were in one woman who was admitted initially with vomiting. She had a concomitant diagnosis of a chest infection and was admitted later in the same pregnancy with a urinary tract infection. Two admissions were for threatened abortion, one of which turned into a complete abortion and two were because of incomplete abortion. Pregnancy was a second diagnosis in three cases. One was a woman admitted with pyelonephritis. One woman was admitted on two occasions with PCP. She was found to be pregnant during the first admission and had a termination during the second.

Other gynaecological diagnoses were vaginal bleeding (9), sterilisation (3) and vaginitis (1).

Urinary tract infections accounted for 13 admissions - 11 women and two men. Total bed days for urinary tract infections were 103 days but excluding two admissions lasting 23 and 24 days, average length of admission was five days. Urinary tract infection was a second diagnosis in 15 patients (13 women, two men) admitted to the City Hospital, six of whom had a primary diagnosis of a chest infection. One woman had four admissions with both chest and urinary tract infections. Two women had pyelonephritis. One was known to have a congenital absence of a left kidney and one was in a woman who was pregnant and altogether had three admissions for urinary tract infections. Two admissions for septicaemia (in one male IDU with CDC stage 3 disease) were secondary to a urinary tract infection - *Escherichia coli* was identified as the cause in one.

Prostatitis was a primary diagnosis in ten men and a second diagnosis in one (his primary diagnosis was a chest infection). Nine of the men were

asymptomatic IDUs and one was a homosexual man with AIDS. Prostatitis accounted for 158 bed days (range 4 - 53 days per admission). The admission lasting 53 days was in an IDU who had a history of recurrent bacterial infections, who had had two previous admissions for prostatitis and who had a concomitant diagnosis of campylobacter enteritis. Two admissions were for epididymo-orchitis and one for vasectomy.

One patient was admitted on three occasions for excision of vulval warts. Second diagnoses of peri-anal herpes were found in two homosexual men and one IDU, of genital herpes in one heterosexual woman, of genital warts in one male IDU and of anal warts in one male IDU and one heterosexual woman.

Gastro-intestinal admissions

Ninety eight admissions were for gastro-intestinal (GI) and hepatic disorders. Additionally, in 19 admissions a secondary GI diagnosis was noted. The most common GI-related reason for admission was diarrhoea. Investigation and treatment of diarrhoea for which no specific cause was found accounted for 14 admissions - 12 IDUs and two homosexual men. Specific pathogens were found only in a minority of cases. There were three cases of enteritis due to *Clostridium difficile*, one of which was associated with pseudomembranous colitis. One patient had a diagnosis of "food poisoning" and there were three cases of campylobacter enteritis. One homosexual patient was admitted with salmonella enteritis in 1987 and campylobacter enteritis in 1988. Constipation accounted for nine admissions (five to the City and four to other hospitals). In eight of these admissions the patients were IDUs and one was a heterosexual woman. Three IDUs had a secondary diagnosis of constipation. Thirteen admissions were for non-specific abdominal pain.

Three patients had acute appendicitis, all of whom required transfer to another hospital. In two cases the diagnosis was complicated - one had a gangrenous appendix and one had sepsis and intra-abdominal adhesions - and these patients spent 26 and 51 days in hospital respectively. In the third patient the histology of the appendix did not show any inflammation.

Six admissions in four women were with acute or chronic cholecystitis or biliary colic. Three patients had a cholecystectomy, in two cases comlicated by a chest infection. These admissions accounted for 70 bed days. Other "surgical" admissions were one case of acute alcoholic pancreatitis and one patient with small bowel obstruction caused by swallowing condoms full of drugs.

Three men and three women (four IDUs, one heterosexual and one homosexual) were admitted because of oesophageal candidosis. One patient had oesophageal herpes simplex and one had a non-specific diagnosis of "oesophagitis". These admissions accounted for 91 bed days.

Eleven admissions were for hepatic diagnoses. One patient with cirrhosis, oesophageal varices and liver failure was admitted on six occasions and spent 37 days in hospital. He subsequently died at home of a massive variceal haemorrhage. One patient had hepatic encephalopathy and died at the end of his 29 day admission. Two admissions were for acute hepatitis and two were in one patient who had chronic active hepatitis and thrombocytopenia. This patient (who was a prisoner at the time) spent 60 days in hospital and was treated with subcutaneous interferon.

Neurological admissions

A total of 91 admissions were recorded with a primary diagnosis of neurological disease. Eighty of these were to the City Hospital where a

further 13 admissions also had a second diagnosis within the neurological category. Of the 80 admissions to the City Hospital 49 were in men and 31 were in women; 44 were IDUs, 23 were homosexual men, eight were heterosexual (this category actually only comprised two women, one of whom was admitted six times) and five were infected through blood products (one woman who was admitted four times and one man). In 30 admissions CDC staging was 2 or 3, eight were in CDC stages 4.1 and 4.32 and 42 were in AIDS defining categories - ten in CDC 4.2 and 32 in CDC 4.31. Total bed days used by the City and other hospitals was 1192 and average length of stay was 13.1 days. Length of admission was much longer in those patients admitted to the City hospital compared with the other hospitals - 14.2 versus 4.8 days. Homosexual men (most of whom had AIDS) had the longest mean length of stay at 19.6 days. Length of stay was much longer in patients with AIDS compared with those without AIDS - 17.7 versus 10.4 days. Only four admissions were for one day or less. Thirty six lasted for ten or more days, 18 for 20 or more and seven for more than 30 days. The longest admission was for 93 days in a homosexual man with cerebral toxoplasmosis. Two patients were admitted for 75 days - one with CMV retinitis and disseminated *Mycobacterium kansasii* infection and one with an HIV myopathy. One female IDU was admitted for 57 days for investigation of blackouts and a second diagnosis of pelvic inflammatory disease.

The most common reason for admission was cerebral toxoplasmosis (18 admissions). All seven patients were homosexual men apart from one heterosexual woman who was admitted five times and spent a total of 90 days in hospital with this diagnosis. One man was admitted five times, one man three times, one twice and three men were admitted once. The man admitted five times, who had a second diagnosis of Kaposi's sarcoma (KS), spent a total of 53 days in hospital and he died in his last admission. The man admitted on three occasions later developed cerebral lymphoma (diagnosed on brain biopsy) from which he died and it is not clear whether

his admissions for presumed cerebral toxoplasmosis were in fact due to cerebral lymphoma. The patient who was admitted twice had a second diagnosis of myelopathy. One of the patients admitted once spent 93 days in hospital (not only the longest admission but also longer than the total days spent in hospital by the two patients who were admitted five times) and another patient admitted for 31 days died during that admission.

Two patients had a diagnosis of cerebral lymphoma. One was discussed above and the other had a primary diagnosis of PCP. In this patient cerebral lymphoma was not diagnosed until post-mortem.

Five patients (four homosexual men, one female IDU) were admitted with CMV retinitis. CMV retinitis accounted for 101 bed days (range 2-75, mean 20). The patient admitted for 75 days also had disseminated *M. kansasii* infection and one other patient had a second diagnosis of oral KS.

One patient was admitted with cryptococcal meningitis and concomitant diagnoses of PCP and high grade B cell lymphoma.

One patient was admitted twice with a diagnosis of dementia. Another four admissions were in patients complaining of memory loss for which an exact cause was not found.

The above 27 admissions were therefore for AIDS defining conditions. Sixty four admissions were for non AIDS defining events. The most common reason was for investigation of blackouts. Fourteen admissions were in this category - nine female and three male IDUs, one heterosexual woman and one woman infected from blood products. Total bed days were 196 with a range from one to 57 and average of 14 days. All these admissions were in patients with CDC disease stage 2 or 3 except one male IDU who had stage 4.32 disease. CD4 counts ranged from 210 to 670 cells/mm^3. In four cases a second diagnosis was recorded (two chest and one urinary tract infections and one case of pelvic inflammatory disease). A

definite diagnosis was not achieved in any of these cases and many were thought to be solely drug related. One patient who was admitted for 57 days had a cardio-respiratory arrest during her admission.

Eleven admissions to the City and six to other hospitals were for seizures. Three of these patients had CDC stage 4.31 disease, 11 had CDC stage 2 or 3 and two had stage 4.32 disease (one unknown). Average length of stay was 7.4 days. One woman was pregnant and had a diagnosis both of epilepsy and of pseudoseizures.

Eight admissions (five in women, three in men) were for headaches of no defined cause. The average admission in this category lasted 10.4 days.

Seven admissions were for neuropathy and one woman was admitted on five occasions for symptoms of cervical disc compression and on the third admission had a C5/6 foraminotomy. Two admissions were for lymphocytic meningitis and one for pneumococcal meningitis. Three patients had a diagnosis of myopathy and one of these admissions lasted 75 days.

Psychiatric admissions

Thirty eight admissions (721 bed days) were for psychiatric disorders. Because the nature of admissions to psychiatric hospitals is very different from all other hospital admissions, the psychiatric admissions to the City Hospital and those to the Royal Edinburgh Hospital were analysed separately.

Eleven admissions with a primary psychiatric diagnosis were recorded for the City Hospital. Length of admission ranged from three to 31 days and totalled 103 days (mean = 9.4 days). Four men were admitted because of anxiety - in one patient with two admissions this was described as anxiety depression and in one it was described as anxiety psychosis. All these

patients had CDC stage 4 disease. Four admissions were for depression and one of these patients had a further admission with acute hypomania. In two admissions there was a secondary diagnosis of depression, in one of whom the primary diagnosis was of poor memory. Two patients were given a diagnosis of unspecified psychosis. In one female IDU the admission lasted 31 days and was thought to have an organic aetiology although the exact cause was not identified. One AIDS patient had a primary diagnosis of exposure dehydration but this exposure was directly precipitated by a paranoid depression.

Twelve patients (8 male and 3 female IDUs and one homosexual man) were admitted on 27 occasions to the Royal Edinburgh Hospital. These admissions accounted for 618 bed days and hospital stays ranged from one day to 217 days (eight months), mean 23 days per admission. For individual patients, who had between one and six admissions each, the range of total bed days used was 3 - 224, mean 51.5, median 26.5 days.

Fourteen of these Royal Edinburgh Hospital admissions were for detoxification, five for "drug abuse", seven for psychosis and one for depression. One patient had six admissions for detoxification and discharged herself from four of them. There were two other self discharges. One admission initially for detoxification lasted for eight months having been complicated by "?organic confusional state, ?severe anxiety state, ?functional psychosis". Most of the admissions for "drug abuse" had additional diagnoses - personality disorder in one, overdose of psychotropics as a suicide attempt in one and adjustment reaction to HIV infection in one. Of the seven admissions for psychosis, three were in one patient (who had diagnoses of hypomania, drug induced psychosis and paranoia), two in one patient (diagnoses of psychotic depression and paranoid psychosis), another was a paranoid psychosis and one was an amphetamine induced psychosis.

Eleven of the Royal Edinburgh Hospital admissions were before 1985, two were in the first year of the admissions study (November 1985 to November 1986), two in the second year, three in the third and nine in the last year. Five of the admissions for psychosis were in the final year of the study. The HIV status of the patient was not known in 13 admissions (including all six in the IDU admitted for six detoxifications, the eight month admission originally for detoxification and the homosexual patient who was admitted with depression). Two patients learnt of their HIV infection during their psychiatric admission. CDC stage was recorded in four admissions (CDC stage 2/3 in three, stage 4c2 in one) and CD4 count in four (two were less than 200 cells/mm^3 and two were between 250 and 350 cells/mm^3).

Other admissions

Haematological admissions

Thirty five admissions to the City Hospital were because of anaemia (17), neutropenia (2) or thrombocytopenia (16) and accounted for 229 days in hospital. Nineteen were male IDUs, seven were female IDUs and nine were homosexual men. One patient with thrombocytopenia was admitted to the Royal Infirmary for a splenectomy. In a further five admissions there was a second diagnosis of anaemia, in four there was a second diagnosis of thrombocytopenia (in one of these the primary diagnosis was of a black eye) and in one there was a second diagnosis of neutropenia (primary diagnosis was a chest infection). Not surprisingly patients with haematological manifestations also had more advanced disease - 34 of the 36 admissions with a primary haematological diagnosis had CDC stage 4 disease (all patients with problematical thrombocytopenia were classified as having CDC

stage 4e disease). Twenty two admissions were for blood transfusion, 15 in patients with AIDS.

Admissions for day treatments

Forty seven admissions, all to the City Hospital, were for treatment pulses, including blood transfusion. Twenty two were for blood transfusion, ten for intravenous immunoglobulin, seven for chemotherapy, three for intravenous dextran, one for platelet transfusion and three were for pentamidine (intravenous in two cases). Two other patients had a blood transfusion and one had an immunoglobulin infusion during admissions for other reasons. One patient received both intravenous immunoglobulin and pentamidine during the same admissions. Most patients were day patients but the total days used for "day" treatments was 103. This includes two patients who remained in hospital for 18 and 12 days each. Of the 47 admissions, 25 were in men, 22 in women, 29 were in IDUs, 12 in homosexual men, four in heterosexuals and two were in blood transfusion recipients. In only five admissions was CDC disease stage 2 or 3. The intravenous immunoglobulin was administered in all cases (to five patients) for prophylaxis of recurrent bacterial infections, the chemotherapy was for Kaposi's sarcoma in all three patients, the pentamidine was for PCP prophylaxis and the dextran was a trial treatment for thrombocytopenia.

Admissions for investigations

Forty five admissions were for investigation of HIV symptomatology which was thought to indicate advancing HIV disease ie "AIDS related complex" symptoms. This category comprised patients admitted for investigation of weight loss (16 admissions), fever (3), lymphadenopathy (3), non-specific investigations (17) and starting zidovudine (6). The 16

admissions with weight loss had an average admission of 12 days (total 194, range 1 - 33) and nine had additional diagnoses (diarrhoea, fever, myalgia). The 17 admissions for general investigations had an average admission of 7.3 days (total 125, range 1 - 24) and four had additional diagnoses (pneumonia in two and a urinary tract infection in one). Of the three admissions for lymphadenopathy, one was to another hospital and a biopsy was carried out which showed "reactive changes". The six admissions to start zidovudine were all in IDUs with CDC stage 4.32 disease and all between October 1987 and January 1988, shortly after zidovudine had become available in the UK. Most of these patients were involved in pharmacokinetic trials and although the trials only involved a short admission, these admissions accounted for 69 days in hospital. In ten admissions a second diagnosis came under this category (weight loss in four, starting zidovudine in two, fever in two).

Of these 45 admissions, 26 were in men, 19 in women, 34 in IDUs, seven in homosexual men, three in heterosexuals and one in a transfusion recipient. Twelve patients had CDC stage 2 or 3 disease (and spent 58 days in hospital) and 33 had stage 4 disease (384 bed days).

Dermatological admissions

Eight patients were admitted because of herpes zoster and this diagnosis accounted for 72 bed days. The site of the zoster was specified in one case only and was ophthalmic. One patient had a second diagnosis of non Hodgkins lymphoma and one of KS. Two of these patients had CDC stage 3 disease (the rest being stage 4), one of whom was also known however to have chronic liver disease. In one patient the primary diagnosis was of neutropenia but the second diagnosis was shingles.

Seven patients were admitted with a variety of other miscellaneous skin conditions; heel sore (2), erysipelas, seborrhoeic dermatitis, skin ulcer, skin

"infection" and thrombophlebitis. Four patients also had a second diagnosis of skin disease; eczema, psoriasis, orbital cellulitis and wound infection.

Cardiac admissions

Six admissions were for primary cardiac reasons. One patient was admitted on two occasions (for a total of 38 days) because of cardiomyopathy and cardiac failure. He was already known to have atypical mycobacterial and CMV infection. One patient was admitted because of progressive valvular disease and one for tricuspid incompetence. One male IDU was admitted for 33 days because of staphylococcal pericarditis. He developed renal failure and cardiac tamponade and was transferred to the Royal Infirmary for pericardial aspiration. There were six admissions due to endocarditis, all of which were before 1986; these admissions have already been documented in the section on drug related admissions.

Admissions for malignancy

Nine admissions were primarily because of malignancy (apart from those already documented for chemotherapy). Five were for KS (two patients died during these admissions), three were in one patient who had lymphoma and who also died in hospital and one was another lymphoma patient. These admissions accounted for 129 bed days. In eight admissions there was a second diagnosis of malignancy - seven KS, one lymphoma.

Admissions for septicaemia

In five admissions the diagnosis was of septicaemia (already discussed in the chest and GU sections). A source was specified in two cases (urinary

tract and chest) and an organism in another two - *E. coli* and pseudomonas. This latter patient who already had CDC stage 4.31 disease was hospitalised for 81 days. The other admissions with septicaemia were all for less than ten days. One patient, who had CDC stage 3 disease, was admitted twice within the space of six months with two episodes of septicaemia.

ENT admissions

Four admissions were for sinusitis, one patient requiring a sinus puncture. One admission was for tonsillitis.

Social admissions

Three admissions were for primary social reasons and this was a second diagnosis in a further two cases.

Tropical admissions

Three patients were admitted because of tropical conditions - two with malaria and one with visceral leishmaniasis.

Miscellaneous admissions

Two admissions to the City Hospital and two to other hospitals were because of atypical mycobacterial infection. One was for disseminated CMV infection. One was for incision of an abscess following which the patient died post-operatively. One admission was solely for terminal care.

Discussion

Drug, alcohol and trauma related diagnoses accounted for 220 admissions and 1403 bed days. This amounts to 24% of all admissions and 16% of all bed days in this study. Only one of these patients had AIDS and in those who had a CD4 count recorded at the City Hospital, none were below 100 cells/mm^3.

Whilst admissions to other hospitals for drug related diagnoses were relatively short, admissions to the City lasted longer, particularly in patients with abscesses, endocarditis and the patient with the hindquarter amputation. Admission to the City Hospital in patients with drug related rather than purely HIV related diagnoses may have been chosen by the referring practitioner because the patient also had a secondary medical problem. Drug related problems may have been complicated by non-specific medical problems and this may account for the longer stays in the City Hospital. Only two patients with overdose (usually short admissions) were referred to the City Hospital. This reflects the policy in Edinburgh of admitting all overdoses to the regional poisons centre in the Royal Infirmary. Undoubtedly other patients admitted to the City Hospital had also "overdosed" on admission but the medical problems (eg related chest infections) overshadowed overdose as a documented reason for admission. The short admissions for overdose reflect the types of drugs taken in overdose. These were predominantly drugs of abuse readily available, with or without a prescription, to IDUs who had "accidentally" taken too much, become unconscious and were therefore admitted to hospital. Most of these patients had not intentionally meant to "overdose". The short duration of stay also reflects the uncomplicated nature of the overdoses and that many of the patients self-discharged.

Only 29 admissions to the City Hospital and 14 to the Royal Edinburgh Hospital were for detoxification. The smaller number of admissions to the

Royal Edinburgh Hospital reflects that hospital's policy on admissions for detoxification. During the years studied, although drugs of dependence were prescribed, the City Hospital RIDU was neither a drug dependency or detoxification unit nor was there a psychiatrist attached to the unit. Nevertheless some patients were stabilised, even if not completely detoxified. Many of the medical admissions amongst the IDUs may have been longer than anticipated because of some degree of drug stabilisation and detoxification. Even admissions for detoxification which were deemed unsuccessful may have resulted in temporary alleviation of a crisis situation.

Clearly many of the drug related admissions may not have been HIV related. This can only be confirmed by a comparative study of HIV negative but otherwise matched drug users which unfortunately has not been possible. But because these admissions are not purely "HIV related" does not mean that they are not part of the HIV epidemic. Patients who are HIV positive are likely to be depressed and may have more ready access to prescibed drugs cf one overdose of prednisolone and one of zidovudine (in a homosexual man).[114] Drug users, in whom the usual response to crisis may be overdose or further substance misuse, may have taken an overdose in reaction to bad news about their HIV infection. They may revert to more chaotic injection use and therefore have more injection related injuries. Injection related injuries may have become more traumatic because of HIV related thrombocytopenia and a predisposition to infection. Endocarditis has been well documented to be a much more serious illness in HIV positive patients[98] but was not the case in this Edinburgh study. The episodes of endocarditis were all before 1986 and therefore occurred very early within the natural history of these patients' HIV infection. Since 1986 there has been a decline in the amount of injection use within Edinburgh.[115,116]

This study does bear out the changing pattern of drug use in Edinburgh as has been documented elsewhere.[115,116] Many injection related problems, most notably endocarditis and acute hepatitis B, were treated in the RIDU before

the advent of HIV in Edinburgh. Indeed it was because of this link that the RIDU became the main referral centre for HIV infection in Edinburgh. However no patients were seen between late 1985 and 1989 with acute hepatitis B and there were only six admissions with endocarditis. The epidemic of injecting was mainly in the early 1980s when there was also an epidemic of acute hepatitis B. The pattern of injecting changed initially because of the difficulty in obtaining heroin, and later because of the widespread knowledge of the HIV epidemic and methadone maintenance prescriptions. Edinburgh IDUs followed their Glasgow colleagues by initially turning to pharmaceutical preparations, particularly buprenorphine, benzodiazepines, Diconal and latterly cyclizine.[93,115,117] Although these tablets when injected are less likely to cause problems with infection than street heroin they are chemically irritant. Diconal and temazepam can cause a characteristic skin necrosis and rhabdomyolysis[92,117-120] which accounted for at least two admissions in this study.

Respiratory admissions were the second most common reason for hospitalisation, the most common reason for admission to the designated HIV unit at the City Hospital and accounted for most hospital bed days overall. That only 27% of the respiratory admissions were due to PCP contrasts sharply with studies from other UK centres where over 50% of chest admissions are due to PCP.[121,122] The preponderance of BCIs in IDUs is one of the most striking findings of the whole Edinburgh admissions study and it is of particular note that most of these patients had not progressed to CDC stage 4 disease.

The annual incidence of chest infections requiring admission to hospital within the general population aged 15 to 44 in Edinburgh in 1985-86 was 0.9 per 1000 (0.3 per 1000 for non pneumonic chest infections and 0.6 per 1000 for pneumonia). Between 1980 and 1986 there were 20 hospital discharges for drug-related pneumonias in Edinburgh ie 2.85 per year (personal communication, Information and Statistics Division, Common Services

Agency, Scotland). During 1985-86 there were an estimated 2000 IDUs within Edinburgh.[104] Thus, before there was any discernable clinical effect of HIV (ie before or within the first two years of the epidemic) the annual drug-related pneumonia rate was 1.4 per 1000, compared with 0.6 per 1000 for the general population. In comparison, for HIV positive patients the annual number of admissions for pneumonia or non pneumonic chest infections was 12. Fifty percent of the estimated 2000 IDUs in Edinburgh are assumed to be HIV infected,[64,104] yielding an estimated annual incidence of 12 per 1000 for pneumonia or non pneumonic chest infections in HIV positive IDUs in the whole of Edinburgh. This represents an eightfold increase in susceptibility to pneumonia compared with other IDUs, and a twentyfold increase compared with the general population. At present there are no statistics specifically for HIV negative IDUs, but the figure of 1.4 per 1000 admissions between 1980 and 1986 would seem to be a reasonable assumption. Thus the high incidence of BCIs in HIV positive IDUs from the above calculations seems to be more a feature of HIV disease rather than of drug use. This conclusion is in line with a previous study from New York which reported a fivefold increase in the incidence of bacterial pneumonia in IDUs with HIV infection but without AIDS compared with their HIV negative counterparts in an out-patient methadone maintenance programme.[89]

Unfortunately this latter study did not report on the clinical state of the patients, ie whether the patients were symptomatic (CDC stage 4 disease without AIDS) or had early stage 2 and 3 disease. In fact, although the 14 HIV positive patients who were admitted with bacterial pneumonia in that study did not have AIDS, two had developed AIDS by the end of their study, two had oral candidosis, one had significant weight loss and three had persistent generalised lymphadenopathy. The Edinburgh study demonstrates a very high incidence of BCIs in IDUs who were still in the early stages of HIV infection. More than 50% of these patients were otherwise classed as "asymptomatic" from point of view of their HIV infection. The associated

morbidity was not insignificant as 43% were hypoxic, 28% were hypercapnic and average admission time was ten days. Nor were the manifestations of BCIs in HIV disease typical of those seen in the general population. The preponderence of haemophilus infections contrasts with the incidence in the general population where *Streptococcus pneumoniae* is the commonest organism to be found in young patients with community-acquired pneumonia.[123]

Apart from the preponderance of BCIs the other striking feature was of only a single case of tuberculosis. This is in marked contrast to other studies of IDUs, from Europe and the US, where tuberculosis is one of the most common manifestations of HIV disease.[96,124] The reasons for these may be the low incidence of tuberculous infection in the UK and the protective effect of BCG vaccination.[125,126] To explore this more fully a further study was carried out to assess the percentage of HIV positive patients who had received BCG vaccination in the schools programme and the percentage who had evidence of tuberculous infection as manifest by a positive Heaf test when aged 11 (see chapter four).

Of the 101 admissions with gynaecological and genito-urinary (GU) diagnoses, 63 were to hospitals other than the City. These diagnoses therefore accounted for the most frequent reason, second to drug-related admissions, for HIV patients to be admitted to other hospitals. Gynaecology and obstetric services in Edinburgh are mainly based in the Royal Infirmary and Eastern General hospitals although at the beginning of the study there was also a unit in the Western General Hospital. Gynaecological and genito-urinary admissions accounted for a total of 546 days although if the two longest admissions of 53 and 38 days are excluded, the average length of admission is short at 4.4 days. It is of note that the admissions to the City Hospital were longer - ten days compared with 2.3 days to other hospitals. Most of the admissions under this category to the City were for prostatitis and urinary tract infections.

Altogether 79 of these GU admissions were in women. It is not surprising that most of these admissions were due to pelvic inflammatory disease - it is only surprising that out of a total of 359 admissions in women during this study, only ten women (26 admissions) were admitted with pelvic inflammation. With 12 of the 26 admissions by heterosexually infected women, these admissions may reflect the high prevalence of sexually transmitted diseases among commercial sex workers. Although data have not been collected on the number of women attending the City Hospital clinic who were commercial sex workers, our impression is that it is a lot lower than in other cohorts of IDUs and heterosexually infected women. The admissions with prostatitis and urinary tract infection, most of which were in patients with CDC stage 2 and 3 disease, reflects the problem of recurrent bacterial infections requiring hospital admission. That more women than men were admitted with urinary tract infection is consistent with the prevalence of urinary tract infection among the general population, but few women in the general population would require hospital admission for a urinary tract infection. This would suggest that HIV infected women were more likely to present with fever and systemic symptoms rather than with localised symptoms and signs. Because of the large number of in patient requests for urine culture compared with the few admissions for urinary tract infection a separate study was carried out to assess the prevalence of bacteriuria in these patients (see chapter four).

The 98 admissions with a primary diagnosis of GI disorder accounted for 984 days in hospital. The longest admission was 85 days in one homosexual patient who had a protein-losing enteropathy. In 77 admissions the patients were IDUs. Sixty nine admissions were in men and the 29 women were disproportionately represented amongst the admissions for cholecystitis and oesophagitis. Why so many more men than women were admitted with other GI diagnoses is not clear. GI related admissions and diseases are much more common in other cohorts, particularly in cohorts of homosexual men.[127]

CMV colitis and cryptosporidiosis are less common as AIDS defining diagnoses amongst IDUs whereas oesophageal candidosis is a more common AIDS defining diagnosis in IDUs and in women.[96,128] Only six admissions were for oesophageal candidosis but this is a condition which is often diagnosed and treated as an out-patient. It is of note that none of the patients in this study were admitted with CMV or cryptosporidial colitis. In fact very few pathogens were identified as a cause of diarrhoea in this study and only 14 admissions were for diarrhoea of unidentified cause. Most of the patients in whom pathogens were identified were homosexual men (four homosexual men, three IDUs) but most (12/14) of the admissons for diarrhoea of unknown cause were in IDUs. In the out-patient setting IDUs presenting with diarrhoea are often diagnosed as having overflow diarrhoea secondary to opiate induced constipation. But from this in-patient data only nine admissions were for constipation. However constipation is often diagnosed and treated as an out-patient and does not usually require hospital admission.

It is also surprising that only 11 admissions were for hepatic diagnoses. Most cohorts show a high incidence of liver related disorders since hepatitis B and C are often acquired via the same route as HIV and heavy alcohol consumption has also been found in homosexual and IDU cohorts.[129-132] Some cohorts of "asymptomatic" HIV patients have shown greater morbidity and mortality from hepatic disease than from HIV,[86,132,133] and hepatitis C is thought to pursue a more aggressive course in HIV infected patients.[132] Of the six patients admitted with liver problems, two died within the study period (one at home and one in hospital). In the patient who was treated with interferon, chronic liver disease was thought to be an important contributing factor to his death. Only two patients were admitted with acute hepatitis. Many of these patients had acquired hepatitis B during the 1982/1983 Edinburgh epidemic and had been admitted before the study period.[64]

With 80 admissions to the City Hospital, neurological diagnoses were the second most common reason for admission there. Only 11 admissions were to other hospitals, eight of which were to the Institute for Neurological Sciences in the Western General Hospital (one for a brain biopsy, one for a cervical foraminotomy and six for seizures). Apart from emergency admissons with seizures, patients with neurological symptoms tended to be admitted to the City Hospital for initial investigations. The low number of patients admitted to the neurological centre reflects the co-operation between the Infectious Diseases and Neurological departments in that most patients who required a specialist neurological opinion were seen in the City Hospital by a consultant neurologist who consulted there regularly. CT brain scans on in-patients in the City Hospital were carried out in the Royal Infirmary or Western General hospitals.

Although only 27 admissions were with AIDS-defining diagnoses (cerebral toxoplasmosis, lymphoma, dementia, CMV retinitis and cryptococcal meningitis) the neurological category contained more admissions to the City Hospital in AIDS (42) than in non-AIDS (38) patients. However, out of 39 admissions with seizures, blackouts and headaches only seven were in patients with AIDS. In many other centres these symptoms would raise a high suspicion of an AIDS defining diagnosis - for example seizures would generally herald a diagnosis of cerebral toxoplasmosis or lymphoma. But in this group of patients, seizures were most likely to be due to withdrawal from benzodiazepines and blackouts were also usually drug related. It is also interesting that 59% (23 of 39 admissions) of these admissions were in women and this may reflect differential patterns of drug taking between men and women or more readiness to seek medical care for symptoms of blackouts.

The long length of hospital stay in this category (13.1 days) reflects the more complicated nature of these admissions. Many of the patients with long admissions had concomitant AIDS diagnoses and three patients died at

the end of these admissions. The particularly long stay for homosexual men (19.6 days) is partly skewed by one patient who remained in hospital for 93 days, but generally reflects the more advanced disease in that patient group compared with the others, particularly the IDUs. The 11 patients admitted to other hospitals had an average length of stay of only 4.9 days. This was because patients admitted to the Institute of Neurological Sciences were admitted there mainly for diagnostic purposes only and were later transfered to the City Hospital for on-going medical care. The admissions with seizures were also short and reflected emergency care only although one woman with status epilepticus was hospitalised for eight days.

It is surprising that in a study of 910 admissions of HIV positive patients, many of whom might be likely to develop depression on learning of their diagnosis and many of whom were IDUs from socio-economically disadvantaged backgrounds, only 38 admissions should be for psychiatric disorders. Admissions for detoxification to all other hospitals other than the Royal Edinburgh Hospital are described in the section on drug related admissions. If the Royal Edinburgh Hospital admissions for detoxification are discounted then only 24 admissions were with psychiatric diagnoses.

Other studies have documented a high level of psychiatric morbidity in IDUs, homosexual men and HIV positive patients.[130,134-136] Reasons for the discrepancy between the Edinburgh study and other studies is that most psychiatric diagnoses are made and treated as out-patients and that other studies often include drug and alcohol dependency, overdose and drug detoxification as psychiatric disorders. Nevertheless an increased incidence of psychoses has been found in HIV infected patients and depression, paranoia, dementia and delirium have all been associated with AIDS.[135,137,138] In a San Francisco study of 60 patients with advanced HIV infection, 60% of the patients had their first psychiatric hospitalisation after their HIV infection.[134] The increased number of Edinburgh admissions in 1989 may have been as a result of the HIV epidemic. In the two IDUs who had five

admissions due to psychosis, all were following a diagnosis of HIV infection. The other two patients admitted for psychosis both learnt of their HIV positivity during that admission.

The low number of admissions for detoxification to the Royal Edinburgh Hospital is a reflection of Edinburgh psychiatric policy. Services for drug users are on an out-patient basis and there is no specific ward for drug users nor for detoxification. The Royal Edinburgh Hospital's policy is that one drug user at a time may be admitted to each of four acute sector wards for inpatient detoxification.[139] Between 1983 and 1988, 538 IDUs were seen at the Royal Edinburgh Hospital, and double that number had been referred to a psychiatrist from the self poisoning unit, prison and other agencies.[139] The Community Drug Problem Service was therefore established in 1988 to co-ordinate services for drug users in the community.[139] In the 18 months after the Community Drug Problem Service was instituted, 373 drug users were referred there by general practitioners.

All admissions for overdose in Edinburgh are to the Regional Poisons Unit in the Royal Infirmary. Overdose inpatients are offered psychiatric consultation with the liaison psychiatrist and any patients requiring further psychiatric in-patient care are then transferred to the Royal Edinburgh hospital.

From 1985 many IDUs with psychiatric diagnoses were seen and admitted to the Infectious Diseases Unit at the City Hospital, although a psychiatric diagnosis may not have been the primary reason for admission. Some patients who were admitted to the City Hospital for medical reasons turned out to have a primary psychiatric diagnosis. Other patients may have been admitted with a psychiatric diagnosis to the City because of easy access to the wards or because the patients had previously been admitted and knew the staff well. The admissions to the City Hospital were with "softer" psychiatric diagnoses and less were for psychosis - four admissions were for

depression, four for anxiety, two for unspecified psychosis and one for ?organic psychosis.

In summary, analysis of hospital admissions by HIV positive patients between 1985 and 1989 in Edinburgh showed a preponderance of diagnoses which were not classically associated with advanced HIV disease. Very few of the admissions to the other hospitals were with AIDS. Drug related and respiratory diagnoses accounted for 45% of all hospital admissions. Many of these admission were in patients with "asymptomatic" HIV disease. To further assess the proportion of admissions by patients who had not progressed either in terms of clinical disease or low CD4 count, analysis was performed of admissions by CD4 count, CDC stage, by diagnosis of AIDS and hospital and year of admission (chapter three). Because risk group and sex were likely to account for many of these differences, these also were analysed. An analysis was also made of AIDS patients and of readmissions.

Figure 2.1

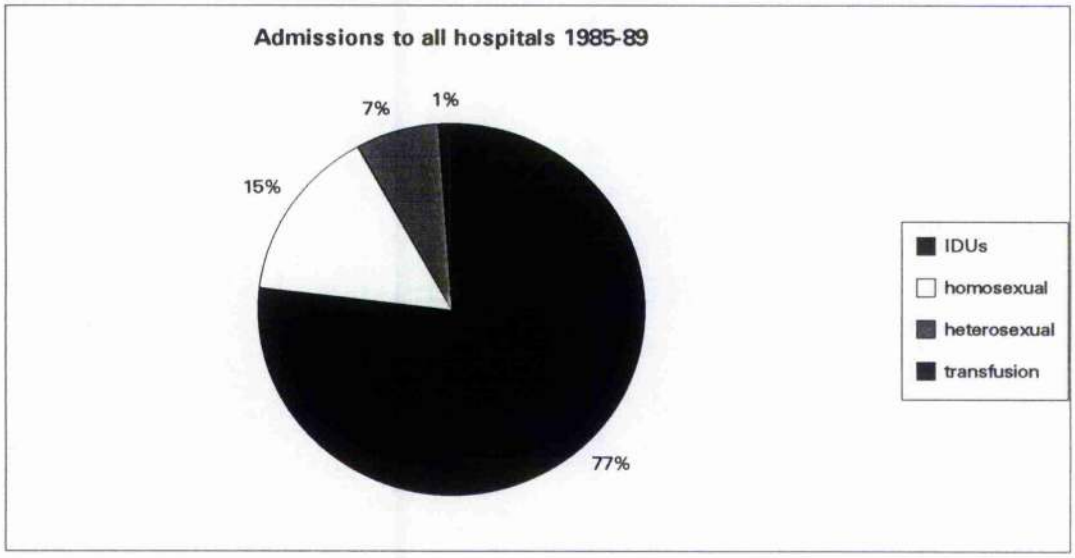


Figure 2.2

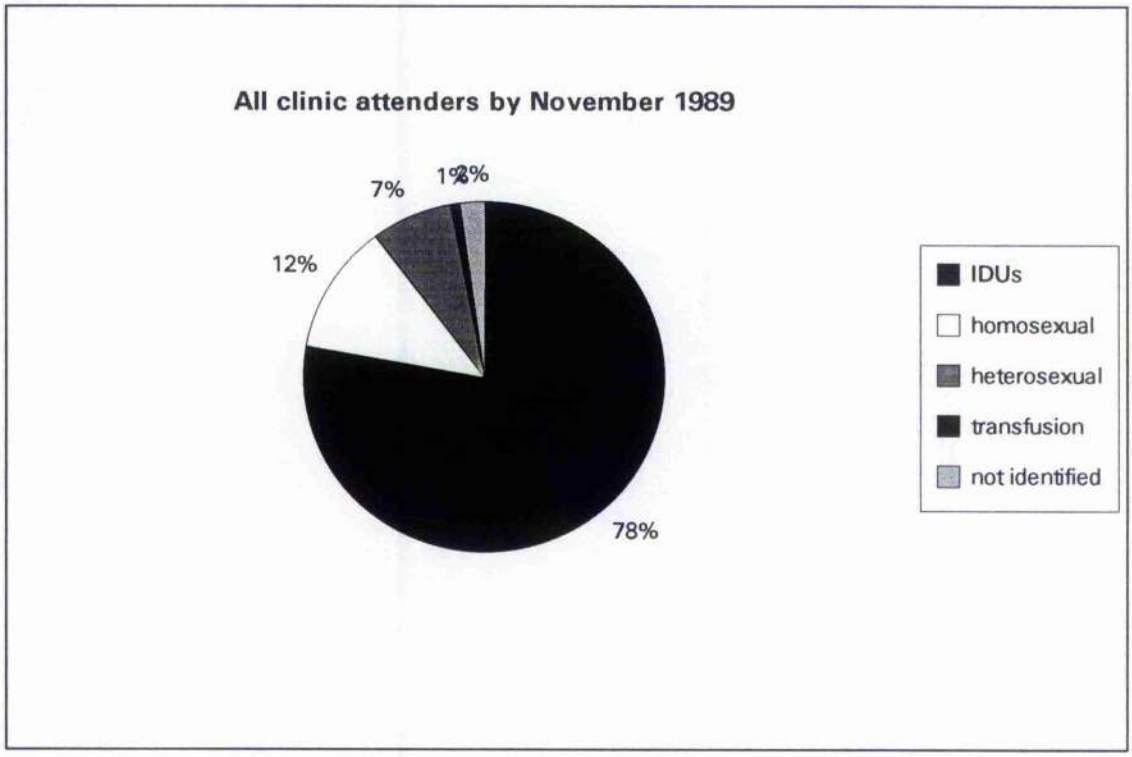


Figure 2.3

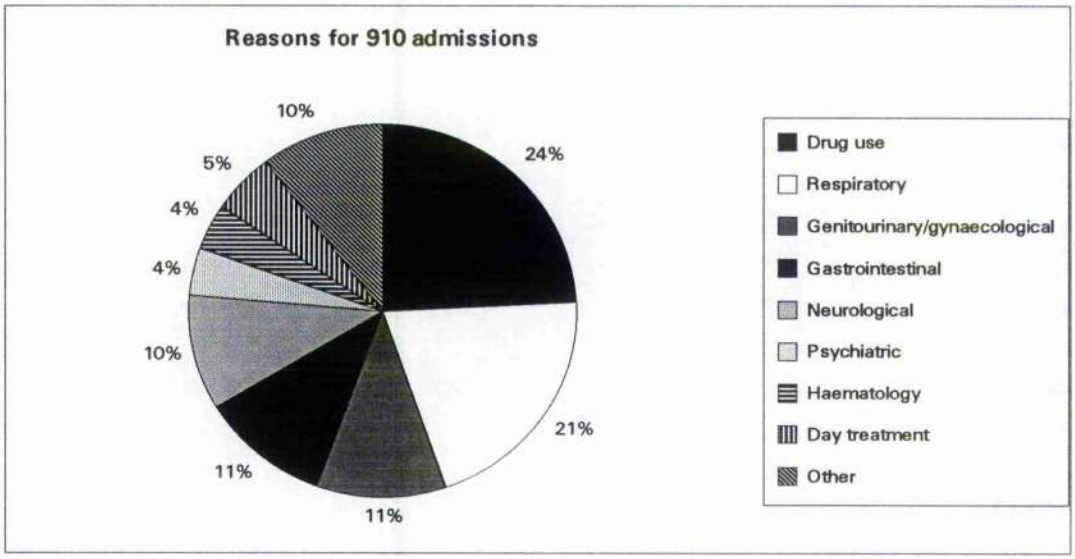


Figure 2.4

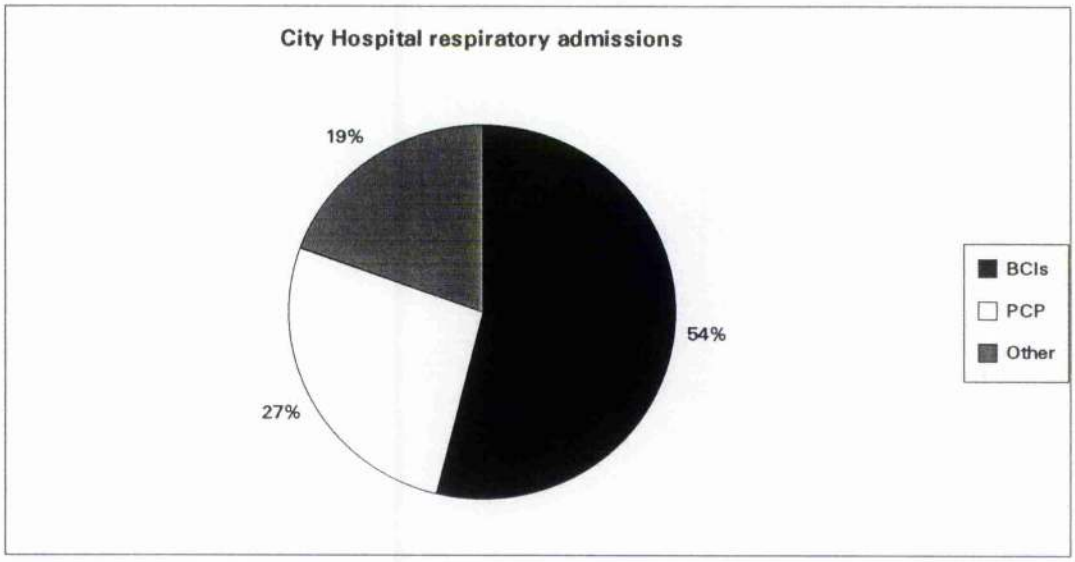
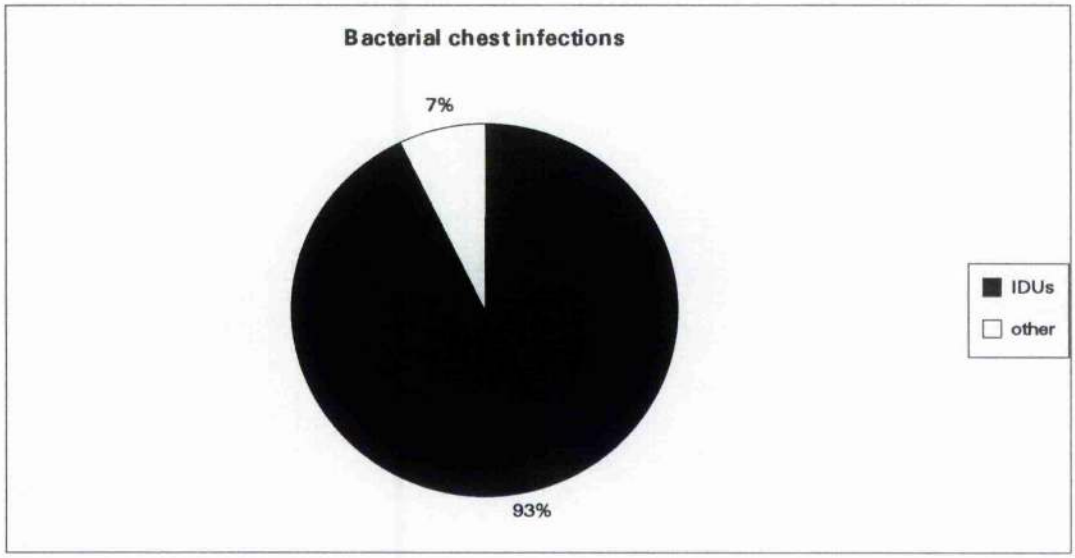


Figure 2.5



CHAPTER THREE

EPIDEMIOLOGICAL ANALYSIS OF EDINBURGH HOSPITAL ADMISSIONS AND READMISSIONS BY HIV POSITIVE PATIENTS BEFORE NOVEMBER 1989

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EPIDEMIOLOGICAL ANALYSIS OF EDINBURGH HOSPITAL ADMISSIONS AND READMISSIONS BY HIV POSITIVE PATIENTS BEFORE NOVEMBER 1989

1. Introduction and methods
2. Results

   Synopsis

   Analysis by risk group

   Analysis by sex

   Analysis by year of admission

   Analysis by hospital of admission

   Analysis by CDC stage

   Analysis of patients with AIDS

   Analysis by CD4 count

   Analysis of readmissions
3. Discussion

Introduction and methods

The analysis of Edinburgh HIV admissions by discharge diagnosis gives a useful picture of the early natural history of HIV infection and the illnesses seen in one city within the early years of an epidemic. A more formal evaluation of these admissions analysed by risk factor, sex and clinical and laboratory stage of disease is necessary to complete the picture. Analysis of these variables along with year and hospital of admission would be of immense value as a study of health care utilisation and for planning future resources. This chapter documents these analyses. An analysis was also performed to assess if the likelihood of readmissions could be determined from patient characteristics on the first admission. Some predictions of the likelihood of readmission could be of use clinically, for preventive strategies, and also to assist in predicting short term health care resource requirements.

The database was as for chapter two. Analysis was mainly in the form of descriptive epidemiology with statistics calculated using the software packages "Epi Info 5.01b" (for chi squared tests) and "GLIM 4" (for logistic regression). Possible associations between outcome and variables of interest were tested using Yates corrected chi squared tests. Confidence limits for odds ratios were calculated at 95%. The models for the logistic regression are described stepwise in the section on readmissions. The readmission analysis used was to predict the likelihood of any readmission within the study period. The analysis did not determine whether the patient would have single or multiple readmissions, nor the likelihood of readmission over shorter time periods. Data for each patient's first admission were extracted from the database file and patients were categorised into two possible outcomes - of single admission or readmission.

Results

Synopsis

A total of 910 admissions were recorded; 612 to the City and 298 to other hospitals (figure 3.1). These accounted for 8738 bed days. Most admissions to the hospitals other than the designated HIV unit were not classically HIV related and mainly comprised complications of drug use and gynaecological admissions. The number of admissions per patient ranged from 1 to 30. Mean length of admission was 9.6 days although this varied markedly between risk groups, sex and year of admission. There was a virtual doubling of admissions to the City Hospital over each one year period with the percentage of admissions by AIDS patients rising from 14% in the first year to 42% in the last. The average length of stay for AIDS patients and for homosexual men fell over the four year period. Longer admissions in patients with CD4 counts <200 cells/mm^3 or with stage 2 or 3 disease were predictors of readmission during the study period.

Analysis by sex did not show great differences between men and women other than the differences accounted for by risk factor. Analysis by risk factor showed marked differences in admission patterns. Admissions among homosexual men were significantly more likely to be for AIDS related conditions, admissions among IDUs were significantly more likely to be for bacterial infections and admissions among patients with heterosexually acquired HIV infection were significantly more likely to be for pelvic inflammatory disease and for AIDS related diagnoses when compared with IDUs. Of the 611 City Hospital admissions in which CDC staging was available, 246 (40%) were in patients with CDC stage 2 or 3, 170 (28%) in patients with stage 4 disease but without AIDS and 195 (32%) were in patients with AIDS. Analysis by CD4 count revealed similar results with 48% admissions in which a CD4 count was recorded being over 200

cells/mm^3. As admissions by AIDS patients rose, the average CD4 count fell over the four year period.

Analysis by risk group

Seven hundred and two (77%) admissions were in IDUs, 136 (15%) in homosexual men, 62 (7%) in heterosexuals and 10 in blood product recipients (figure 2.1).

Analysis by discharge diagnosis showed very different patterns between risk groups (table 3.1). For the homosexual men the most striking feature was the preponderance of AIDS related diagnoses. Of the 105 admissions for purely AIDS related diagnoses (PCP, toxoplasmosis, KS, CMV disease, lymphomas, disseminated mycobacteriosis, oesophageal candidosis and herpes and AIDS dementia), 65 were in homosexuals, 28 were in IDUs and 12 in heterosexuals. These 105 admissions were not the only ones in AIDS patients but were those specifically related to AIDS (therefore excluding for instance an overdose admission by an IDU who had AIDS). Admissions by homosexual men were 12 times more likely to be for AIDS specific diagnoses than admissions by IDUs (odds ratio (OR) = 22.04, confidence limits (cl) 12.91-37.78, relative risk (RR) = 11.98, chi square = 217, $p<0.0001$). The 65 AIDS related admissions in homosexuals included 26 for PCP, 14 (in six patients) for toxoplasmosis, five for CMV disease, five for KS, five for lymphoma and seven for chemotherapy for either KS or lymphoma. Indeed homosexuals were the only risk group to be admitted with KS or lymphoma. Homosexuals also accounted for the only admissions with disseminated tuberculosis (two admissions in one patient) and atypical mycobacteriosis (two admissions). The 26 admissions with PCP compares with 16 in IDUs and six in heterosexuals. Therefore admissions among homosexual men were seven times more likely to be for PCP compared with admissions by any other risk group (RR=6.73, OR=8.08, cl 4.25-15.38,

p<0.0001). This difference was particularly marked when comparing homosexual with IDU admissions alone (OR=10.13, cl 5.04-20.52, p<0.0001) whereas although admissions by homosexuals were twice as likely to be for PCP compared with admissions by heterosexuals, this did not reach statistical significance. The five admissions among homosexual men for CMV disease compares with only one other admission by a female IDU for this condition (OR=26.76, cl 2.94-1267.17, p<0.0001). The 14 admissions for toxoplasmosis compares with the five admissions by one female heterosexual for cerebral toxoplasmosis; this was not statistically significant. Of all the other ("non AIDS") diagnoses there was no preponderance of homosexuals. Of the 41 admissions for anaemia, neutropenia and blood transfusion, 11 were in homosexuals and 28 in IDUs; but of the 27 admissions for thrombocytopenia and immunoglobulin treatment, 24 were in IDUs and only one in a homosexual (neither of these were statistically significant). In conclusion, admissions by homosexual men were significantly more likely to be for AIDS related diagnoses when compared with admissions by any other risk group and this was mostly related to diagnoses of KS, lymphoma, CMV and PCP. The main reason for these AIDS related differences is because the homosexual men had been infected longer than the IDUs and heterosexuals and were therefore in a more advanced stage of disease.

With only 28 of 105 AIDS related diagnoses in IDUs, IDUs were significantly less likely to be admitted with AIDS related conditions. In fact the only AIDS categories where there were more admissions by IDUs than by other risk groups were for oesophageal candidosis (four IDU, one heterosexual and one homosexual admission) and AIDS related dementia (five IDU, one homosexual). Clearly most of the admissions by IDUs were for diagnoses not specifically AIDS related. Although more admissions for investigation of headaches, fits, drop attacks, weight loss, pyrexia and lymphadenopathy, and for psychiatric and haematological diagnoses were by

IDUs than other risk groups, the proportion of admissions is as expected given the preponderance of IDUs attending the clinic and being admitted. The main excess of admissions by IDUs lay in the 220 admissions for drug related diseases (injection injuries, overdose, withdrawal) and trauma. The other main reason for admission by IDUs was for chest and other bacterial infections and it was clear that there was a significant difference between IDUs and all other risk groups for these admissions (chi square with Yates correction=7.11, $p<0.01$). This difference was particularly striking for bacterial chest infections alone, as was the difference between admissions by IDUs and homosexuals for all bacterial infections.

With only 62 admissions by heterosexuals it was more difficult to assess if they were any more likely to be admitted with any particular diagnoses. However their admissions were five times more likely to be with AIDS related diagnoses when compared with IDUs (OR=5.78, cl 2.60-12.71, RR=4.85, $p<0.0001$). Admissions for pelvic inflammatory disease (PID) were nine times more common amongst heterosexuals than amongst IDUs (12 heterosexual and 14 IDU admissions, OR=11.79, cl 4.81-28.85, RR=9.71, $p<0.0001$) although they were no more likely to have been admitted for termination of pregnancy (one heterosexual, nine IDUs), pregnancy (four IDUs only), urinary tract infection (12 IDUs, three heterosexuals) or other gynaecological disorders.

There was a striking difference among risk groups with respect to lengths of admission - ranging from a mean of 16.7 days in the homosexual men to 8.5 days in the IDUs and 7.6 days in the heterosexual group. This variation probably accounted for the difference in length of stay between men (10.1 days) and women (8.9 days). Analysis by year shows this effect to be even more pronounced (table 3.2). Eleven homosexual men were admitted in the first year and average length of admission was 30.7 days; in the second year it fell to 20.6 days in the 22 homosexual admissions; in the third year it was 12.3 days for the 42 admissions and in the last year it was 15.7 days for the

61 admissions. The percentage of admissions among the homosexual men rose over the study period. In the first year 7% (11) admissions were in homosexual men, 15% (22) in the second year, 19% (42) in the third and 16% (61) in the last. Concomitantly the percentage of admissions amongst IDUs fell from 87% (139) in the first year to 78% (117) in the second year, 76% (168) in the third and 73% (278) in the final year.

Analysis by sex

Men accounted for 551 (61%) admissions and women for 359 (39%). Most differences between the sexes when analysed by diagnostic category were probably related to risk group. Diseases specific to women (PID, pregnancy, termination of pregnancy and other gynaecological conditions) accounted for 56 admissions. All the female genito-urinary conditions (ie adding urinary tract infections and genital warts to the above list) accounted for 79 of the 359 admissions in women. Urinary tract infections were a more common reason for admission in women than in men (11 female and two male) and another classically female disease - gall bladder disease - accounted for six admissions in four women and no men. Investigation of fits, headaches and drop attacks were more than twice as common in women as in men (24 female and 15 male admissions, OR=2.56, cl 1.27-5.21, chi square = 8.32, $p<0.005$). Women were also over-represented in admissions with bacterial chest infections (42 women, 55 men), detoxification (15 women, 14 men) and overdose (45 women, 55 men) but these differences were not statistically significant. Excluding homosexual men, AIDS defining admissions followed the general 3:2 pattern except for admissions for oesophageal candidosis, the six admissions of which were split equally between the sexes.

Of the 220 admissions in women to the City Hospital, 180 were in IDUs, 33 in heterosexual women and seven in women infected via blood products.

Almost 52% (113) admissions were in women with CDC disease stage 2 or 3 and 34% (74) were in women with AIDS. The women with AIDS accounted for 36% (903) of the female bed days whereas the women with CDC disease stage 2 and 3 accounted for 50% (1258) bed days. Of the 33 admissions in heterosexually infected women, 20 (237 days) were in women with CDC disease stage 4c1, two in women with stage 4c2, five in women with stage 2 and six in women with stage 3 disease. Of the 180 admissions in women who were IDUs, 54% (98) were in women with CDC disease stage 2 or 3, 26% (46) in women with stage 4c1, three with stage 4a, five with 4b, 23 with 4c2 and five with 4e. The seven admissions in women infected via blood products were all in one woman who initially had CDC stage 3 disease and later progressed to stage 4b. Therefore, most (82%) women who were admitted were IDUs and most (66%) did not have AIDS. Nevertheless these admissions in women without AIDS accounted for 1613 bed days. A greater percentage of the admissions in heterosexual women (61%) were in women with AIDS compared with female IDUs (28%) (OR=4.00, cl 1.74-9.28, chi square with Yates correction = 12.17, $p<0.001$). Despite the fact that more of the heterosexually infected women had AIDS, lengths of admission were similar between the two risk groups (11.8 days for the IDUs, 11.4 days for the heterosexuals).

More admissions were in men in almost every category, generally following a 3:2 pattern. Of the IDUs, more men than women attended the clinic and more male than female IDUs were admitted, added to which were the admissions by the homosexual men. Only 11 admissions were for male-specific diseases (prostatitis and epididymo-orchitis). Only male homosexuals were admitted with KS and lymphoma and only men were admitted with liver disease. Men were also over-represented in admissions for thrombocytopenia and immunoglobulin treatment (19 men, eight women) but this was not statistically significant.

Of the 392 male admissions to the City Hospital, 258 (66%) were in IDUs, 126 in homosexual men, seven in heterosexual men and one in a man infected via blood products. There were marked differences in CDC classification and lengths of stay between risk groups. One hundred and nineteen (46%) admissions amongst the IDUs were in men with CDC disease stage 2 or 3, 46 in men with stage 4a, 18 with stage 4b, 21 with stage 4c1, 34 with stage 4c2 and 20 with stage 4e. Mean length of admission in male IDUs was 9.9 days. This compares with the 17.1 days for the 126 homosexual admissions. CDC staging for the homosexual men was; 81 in stage 4c1, 22 in stage 4d and only 23 in all the other stages. Thus 82% (103) admissions amongst the homosexual men were in men with AIDS. These 103 men accounted for 1981 bed days (average 19.2 days).

Analysis by year of admission

Of the 910 admissions, 160 (1597 days) were in the first year of the study, 150 (1563 days) in the second, 221 (1863) in the third and 379 (3715) in the last year (table 3.3). When the 612 City Hospital admissions are analysed by year a slightly different pattern emerges from analysis of the whole study. Fifty six admissions (1038 days) were to the City Hospital in the first year, 85 (1304 days) in the second, 171 (1719 days) in the third and 300 (3241 days) in the last year (table 3.3). Therefore there was virtual doubling of admissions over each year. Concomitantly, lengths of admission fell each year from 18.5 days in the first year to 15.3 in the second, 10.1 in the third and a stabilisation at 10.8 in the last year (table 3.4). Of the 56 admissions before November 1986, 44 (79%) were in IDUs, ten in homosexual men and two in the other risk groups; eight admissions were in AIDS patients (who accounted for 298 bed days, i.e. mean length of admission = 37 days), 42 were in patients with CDC disease stage 2 or 3 and the rest were in patients with disease stage 4a, 4c2 or 4e. So in this first year 14% (eight) of

admissions were in AIDS patients but they accounted for 29% (298) of the bed days (table 3.5). The ten admissions in homosexual men were the longest at 31.1 days on average (vs. 16.3 days for the IDUs). Of the 85 admissions in the second year, 56 (66%) were in IDUs, 22 in homosexuals and seven in other risk groups. Admissions in the homosexual group were again longer (20.6 vs. 14 days). Almost 24% (20) admissions were in AIDS patients and accounted for 41% (535) bed days. In the third year, 72% (123) admissions were in IDUs, 24% (40) in homosexual men and seven admissions were in heterosexuals and one in a blood product recipient. In this year 38% (65) admissions were in AIDS patients (accounting for 42% (721) bed days) and 40% (68) admissions were in patients with CDC disease stage 2 and 3. In the final year the admissions were as follows: 215 (72%) in IDUs, 54 in homosexual men, 28 in heterosexuals and three in blood product recipients. CDC staging was: stage 2 = 15 admissions (109 days), stage 3 = 68 admissions (548 days), stage 4a = 37 (323 days), stage 4b = 18 (244 days), stage 4c1 = 102 (1477 days), stage 4c2 = 38 (378 days), stage 4d = 5 (58 days), stage 4e = 16 (86 days) and one admission where CDC staging was not documented. Therefore AIDS patients accounted for 42% (125) admissions and 55% (1779) bed days.

Admissions for most diagnoses, particularly those which were AIDS related, followed a stepwise increase (almost doubling) over the years studied. However there were some anomalies. Most of the admissions for drop attacks were in 1988 (no admissions in the first year, two in the second, eight in the third and three in the last). Admissions for psychiatric conditions were mainly in the last year as were admissions for investigation (10 of 13 admissions) and for anaemia, neutropenia or transfusion (17 in the third year and 24 in the last year). This latter finding is probably due to the effect of zidovudine which did not become available in the UK until late 1987.

Thus of the 612 City Hospital admissions, not only did the admission numbers double every year but the pattern of admissions changed. Proportions analysed by risk groups and by sex stayed relatively stable. The percentage of AIDS admissions rose yearly from 14% (8) admissions in the first year to 24% (20) in the second year, 38% (65) in the third and 42% (125) in the last (table 3.5). Concomitantly, although the average length of stay of AIDS patients fell during the study period, the percentage of bed days occupied by AIDS patients also rose from 29% (298) in the first year to 41% (535) in the second, 42% (721) in the third and 55% (1779) in the last.

The pattern in the 298 admissions to the other hospitals was quite different. One hundred and four admissions were recorded in the first year, 65 in the second, 50 in the third and 79 in the last year. Mean length of admission was 4.8 days, ranging over the study from 5.4 days in the first year to 4 in the second, 2.9 in the third and six days in the last year. Data from the first year are skewed by the psychiatric admission lasting 278 days and if this is discounted the average in the first year falls to 2.5 days.

The main diagnoses accounting for the decrease in admissions to other hospitals over time were overdose and other admissions related directly to drug use. Of the 100 admissions to other hospitals with overdose, 38 were in the first year of the study, 29 in the second, 16 in the third and 17 in the last. Admissions for overdose, injection injury and detoxification to all the hospitals (including the City) decreased from 63 in the first year to 42 in the second year, 38 in the third year and 43 in the final year. Admissions with endocarditis were only in the first year of the study. Other admissions to the other hospitals which decreased over the years were admissions for PID, termination of pregnancy and other gynaecological disorders.

Analysis by hospital of admission

The 612 admissions to the City Hospital were accounted for by 208 patients. Of these 208 patients, 145 were men and 63 were women; 151 were IDUs, 42 were homosexual men, 13 had acquired their infection heterosexually and two from blood products. Seventy one percent admissions (438) were in IDUs, 21% (126) in homosexual men, 7% (40) in heterosexual patients and 1% (8) in transfusion recipients (figure 3.2).

The 298 admissions (1436 bed days) to other hospitals were accounted for by 121 patients. Most (221) admissions were to the Royal Infirmary, 44 were to the Western General, 27 to the Royal Edinburgh and six were to the Eastern General Hospital (figure 3.1). They were mostly accounted for by the 144 admissions for overdose, injection injuries and trauma and by the 63 admissions for gynaecological and genito-urinary diagnoses. Thirty three admissions were for gastro-intestinal and 11 for neurological diagnoses. The proportion of women admitted to the other hospitals was much higher at 47% (139 admissions were in women, 159 in men). Hospital stays for the women were much shorter (2.4 vs. 3.6 days). In 264 of the admissions the patients were IDUs, 22 were in heterosexuals, ten were in homosexuals and two in blood transfusion recipients (figure 3.3). Apart from one admission in 1986, the homosexual men were not admitted until the last two years of the study period. CDC classifications were not available for patients admitted to the other hospitals but most of the admissions (mainly because of the nature of the admission) were in patients without symptomatic HIV disease. Of the 105 admissions with AIDS specific diagnoses, only six were not admitted to the City Hospital.

Analysis by CDC stage

The 612 admissions (7302 days) to the City Hospital were analysed in more detail by CDC stage and CD4 count. Forty percent (246) admissions

were in patients with "asymptomatic" HIV disease i.e. CDC disease stage 2 and 3. Thirty six percent (218) admissions were in AIDS patients, accounting for 46% (3333) bed days. CDC staging was available for 611 of the 612 admissions and was as follows (figure 3.4): stage 2 = 59 admissions (711 days), stage 3 = 187 admissions (1875 days), stage 4a = 58 admissions (517 days), stage 4b = 26 admissions (325 days), stage 4c1 = 170 admissions (2806 days), stage 4c2 = 63 admissions (656 days), stage 4d = 22 admissions (202 days), stage 4e = 26 admissions (192 days).

Clearly the AIDS specific admissions accounted for most of the 218 admissions in patients with AIDS. Of the 105 admissions with AIDS specific diagnoses, 99 were to the City Hospital. Admissions in patients with CDC stage 4 disease were also significantly more likely to be for haematological diagnoses (38 admissions in patients with CDC stage 4, three admissions in patients with CDC stage 2 and 3 disease, OR=9.41, cl 2.93-48.10, chi square with Yates correction = 18.39, $p<0.0001$).

Of the 65 admissions to the City Hospital for detoxification (28), overdose (two) and injection related injuries (35), 52 were in patients with CDC disease stage 2 or 3 and 13 in patients with CDC stage 4 disease (OR=7.26, cl 3.72-14.39, chi square with Yates correction, $p<0.00001$). Admissions in patients with CDC stage 2 or 3 disease were significantly more likely to be for drop attacks (OR=20.31, cl 3.60-865.39, chi square with Yates correction = 14.32, $p<0.0005$) but not for fits or headaches. Admissions in patients with CDC stage 2 or 3 disease were also significantly more likely to be for bacterial infections. Of the 110 admissions to the City Hospital with bacterial chest and urinary infections, 64 were in patients without stage 4 disease and 46 had stage 4 disease (OR=2.44, cl 1.59-3.79, chi square = 17.01 with Yates correction, $p<0.0001$). This effect was even more pronounced on analysis of all 144 admissions to the City Hospital for bacterial infections (89 in CDC stage 3, 55 in stage 4, OR=3.20, cl 2.13-4.80, chi square with Yates correction = 35.19, $p<0.00001$).

Admissions by patients with AIDS

There were 218 admissions to the City Hospital in patients with disease stages 4c1 (170), 4d (26) and 4b (26). However only three of the admissions in stage 4b were AIDS defining (AIDS dementia). The other admissions by patients in this stage were for patients with memory loss (13 admissions by two patients), peripheral neuropathy (five admissions by two patients), HIV related myopathy (four admissions by one patient) and organic psychosis (one admission by one patient). Therefore a total of 195 (32%) City Hospital admissions were in patients with AIDS. These admissions were made by 57 patients whose number of admissions with and following their AIDS defining diagnosis ranged from one to 20 per patient (figure 3.5). Of these 57 patients, 33 were homosexual men, 20 were IDUs and four were heterosexual women. Homosexual men were significantly more likely to be admitted with AIDS than any other risk group (OR=28.88, cl 13.20-64.05, chi square with Yates correction = 127.39, p <0.00001). Ten of the AIDS patients were women, 47 were men. AIDS defining diagnoses were; PCP (34), PCP and lymphoma (one), PCP and KS (one), PCP and cryptococcal meningitis and lymphoma (one), oesophageal candida (five), KS (four), cerebral toxoplasmosis (two), toxoplasmosis and KS (one), CMV (two), lymphoma, candidal pneumonitis, oesophageal herpes, AIDS dementia, disseminated TB and atypical mycobacteriosis (one of each). Therefore PCP was the AIDS defining diagnosis in 65% of patients, with oesophageal candidosis the second most common diagnosis. All the heterosexual AIDS patients presented with PCP (including one African woman who had both PCP and KS), 14 of the IDUs presented with PCP (including one man with both PCP and lymphoma) and 19 of the 33 homosexual men presented with PCP. Of the other AIDS defining diagnoses amongst the IDUs, four were with oesophageal candidosis, one with AIDS dementia and one with disseminated TB. Of the ten women with AIDS, eight presented with PCP and two with oesophageal candidosis. None of these differences between

risk groups and between sexes were statistically significant. Mean CD4 count at diagnosis of AIDS was 77 cells/mm^3 (range 4-270). Patients lived on average 11.3 months (range two days to 45 months) and spent 71 days (range 2 - 208) in hospital from a diagnosis of AIDS to death. Nineteen patients died from AIDS (see chapter five).

Analysis by CD4 count

Analysis by CD4 count was restricted to the 612 City Hospital admissions, in 563 of which (92%) a CD4 count was recorded. CD4 count was less than 50 cells/mm^3 in 167 admissions, between 50 and 100 cells/mm^3 in 42 admissions, between 100 and 200 cells/mm^3 in 86, between 200 and 500 cells/mm^3 in 166 and above 500 cells/mm^3 in 102 admissions (figure 3.6). CD4 counts clearly became more routine as the years progressed since no CD4 count was available in 43% of admissions in the first year of the study but this had decreased to 4% in the last year. CD4 count correlated with clinical markers of disease progression as defined by CDC staging and presence or absence of AIDS. Of the 99 admissions to the City Hospital with AIDS specific diagnoses, 65 (66%) had a CD4 count of less than 50 cells/mm^3 and all but 6 (6%) had a CD4 count of less than 200 cells/mm^3. The diagnoses in the AIDS related admissions with CD4 counts of more than 50 cells/mm^3 were; PCP (17 of 47 admissions), cerebral toxoplasmosis (three of 17 admissions), AIDS related dementia (three of six admissions), CMV disease (two of six admissions), oesophageal candidosis (five of six admissions), KS and lymphoma (two of 11 admissions) and the only admission to the City Hospital with tuberculosis. Of admissions in patients with disease stage 4.31, 70% (119 of 170 admissions) had a CD4 count of less than 50 cells/mm^3. Ten (6%) had a CD4 count of over 200 cells/mm^3. Of the 246 admissions in patients with stage 2 and 3 disease, 76 (31%) had CD4 counts of over 500 cells/mm^3, 94 (38%) had CD4 counts between 200

and 500 cells/mm³, and interestingly, 18 (7%) had CD4 counts of below 100 cells/mm³. Of the admissions in patients with symptomatic HIV disease but without AIDS (i.e. CDC stages 4a and 4c2), 42 (35%) had a CD4 count of less than 100 cells/mm³ and 78 (64%) had a CD4 count of above 100 cells/mm³.

When the AIDS specific admissions are excluded, most of the admissions are in patients with higher CD4 counts. Of the 65 admissions to the City Hospital for detoxification, overdose and injection injuries, 48 (74%) were in patients with a CD4 count of above 200 cells/mm³. Of the 144 admissions to the City Hospital for bacterial infections, 75 (52%) were in patients with a CD4 count of above 200 cells/mm³ and 38 (26%) in patients with a CD4 count of less than 100 cells/mm³.

Of the 135 City Hospital admissions by homosexual patients, 75 (55%) were in patients with a CD4 count of less than 50 cells/mm³ (12% were in patients with a CD4 count of over 200 cells/mm³). By comparison a CD4 count of less than 50 cells/mm³ was found in 11% of City Hospital admissions by IDUs and in 24% of admissions by heterosexuals, and a CD4 count of above 200 cells/mm³ was found in 35% of admissions by IDUs and in 18% of admissions by heterosexuals.

Analysis of CD4 count by year of admission reveals similar results to analysis by any other measurement of disease progression (CDC stage, percentage of admissions in patients with AIDS) in that more admissions towards the end of the study were in patients with more advanced disease. Patients with a CD4 count above 200 cells/mm³ accounted for 43% of admissions in the first year, 60% in the second, 54% in the third year and 34% in the last year. In the last year only 8% of patients had a CD4 count above 500 cells/mm³ (compared with 27% just one year before) but 37% of patients had a CD4 count of less than 50 cells/mm³.

Analysis of readmissions

Analysis was performed on the likelihood of readmission with relation to patient characteristics on the initial admission. The 612 admissions to the City Hospital were accounted for by 208 patients, 89 of whom were admitted on one occasion only and 119 who were admitted more than once. Of the 119 patients readmitted, 83 were male and 36 were female; therefore 57% of all men and 57% of all women were readmitted. Initial variables used were sex, risk factor, CDC stage and CD4 count. Information on CDC stage in the initial database was divided into two categories for comparison (CDC stages 2 and 3, compared with CDC stage 4) as was that on CD4 counts (CD4 count of <200 cells/mm^3 compared with CD4 count >=200 cells/mm^3). Single variable analysis was performed using "Epi-Info" to test for associations between outcome and these variables. None of these were significantly associated with readmission (table 3.6). Although 71% of homosexual men were readmitted compared with 54% of both IDUs and heterosexual patients, this difference was not statistically significant (p=0.2). Variables of age and days were analysed as continuous variables, testing for differences in means among the two outcomes and no significant difference was seen with age, nor with the number of days spent in hospital during the first admission. This single variable analysis was also carried out for three diagnostic categories. The categories chosen were of all respiratory admissions (the commonest reason for admission by HIV positive patients to the City Hospital), bacterial chest infections and PCP (two salient respiratory diagnoses which can be difficult to differentiate clinically). The results showed that patients admitted with respiratory conditions were no more likely to be readmitted than patients admitted for any other reason. There was also no significant likelihood of readmission for patients with PCP or with bacterial chest infections compared with patients without these conditions.

All of the above variables were then used in a multi-variable logistic regression analysis using the "GLIM" statistics package. Because of some

missing data (on CD4 count, CDC stage), 186 observations were used in this initial model. The significance of the variables in the model were assessed by fitting the model with and without each variable in turn and using the difference in deviance as a likelihood ratio chi squared test statistic (table 3.7). Again, none of the variables were associated with readmission.

A second model was fitted with all two way interactions. In this model, days were not treated as a continuous variable but initial admissions of seven days or less were compared with those lasting over seven days. This model was then compared with the initial model (table 3.8) with a resultant p=0.0171 suggesting that there were some factors whose effects were mediated by those of another. This was investigated using a further model (table 3.9). From this, the interactions between days and age (p=0.0792), between all respiratory admissions and days in hospital during the initial admission (p=0.0499) between CDC stage and days (p=0.0377) and between CD4 count and days (p=0.0133) were the interactions which tended towards statistical significance. A final model was constructed by removing all the non-significant (p>=0.05) interactions (tables 3.10, 3.11). From this final model, statistical significance was reached for the interaction between CD4 count and days, and between CDC stage and days, on the likelihood of readmission. The interaction was such that patients with a CD4 count >=200 cells/mm^3 who were admitted initially for more than seven days were less likely to be readmitted than those with a CD4 count <200 cells/mm^3 (table 3.12). The interaction between CDC stage and days in hospital was in the opposite direction from the CD4 count results. Patients with CDC stage 2 or 3 disease who were admitted initially for more than seven days were more likely to be readmitted than patients with CDC stage 4 disease (table 3.13).

Discussion

The overwhelming finding from the above analyses is that despite the rising percentage of admissions due to AIDS over the four year period, the vast majority of admissions were in patients who did not have AIDS and, by CDC staging, many of these patients were classed as having "asymptomatic" HIV infection. Of the 611 City Hospital admissions where CDC staging was available, 40% of admissions were in patients with CDC stage 2 and 3 disease. It is likely that most of the 298 admissions to the other hospitals were also in patients with disease stage 2 or 3 because most of the admissions to other hospitals were for drug related or gynaecological diagnoses (and only six were for AIDS specific diagnoses). Therefore a figure of 40% of admissions in patients with "asymptomatic" disease stage 2 or 3 is probably a vast underestimation for the whole 910 admissions. This large percentage of admissions by patients with "asymptomatic" HIV infection has not been documented in other studies and clearly reflects the early years of an epidemic and the large number of admissions in IDUs. The proportions of admissions in CDC stage 2 and 3 patients fell from 75% to 62% to 40% and then to 27% over the four years studied. It might be easy on first glance to surmise that this was merely due to the effects of drug use in the early years of the study. However the actual number of admissions in patients with CDC stage 2 and 3 disease rose over the course of the study (42, 53, 68 and 83 admissions in the consecutive years of the study) and these admissions were to the City Hospital where few of the admissions were solely drug related and most were due to bacterial infections.

But the effects of drug use on hospital admissions can clearly be seen. Firstly, one striking feature of the analysis of admissions to the other hospitals is the higher number of admissions to the other hospitals in the first years of the study. Indeed in the first year, there were nearly double the admissions to the other hospitals than to the City Hospital. This may be related to local knowledge about the City Hospital unit. It is possible that in

the later years, once the City Hospital became well known as an admission centre for HIV positive patients, that patients with HIV infection and a related or unrelated problem were immediately referred up to the City Hospital. In earlier years it is possible that HIV positive patients were referred to the usual hospitals and through the usual channels. In some of the admissions the patients may not even have been known to have been HIV positive at the time of their admission. However, most of the admissions to the other hospitals were as a consequence of drug use and the most likely explanation is that the amount of injection drug use by HIV positive patients decreased over the four years. This is also reflected in the fact that the percentage of admissions amongst IDUs fell steadily over the four years from 87% in the first year to 73% in the last. No admissions for endocarditis were recorded after the first year of the study. Admissions for blackouts were almost entirely in IDUs in 1988 which would suggest that these admissions were related to a particular type of street drug which was only available for a short time. Admissions for detoxification and for overdose decreased over the four year period and only a small cohort of patients accounted for the overdose admissions in later years of the study. During the time of the study period, changing patterns of drug using behaviour were recorded in Edinburgh and it may have been that less injecting and more awareness of the risks of injecting accounted for the fewer admissions due to overdose as the years progressed.[93,115,116]

Apart from drug use the other main factor accounting for the high number of patients admitted with "asymptomatic" HIV disease are the admissions for bacterial infections. Bacterial infections accounted for 21% of all admissions (189 admissions). Most patients admitted with bacterial infections did not have advanced disease. Of the 144 admissions to the City Hospital with bacterial infections, 62% had "asymptomatic" HIV disease and 52% had a CD4 count above 200 cells/mm^3. There is however a clear interaction between the effects of drug use and bacterial infections. IDUs

were significantly more likely to be admitted with bacterial infections than any other risk group, particularly for BCIs. The large number of admissions for bacterial infections could be due to the difficulty in differentiating BCIs from opportunistic infections in IDUs and lack of physician familiarity with HIV related diseases. But this is not the entire explanation since the "asymptomatic" patients with bacterial infections admitted to the City Hospital spent longer in hospital than the "symptomatic" patients and admissions for bacterial infections continued to rise over the four years despite improved physician familiarity with HIV disease. Bacterial infections cannot be ascribed solely to the effects of drug use. Admissions for PID were significantly more common amongst heterosexual women than among female IDUs, although this may be more related to the prevalence of sexually transmitted diseases among women who may have a higher number of sexual partners or are commercial sex workers. It is not clear why the number of admissions for PID fell over the four year period. The concomitant fall in the number of admissions for termination of pregnancy may be related to more widespread adoption of safer sex techniques and the desire to keep a pregnancy before the advent of more advanced disease.

Among admissions to the City Hospital, it was expected that the percentage of admissions in patients with AIDS should rise (from 14% in the first year to 42% in the last) as the epidemic progressed. It is interesting that, although bed days for AIDS patients also rose during the four years, the rise was not in parallel and the mean admission time for AIDS patients fell. This probably reflects physician familiarity with the disease and more out patient treatments and care. Admissions in AIDS patients were usually with AIDS specific diseases but admissions for haematological diagnoses were also significantly more common amongst AIDS patients and these were mainly related to the use of zidovudine which became available for patients with AIDS in late 1987. Admissions with bacterial infections were less common among patients with AIDS. This may be mainly because most AIDS patients

were homosexual men who were significantly less likely to be admitted with bacterial infections. PCP was the most common AIDS defining diagnosis (65% of AIDS defining illnesses) and remained so throughout the four year period without any concomitant fall in length of admission. In general, CD4 count correlated with clinical HIV staging although it is of note that in 7% of admissions in patients with CDC stage 2 or 3 disease the CD4 count was less than 100 cells/mm^3 and that in 6% of admissions in patients with CDC disease stage 4c1 the CD4 count was above 200 cells/mm^3. The multivariable analysis of readmissions with reference to CD4 count and CDC staging is difficult to explain. That patients with a CD4 count <200 cells/mm^3 and admitted initially for more than seven days were more likely to be readmitted than those with a CD4 count >=200 cells/mm^3 is presumably because the former patients had more advanced disease and were more likely to be readmitted. That patients with CDC stage 2 or 3 disease who were admitted initially for more than seven days were more likely to be readmitted than those with stage 4 disease could be explained by these patients being less likely to die and therefore having more chance of being readmitted during the study period. An admission of more than seven days in these patients might also suggest that they were about to progress to stage 4 disease.

Most differences by sex were related to risk group and most differences by risk group were related to the more advanced stage of illness of the homosexual men. This is because most of the admissions in homosexual patients were in men who had AIDS. Whereas none of the IDUs had seroconverted before 1984, many of the homosexual men (whose seroconversion dates are unknown) already had advanced HIV infection before the start of the study period. The percentage of admissions in the homosexual group rose steadily over the study period from 7% in the first year to 16% in the last. This again reflects the more advanced stage of HIV infection and earlier seroconversions in these men. If City Hospital

admissions only are analysed (i.e. excluding purely drug related admissions) it is seen that a greater proportion of homosexuals were admitted compared with the proportion attending the clinic; 78% clinic attenders were IDUs and 12% were homosexual but 72% City Hospital admissions were in IDUs, 21% in homosexuals. The mean length of hospital admission was longer for homosexuals than for other risk groups. Many of these longer admissions were also in the early part of the study when patients with AIDS had longer admissions perhaps partly due to less physician familiarity with the disease and partly because of less community care support for AIDS patients. However, although mean length of stay amongst homosexual men had decreased from 31 days to 16 days over the four years of the study, even at the end of 1989 the mean of 16 days was considerably longer than the mean of nine days for all the other risk groups. This is also largely the effect of more advanced disease among the homosexual men, although the length of admission for IDUs is skewed by the 100 admissions for overdose which were usually less than 24 hours.

There were some differences in admission patterns by sex and by risk group which were not entirely accounted for by disease staging nor by the effects of drug use. The admissions for bacterial infections have already been described. Women were significantly more likely to be admitted with fits, headaches and drop attacks and with bacterial infections. The latter difference is not entirely accounted for by admissions with PID which was a significantly more common reason for admission amongst heterosexual women than amongst female IDUs. Women who acquired their HIV infection heterosexually might be more likely to have a higher incidence of PID because of previous sexually transmitted diseases and higher number of sexual partners (or vice versa) or a genetic or other predisposition to both. Heterosexual women had more advanced stage of disease and were also significantly more likely to be admitted with AIDS related diseases than female IDUs. The reasons for this are not entirely clear. One heterosexual

woman with AIDS had acquired her infection in Africa but most of the others had acquired their infection from male IDUs in Edinburgh. Therefore many of the heterosexual women seemed to have progressed faster than their IDU counterparts. However since only ten women had progressed to AIDS by the end of the study it is not possible to attach any significance to the differences between the four heterosexual and the six IDU women. No significant differences were found for AIDS defining diagnoses by risk group or by sex as a whole, even for KS and lymphoma, although these admissions were significantly more common amongst homosexual men.

Figure 3.1

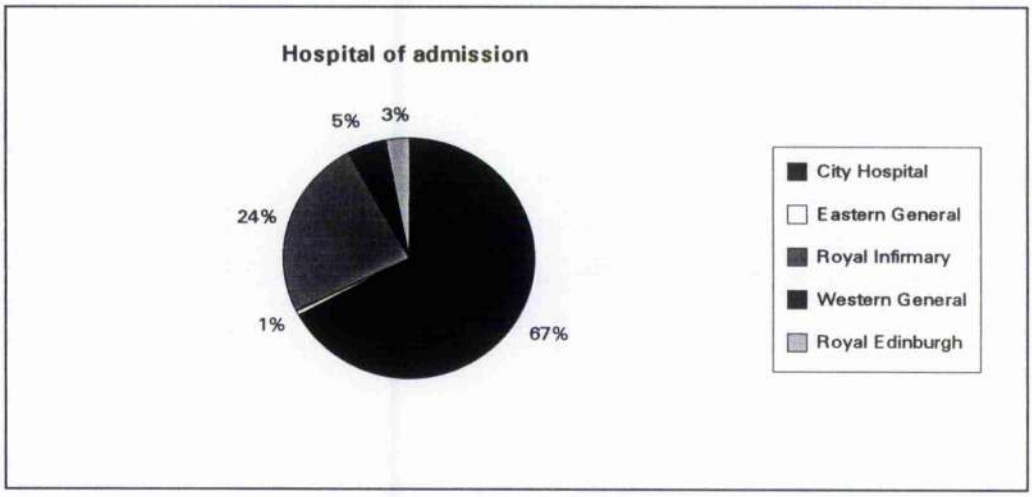

Figure 3.2

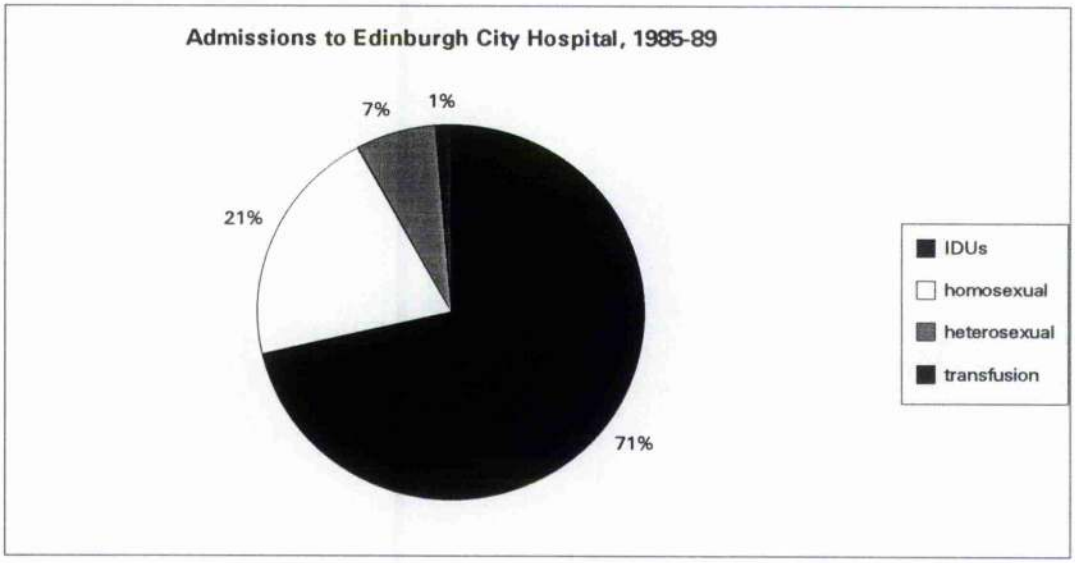

Figure 3.3

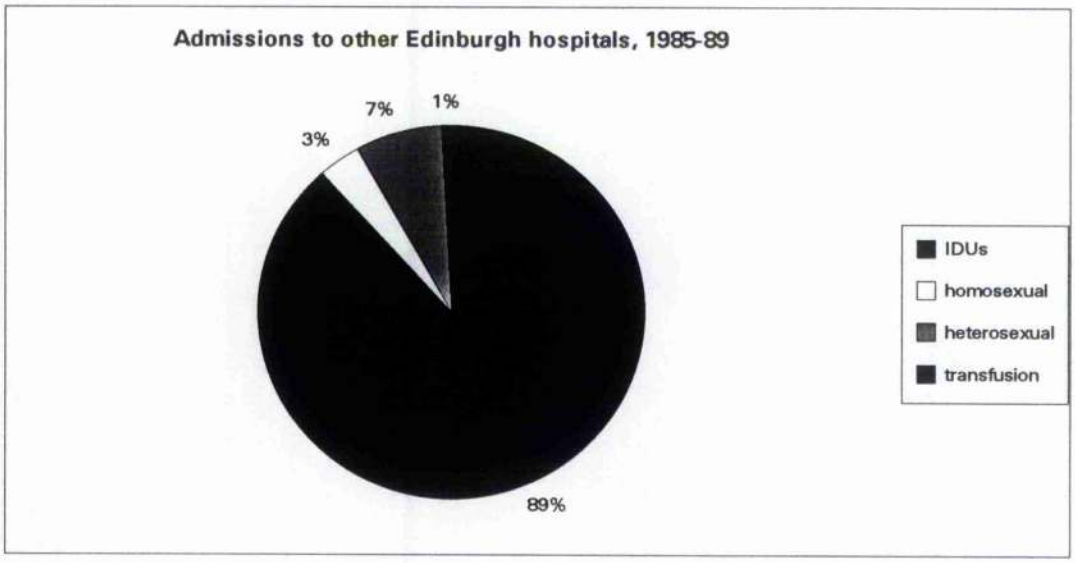

Figure 3.4

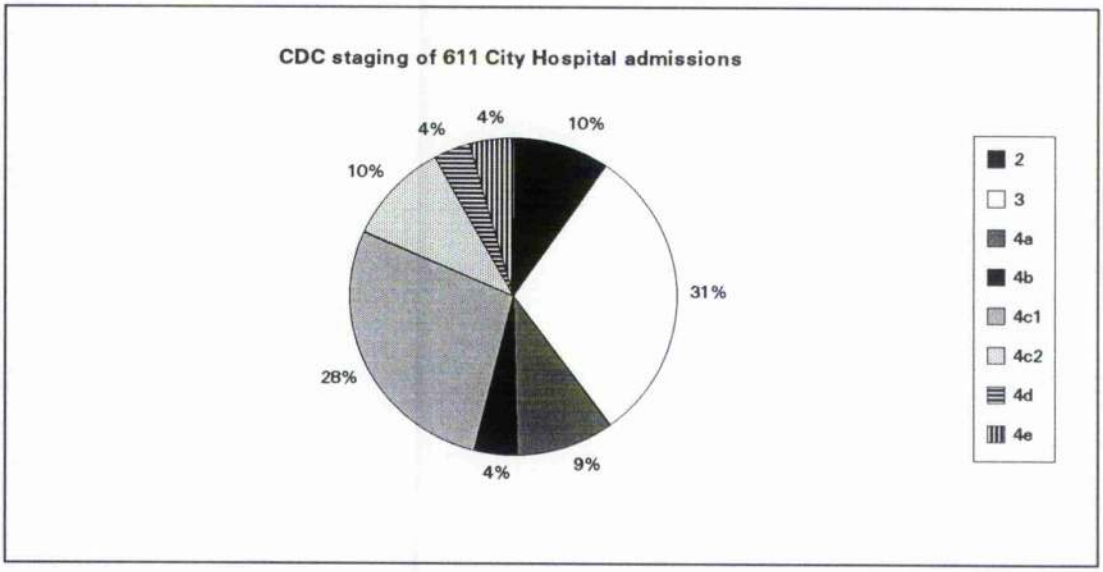

Figure 3.5

AIDS defining diagnoses
57 patients

PCP	34
PCP + lymphoma	1
PCP + KS	1
PCP + cryptococcal meningitis + lymphoma	1
Oesophageal candidiasis	5
KS	4
Cerebral toxoplasmosis	2
Cerebral toxoplasmosis + KS	1
CMV	2
Lymphoma	1
Candidal pneumonitis	1
Oesophageal herpes	1
AIDS dementia	1
Disseminated tuberculosis	1
Atypical mycobacteriosis	1

Figure 3.6

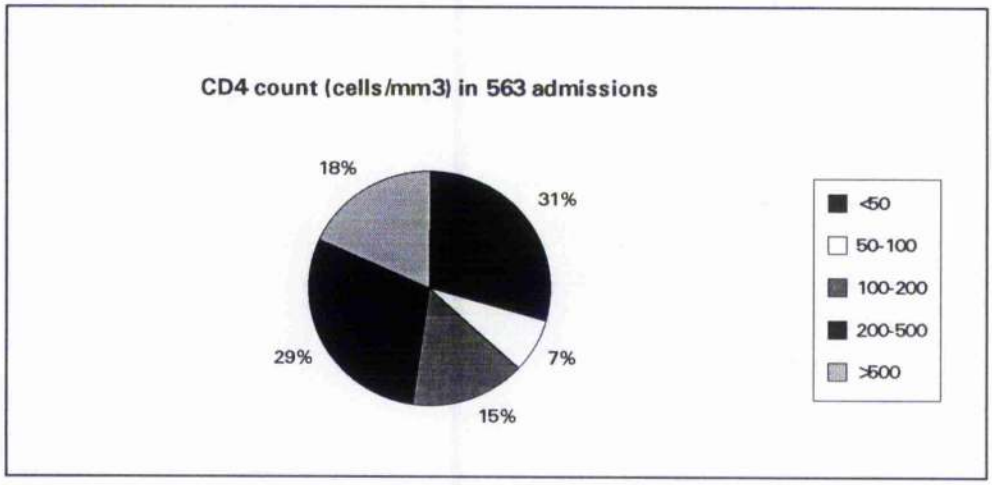
CD4 count (cells/mm3) in 563 admissions
18%
31%
29%
7%
15%
<50
50-100
100-200
200-500
>500

Table 3.1

Comparison of admission diagnoses by risk factor

Diagnosis	Homosexual men	IDUs	Hetero-sexuals	All others	Confidence limits	p value
All AIDS specific diagnoses	OR 22.04	-	NA	NA	12.91-37.78	<0.0001
	NA	-	OR 5.78	NA	2.60-12.71	<0.0001
PCP	OR 10.13	-	NA	NA	5.04-20.52	<0.0001
KS/lymphoma	undefined	NA	NA	-	undefined	<0.0001
CMV	OR 26.76	NA	NA	-	2.94-1267.17	<0.0001
Bacterial infections	NA	OR 1.82	NA	-	1.16-2.87	<0.01
	-	OR 3.05	NA	NA	1.59-5.96	<0.0005
Pelvic inflammatory disease	NA	-	OR 11.79	NA	4.81-28.85	<0.0001

Table 3.2

Analysis by year of admission and by risk factor

	Homosexual men	IDUs	Other	Total
1st year	11 (7%)	139 (87%)	10 (6%)	160
2nd year	22 (15%)	117 (78%)	11 (7%)	150
3rd year	42 (19%)	168 (76%)	11 (5%)	221
4th year	61 (16%)	278 (73%)	40 (11%)	379
Total	136 (15%)	702 (77%)	72 (8%)	910

Table 3.3

Analysis by year and by hospital of admission

	City Hospital	Other hospitals	Total
1st year	56 (1038 days)	104 (559 days)	160 (1597 days)
2nd year	85 (1304 days)	65 (259 days)	150 (1563 days)
3rd year	171 (1719 days)	50 (144 days)	221 (1863 days)
4th year	300 (3241 days)	79 (474 days)	379 (3715 days)
Total	612 (7302 days)	298 (1436 days)	910 (8738 days)

Table 3.4

Average length of hospital admission by year

	City Hospital	Other hospitals	Total	Homosexual men
1st year	18.5 days	5.4 days	9.9 days	30.7 days
2nd year	15.3 days	4 days	10.4 days	20.6 days
3rd year	10.1 days	2.9 days	8.4 days	12.3 days
4th year	10.8 days	6 days	9.8 days	15.7 days
Mean for all years	11.9 days	4.8 days	9.6 days	16.7 days

Table 3.5

Admissions by patients with AIDS to the City Hospital analysed by year

	Number (%) admissions	Number (%) bed days	Average length admission per AIDS patient
1st year	8 (14%)	298 (29%)	37.2 days
2nd year	20 (24%)	535 (41%)	26.8 days
3rd year	65 (38%)	721 (42%)	11.1 days
4th year	125 (42%)	1779 (55%)	14.2 days
Total	218 (36%)	3333 (46%)	15.3 days average

Table 3.6

Subject characteristics and readmissions to the City Hospital - results from single variable analysis

Variable	Admitted (89)	Readmitted (119)	Percent readmitted	Total	p value (Yates corrected)
Sex					
male	62	83	57.2	145	
female	27	36	57.1	63	0.889
Risk					
heterosexual	6	7	53.9	13	
blood product	1	1	50.0	2	
homosexual	12	30	71.4	42	
IDU	70	81	53.6	151	0.197[F]
CDC stage					
stage 2 or 3	35	55	61.1	90	
stage 4	54	64	54.2	118	0.395
CD4 count					
<200	28	46	62.2	74	
>=200	51	61	54.5	112	0.375
All respiratory admissions					
no	63	85	57.4	148	
yes	26	34	56.7	60	0.957
BCIs					
no	77	105	57.7	182	
yes	12	14	53.9	26	0.874
PCP					
no	80	106	57.0	186	
yes	9	13	59.1	22	0.969

F = Fisher's exact test

Variable	p value*
age	0.253
days	0.208

* based on F test for difference in mean age/days among admitted and readmitted group

Table 3.7

Multivariable analysis - initial model, including all variables from table 3.6

Variable	Odds ratio	95% confidence interval	p value
Age	1.0039*	0.9574, 1.053	0.8732
Days	1.0045*	0.9860, 1.023	0.6283
Sex			
male	1.00**		
female	1.0502	0.5233, 2.108	0.8905
Risk			
heterosexual	1.00**		
blood products	0.7713	0.0376, 15.826	
homosexual	2.2564	0.5251, 9.696	
IDU	0.9874	0.2967, 3.286	0.4171
CDC stage			
stage 2 or 3	1.00**		
stage 4	1.0063	0.4642, 2.182	0.9871
CD4 count			
<200	1.00**		
>=200	0.8729	0.3811, 1.999	0.7477
All respiratory admissions			
no	1.00**		
yes	0.7180	0.1988, 2.593	0.6143
BCIs			
no	1.00**		
yes	1.3637	0.3054, 6.09	0.6848
PCP			
no	1.00**		
yes	0.8966	0.1828, 4.397	0.8929

* odds ratio for the change in risk per daily increase in admissions
** baseline category

Table 3.8

All two way interactions from table 3.7

Model (79 admissions 107 readmissions)	**Deviance**	**Degrees of freedom (df)**	**Change in deviance/df from initial model**	**p value**
Initial model	192.03	138		
Current model testing for interactions	248.25	174	56.21/36	0.0171

Table 3.9

Fitting main effects plus all significant interactions from table 3.8

Model (79 admissions 107 readmissions	**Deviance**	**df**	**Change in deviance/df from initial model**	**p value**
Initial model	234.43	169		
Days/age	237.51	170	3.081/1	0.0792
Sex/age	237.02	170	2.593/1	0.1074
CDC stage/days	238.75	170	4.320/1	0.0377
CD4 count/days	240.56	170	6.129/1	0.0133
All respiratory admissions/days	238.28	170	3.845/1	0.0499

Table 3.10

Removing all non-significant interactions from the model in table 3.9

Model (79 admissions 107 readmissions	**Deviance**	**df**	**Change in deviance/df from initial model**	**p value**
Initial model	240.51	171		
All respiratory admissions/days	242.18	172	1.673/1	0.1959
CDC stage/days	244.33	172	3.827/1	0.0504
CD4 count/days	247.31	172	6.802/1	0.0091

Table 3.11

Removing the non-significant interactions from table 3.10

Model (79 admissions 107 readmissions	**Deviance**	**df**	**Change in deviance/df from initial model**	**p value**
Initial model	242.18	172		
CDC stage/days	246.54	173	4.359/1	0.0368
CD4 count/days	248.18	173	6.005/1	0.0143

Table 3.12

The significant interactions relating to readmissions

CD4 count/days: Patients with CD4 counts above 200 cells/mm^3 and initially admitted for more than seven days were less likely to be readmitted than those with a CD4 count less than 200 cells/mm^3.

CD4 count	**<200 cells/mm^3**		**>=200 cells/mm^3**	
Admission status	admit	readmit	admit	readmit
Days/count				
<= 7 days	14	18	29	31
> 7 days	14	28	22	30
Odds ratio	1.6		1.3	

Table 3.13

CDC stage/days: patients with stage 2 or 3 disease and initially admitted for more than seven days were more likely to be readmitted than patients with stage 4 disease

CDC stage	**Stage 2 or 3**		**Stage 4**	
Admission status	admit	readmit	admit	readmit
Days/CDC stage				
<= 7 days	21	22	29	31
> 7 days	14	33	25	33
Odds ratio	2.25		1.2	

CHAPTER FOUR

BACTERIAL INFECTIONS IN EDINBURGH HIV POSITIVE PATIENTS

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BACTERIAL INFECTIONS IN EDINBURGH HIV POSITIVE PATIENTS

1. Introduction
2. Study on diagnosis of *Pneumocystis carinii* pneumonia with particular reference to sputum induction and fluorescent antibody techniques
3. Study of previous tuberculous infection and BCG status in HIV infected patients
4. Study of bacteriological screening of urine samples from HIV infected patients

Introduction

Twenty one percent of all admissions were due to bacterial infections. These comprised: all bacterial chest and upper respiratory infections (excluding cases with concomitant PCP); all urinary tract infections, prostatitis, epididymo-orchitis and pelvic inflammatory disease; colitis due to campylobacter, salmonella and *Clostridium difficile*; appendicitis, sinusitis, osteomyelitis; pericarditis and endocarditis; cellulitis, abscesses and septicaemia. Admissions for all bacterial infections were therefore analysed more fully and further studies arising from these results were conducted.

A total of 189 admissions (1931 days) were found for bacterial infections. A further 49 admissions to the City Hospital had a second diagnosis of a bacterial infection. Most (144) of the admissions were to the City Hospital, where the median length of stay was 12.1 days compared with 4.2 days for the 45 admissions to other hospitals. The admissions because of bacterial infection to the other hospitals were mainly due to pelvic inflammatory disease (22 admissions) and direct complications of injection drug use i.e. skin abscesses, cellulitis and endocarditis (12 admissions). A total of 15% of admissions to other hospitals were therefore directly due to bacterial infection.

Eighty five percent of the admissions (160) were in IDUs, 17 were in heterosexuals and 12 were in homosexual men whose average length of stay at 16.5 days was longer than that of the IDUs (10.3 days) and the heterosexual patients (4.5 days). Men accounted for 103 admissions (and 1163 days) and women for 86 (and 89 days). Therefore whereas 77% of the total 910 admissions were in IDUs, IDUs were disproportionately represented and homosexual men disproportionately underrepresented among these admissions with bacterial infections. This was a significant difference, such that admissions among IDUs were three times more likely to be for bacterial infections compared with admissions by homosexual men

(OR=3.05, confidence limits 1.59-5.96, chi square = 13.63, $p<0.0005$). There was no difference when IDUs were compared with heterosexuals, the main reason for this being the greater number of admissions for pelvic inflammatory disease in heterosexual women. Of the 12 admissions in the homosexual group, four were the only four admissions with bacterial colitis, one was the only admission with epididymo-orchitis, one was with appendicitis, one a urinary tract infection, one prostatitis, two were unspecified septicaemia and two were primary bacterial chest infections. Most (73%) of the 189 admissions with bacterial infections were in the categories of chest and urological infections and pelvic inflammatory disease (135 admissions). The admissions with pelvic inflammatory disease were mainly to other hospitals but further information is available on the 110 admissions (1037 days) with chest and urinary tract infections to the City Hospital. One hundred and one of these were in IDUs, six in heterosexuals and three in homosexual men (chi square = 15.35 with Yates correction, $p<0.0001$). Fifty eight admissions were in men, 52 in women. Admissions in women to the City Hospital were significantly more likely to be for bacterial chest and genito-urinary infections when compared with the men (OR=1.78, confidence limits 1.15-2.76, chi square = 6.88, $p<0.01$). The average length of stay was also longer for the women (10.5 vs. 8.5 days). Sixty four (58%) of these admissions were in patients with CDC stage 2 and 3 disease and 46 admissions were in patients with CDC stage 4 disease. Mean length of stay was the same, regardless of CDC stage (9.4 days).

Of the total 144 admissions with bacterial infections to the City Hospital, 62% (89/144) were in patients who did not have CDC stage 4 disease. Interestingly, in total the "asymptomatic" patients spent longer in hospital (12.9 days vs. 10.7 days).

Chest infections accounted for the largest number of admissions with bacterial infections. In many other patient groups, PCP and not bacterial infection, would account for most admissions with respiratory symptoms.[122]

BCIs concomitant with PCP were excluded from this section of the analysis but accounted for seven admissions. Diagnosis of both infections together is difficult. The diagnosis of PCP is further complicated in the IDU because of poor pre morbid pulmonary function,[140,141] the lack of specificity of chest X-rays and arterial blood gases and the difficulty in assessing oxygen and opiate requirements for bronchoscopy. A separate study was therefore performed to assess the usefulness of sputum induction techniques in the diagnosis of PCP in this patient group.

Despite the preponderance of respiratory infections, there was only one admission with tuberculosis. Most other studies of IDUs and those in which a high incidence of BCIs have been recorded have also documented a high incidence of tuberculosis.[88] A study was therefore carried out to assess whether the low incidence of tuberculosis is due to the low rate of tuberculous infection in the UK population or to the schools BCG vaccination programme.

Urinary tract infections accounted for a primary diagnosis in 13 and a secondary diagnosis in 15 admissions. Because bacteriuria is often asymptomatic and because its prevalence has been reported at much higher rates in other series,[142,143] a separate study was conducted to assess the prevalence of bacteriuria in Edinburgh patients and the usefulness of routine screening urine samples.

Study on diagnosis of *Pneumocystis carinii* pneumonia with particular reference to sputum induction and fluorescent antibody techniques.

Introduction

The finding of most clinical significance from the study of admissions in Edinburgh was the high percentage of admissions due to chest infections. Although in this study 54% of respiratory disorders were due to BCIs and only 27% to PCP it is important that the two should be distinguished clinically and treated appropriately. A missed diagnosis of PCP (for example in an IDU who had suffered frequent previous BCIs) could have serious implications. Differentiating BCIs from PCP in IDUs is difficult and neither chest X-rays, arterial blood gases nor culture of sputum are specific.[144] For example, in Edinburgh patients admitted with BCIs, 43% were hypoxic and 28% were hypercapnic. The position is further complicated by the fact that in 15% of episodes of PCP a concomitant BCI was diagnosed. Diagnosis of PCP is confirmed by identification of the organism in respiratory secretions.[145] Secretions can be obtained by bronchoalveolar lavage,[145] but reliance on bronchoscopy would be demanding both for the health service and individual patients particularly because so many IDUs have frequent readmissions because of chest infections. In many centres in the late 1980s, sputum induction techniques replaced bronchoscopy as first line investigation in cases of suspected PCP.[146-148] Experience was gained at the City Hospital in both bronchoscopy and sputum induction for making a diagnosis of PCP and the latter technique was found to be so useful that from 1989 sputum induction replaced bronchoscopy as the initial investigation to confirm a clinical diagnosis of PCP.

A study was therefore undertaken to assess the value of sputum induction with particular reference to sensitivity, specificity and patient acceptability

of the technique, and thereafter to make recommendations for the management of respiratory infections in IDUs.

Consequently all sputum inductions performed over a one year period between June 1990 and May 1991 in the City Hospital were reviewed.

Methods

The medical case records of all patients on whom sputum induction was requested during the study year were retrospectively reviewed.

All sputum inductions were supervised by an experienced physiotherapist. Sputum was induced by inhalation of 2.7% hypertonic saline using an ultrasonic nebuliser (Devilbiss ultraneb 99, Devilbiss Health Care UK Ltd, Heston, Middlesex, UK) with patients breathing for ten minutes through an open mouth. Patients were then encouraged to cough deeply. If little or no sputum was produced, chest physiotherapy was carried out with postural drainage and percussion. The whole procedure took 30 minutes including ten minutes spent on the nebuliser. If a poor sample was produced, the procedure was repeated up to three times and the results were pooled.

The presence of *Pneumocystis carinii* (PC) in respiratory secretions was demonstrated using a combination of a fluorescent antibody test (FAT) employing a fluorescein isothyocyanate conjugated monoclonal antibody (PC Immunofluorescence Test Kit, Genetic Systems, Syva UK, Maidenhead, Berks, UK) which recognises an antigen, considered to be a glycoprotein, in the 40KD band, and diamidinophenylindole (DAPI).[149] In addition in 1990 all samples were stained with a modified toluidine blue O stain.[150] The induced sputa were transported rapidly to the laboratory where they were processed immediately (in class 1 containment safety cabinets until the fixation stage was completed) or stored at 4°C for up to 24 hours. The sample was mixed with an equal volume of sputolysin (Behring

Diagnostics, Hounslow, Middlesex, UK) in a "V" bottomed container. After vortexing the sealed container with glass beads the sample was incubated in a water bath at 37°C. 15mls of phosphate buffered saline were added and the sample centrifuged at 600rpm for 30 minutes. The supernatant was discarded and the pellet resuspended in 1ml of buffered saline. Cytospin preparations were made using a cytocentrifuge (Shandon). In 1990 one slide was stained with toluidine blue O and the other by FAT following manufacturers instructions with the addition of DAPI in the mountant. From 1991 onwards the toluidine blue O was omitted because it had no benefit over FAT. Slides were viewed at a magnification x400 using a Zeiss Axioskop 20 fluorescence microscope with a reflector slide with two filter sets, 450-490mm for the conjugated monoclonal antibody and 355-450mm for DAPI. This allowed examination of each field with both stains without moving the preparation. Pooled samples were regarded as positive when two to three cysts with or without trophozoites were seen in a preparation. All slides were read by experienced staff. Consultant time for this was on average five minutes to check each slide - less time for good positives and more for negatives. The conventional method of silver staining was not used for identification of PC during this study period since FAT had already been chosen by the City Hospital laboratory staff as being a more useful technique (faster, at least as sensitive and specific and less labour intensive) than silver staining. These two techniques were therefore not compared in this sputum induction study although most published papers on sputum induction used silver staining as their laboratory method of choice.[151]

Results

Over the one year period from June 1990 until May 1991 inclusive, 220 requests were made for PC FAT tests on induced sputa. One hundred and sixty four sample results were negative, 20 were unsuccessful (no sputum

was obtained despite physiotherapy) and 36 were positive. All patients tolerated the procedure and no adverse events, such as worsening dyspnoea, were reported by the supervising physiotherapist.

Positive Samples

A total of 38 diagnoses of PCP were made during this one year period in the Infectious Diseases Unit. PC was found in 36 by FAT testing of induced sputa. One further positive PC sample was a nasopharyngeal aspirate (taken following a recent successful diagnosis of PCP in a child by this method[113]), and one patient was treated on clinical grounds alone. This latter patient had consistently negative FAT for PC on the induced sputum samples, did not have a bronchoscopy and died two months later of pulmonary Kaposi's sarcoma. In retrospect the illness for which he was treated with three weeks anti-PCP therapy may have been pulmonary Kaposi's rather than PCP.

Of the 38 episodes of PCP (in 26 men and seven women), 29 occurred in IDUs, seven in homosexual men and two in patients with heterosexually acquired disease.

In 19 cases this was the AIDS-defining diagnosis and in the remaining 19 the patient's clinical staging was already CDC 4c1. In 17 episodes the patient had received no prior PCP prophylaxis, in 16 prophylaxis had been with monthly nebulised pentamidine (five patients were known to be poor compliers), one patient received regular intravenous pentamidine, one patient was taking cotrimoxazole and three patients were on clindamycin and pyrimethamine for *Toxoplasma gondii* infection.

In 17 of the 38 episodes of PCP (45%) chest X-rays were reported by the radiologist at the time of admission as normal (18 were abnormal and three were not X rayed) and in 12 (32%) the pO2 was >10kPa (20 (53%) were <10kPa and in six cases the results were not available). In seven (18%)

cases both chest X-ray and pO2 were normal. Of the 38 episodes, 35 were thought likely to be PCP by the admitting team, but one was thought to be solely a BCI, and two were found in the course of investigations in patients who initially presented with jaundice and back pain. The final diagnosis in these last three patients was of PCP. In 14 episodes of PCP (37%) a concomitant BCI was found. No patients died nor required ventilation although one patient (who had taken nebulised pentamidine as PCP prophylaxis) developed bilateral pneumothoraces. Median CD4 count at diagnosis of PCP was 10 cells/mm^3 (range 0-330, mean 52 cells/mm^3). 95% of CD4 counts were <250 cells/mm^3 and in 28 cases the CD4 count was <30 cells/mm^3 (normal range 500-1500 cells/mm^3).

Unsuccessful Samples

Twenty samples (9%) were "unsuccessful". In 15 cases this was because no sputum was produced. Two patients who were demented were unable to co-operate with the procedure and three patients were considered too unwell to have the procedure carried out. No patients became unwell as a direct result of the procedure. In none of these 20 cases was further investigation for PCP carried out and no patient was diagnosed with clinical PCP during that admission. All patients received regular follow up. One patient (5%) had a positive induced sputum sample three months after his unsuccessful attempt.

Negative Samples

Of the 184 unsuccessful or negative samples there was only one possible false negative result (the patient with Kaposi's sarcoma described above). One patient underwent bronchoscopy (the only bronchoscopy carried out on an HIV positive patient during the study period). This IDU who did not have

AIDS and who had not taken any PCP prophylaxis had unexplained symptoms of weight loss and malaise. He had a CD4 count of 50 cells/mm^3, his chest X ray showed interstitial shadowing and he had a pO2 = 9.4 kPa. *Haemophilus influenzae* had already been isolated on microbiological examination of his sputum, FAT for PC was negative on five occasions and no further information was gained after bronchoscopy and bronchoalveolar lavage. An AIDS-defining diagnosis of AIDS dementia complex was made four months following his bronchoscopy.

Of the remaining 162 negative sputum results final diagnoses were; BCI in 77, bacterial pneumonia in 16, atypical mycobacterial infection in nine, pulmonary tuberculosis in one and non respiratory diagnoses in 59. CDC staging was; 2 and 3 = 17, 4a = 16, 4b = 2, 4c1 = 69, 4c2 = 38, 4d = 3, 4e = 11, not recorded = 6. Median CD4 count in this group was 50 cells/mm^3 (range 0-570, mean 101 cells/mm^3). In 142 cases (88%) the CD4 count was <250 cells/mm^3. The treatment schedule in these patients did not include cotrimoxazole nor pentamidine.

All patients were followed up regularly in the clinic. In 154 cases PCP did not occur over the ensuing three months. However in five patients (nine negative sputum inductions) PCP was diagnosed within the next three months. One patient had negative induced sputum samples in July, September and January and positive samples in October, December and February (the latter was the nasopharyngeal aspirate documented above). In this patient repeated samples were being taken because of recurrent admissions with respiratory symptoms usually due to BCIs. In the remaining four patients at the time of diagnosis of PCP (by positive FAT on induced sputum samples) only one patient had a pO2 <10kPa (9.2 kPa). All five of these patients already had advanced AIDS (CDC 4c1) and CD4 count <30 cells/mm^3 and none appeared disadvantaged by any possible delay in diagnosis. Therefore, of the 184 unsuccessful or negative samples, ten (5%)

progressed to induced sputum confirmed PCP within the ensuing three months.

Discussion

Although only 36 (16%) samples of 220 were positive on FAT, the sensitivity was 95% and specificity was 100%. If one assumes that a positive FAT within three months of a negative FAT represents failed detection of PCP, the sensitivity falls to 75% (the specificity remains 100%). The occurrence of a positive result within three months of a negative one continues to represent early detection of PCP rather than a failure of sputum induction and FAT for PC. Because of the good patient acceptability of the induced sputum procedure it was used in the City Hospital as an early screening test. Patients may tolerate the procedure better when it is carried out in the early stages of disease and therefore have not suffered the adverse events such as nausea and vomiting which have been documented in other centres.[151-154] Arterial desaturation in HIV positive patients undergoing sputum induction has been documented in one study.[152] Arterial blood gases were not directly measured in this study but none of the patients became more dyspnoeic nor cyanosed during the procedure. Other possible reasons for good acceptability of the procedure and the low number of unsuccessful samples compared with other studies[151] are the use of a dedicated physiotherapist and the fact that the patients were mainly IDUs who often have smoking related chronic obstructive pulmonary disease with resultant chronic productive cough. Conversely, the procedure of bronchoscopy is perhaps more complicated in IDUs compared with other patients because of the difficulty in assessing the pre-medication and oxygen requirements of patients who are already taking large amounts of opiates and benzodiazepines and who are chronically hypoxaemic. Since IDUs rarely

suffer from Kaposi's sarcoma, direct visualisation of the bronchoscopic tree is less frequently indicated compared with other patients.

What has been saved by performing so many sputum inductions? Of the 184 negative and unsuccessful samples, in 82 cases the patient already had AIDS and in a further 67 the patient had CDC stage 4 disease without AIDS. In 97 cases the CD4 count was below 50 cells/mm^3, in 54 of whom the diagnosis was thought likely to be PCP on clinical grounds. Therefore using the criteria of a high clinical suspicion of PCP (weight loss, fever, cough or breathlessness) and a CD4 count of less than 50 cells/mm^3, if sputum induction had not been available in the City Hospital then at least 54 cases would have required bronchoscopy and bronchoalveolar lavage. In seven patients this would have necessitated more than one bronchoscopy. Since PCP may occur with increasing frequency in patients with CD4 counts <250 cells/mm^3, 142 bronchoscopies might have had to be undertaken (the number of negative induced sputum samples in patients who also had a CD4 count <250 cells/mm^3), excluding those patients with positive results.

By 1991 local pricing the cost of 54 bronchoscopies was £13,500 (£250 per bronchoscopy excluding £7,000 for the initial purchase of the bronchoscope). By comparison the cost of 220 induced sputa was £1,840 (nebuliser £1,000, 110 hours of physiotherapy time £840). FAT testing cost £2,500 (20 hours of consultant virology time £300, reagents and laboratory time £2,200).

A more recent Edinburgh study analysed all episodes of PCP in the 11 year period from January 1984 until December 1994 (Dr RLS Laing, unpublished data). During this period 176 episodes of PCP were treated in 126 patients. Although this indicates that there has been an increasing number of admissions since November 1994, the incidence of PCP as the AIDS indicator diagnosis has declined remarkably in recent years (Dr CLS Leen, personal communication). This is likely to be due to systematic use of

PCP prophylaxis. Despite increasing numbers of patients with PCP the method of diagnosis has not changed. Few patients undergo bronchoscopy and induced sputum samples are still examined by FAT (Dr CLS Leen, personal communication).

Although BCIs are a more common reason for respiratory symptoms and hospital admission than PCP amongst IDUs, it is worthwhile excluding PCP in an IDU with any suspicious symptoms and a CD4 count of <250 cells/mm^3 because of the possibility of both infections occurring concomitantly. In this study 37% episodes of PCP were associated with a BCI. Diagnosis and treatment of these 14 patients might have been delayed by the finding of a BCI if sputum induction had not been available in the RIDU; bronchoscopy would not have been performed until after treatment of the BCI.

If yield of positivity of sputum inductions is analysed by CD4 count alone, 25% of samples sent in patients who had a CD4 count <50 cells/mm^3 were positive compared with 10% positive yield in patients with CD4 count >50 cells/mm^3.

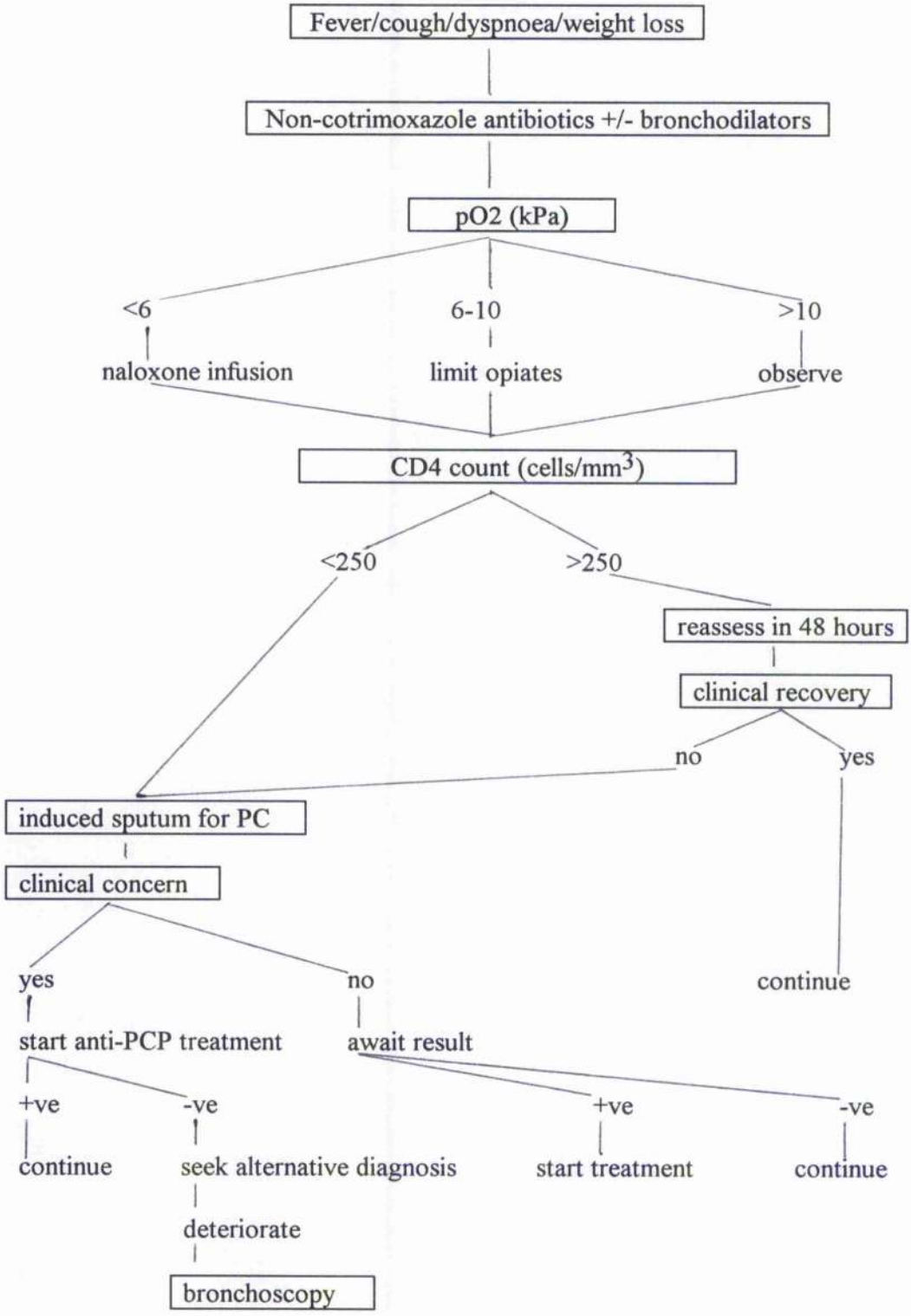
A management strategy for investigation and treatment of HIV positive IDUs presenting with respiratory symptoms was therefore drawn up (figure 4.1). All patients with symptoms of cough or breathlessness with or without fever and weight loss are treated initially with broad-spectrum antibiotics (not cotrimoxazole) whilst awaiting results of sputum culture. Bronchodilators are added to the regime if there is any evidence of bronchoconstriction. Patients who are known to be receiving opiates and benzodiazepines (with or without a prescription) and who have a pO2 <10 kPa are closely monitored and are advised to voluntarily restrict their intake of drugs whilst in hospital. If the pO2 falls to <6 kPa, a naloxone infusion is started with the aim of increasing the respiratory rate and pO2. Further action would then depend on the results of the patient's most recent CD4

count. If this was <250 cells/mm^3 or if the patient was not responding to broad spectrum antibiotics, a sputum induction sample for PC FAT would be taken. All positive results would be treated with a three week course of anti-PCP medication. In patients with negative results, further investigations would be carried out only if the patient was not responding to antibiotics, bronchodilators and oxygen. This plan obviates the need for bronchoscopy in most cases although it is not ruled out for patients with negative sputum induction and poor clinical progress.

Whilst the acceptability of bronchoscopy was not specifically assessed, induced sputum techniques proved safe, were well tolerated by patients, and were reasonably fast and inexpensive. FAT was also found to be as sensitive and specific as histochemical staining and has the additional advantage of being faster.

Figure 4.1

Management plan for HIV +ve IDUs with respiratory symptoms



Study of previous tuberculous infection and BCG status in HIV infected patients

Introduction

One of the striking findings from the study of admissions was the low number of admissions recorded for tuberculosis (TB). Only one patient (a 24 year old IDU) was admitted with pulmonary and disseminated TB. He was sputum smear positive for AAFB on admission, and *Mycobacterium tuberculosis* was later grown on culture of his sputum and bone marrow. It was his first presentation with HIV infection, he had no other concomitant AIDS defining illness and his CD4 count on admission was relatively well maintained at 130 cells/mm^3. It would be unlikely that any patients would be diagnosed with TB in the community without a hospital admission. Therefore one out of 702 admissions in IDUs represents a very low incidence of TB when compared with other cohorts.[124]

From American data, the incidence of TB in patients with AIDS is almost 500 times the incidence of the general population.[155] Although extrapulmonary TB was an AIDS defining condition by the 1987 CDC classification, pulmonary TB alone was not.[5] Pulmonary TB is a common disease in HIV positive IDUs and in heterosexual African, Haitian and Hispanic patients and often occurs at a relatively early stage of HIV infection, preceding an AIDS defining diagnosis by many months, if not years.[96,124,156-158] The incidence amongst homosexual and haemophiliac patients is much lower.[124,157] Two mechanisms may account for this discrepancy between risk groups. Firstly it may reflect the different natural history of HIV disease in different risk groups. IDUs are more likely than the rest of the population to have had previous exposure to *M. tuberculosis* and to have particularly poor living conditions.[88,157] But secondly the incidence of TB may not be a feature of the risk category but instead may be

a feature of the incidence of TB in the countries from which most HIV positive IDUs and African heterosexuals have been reported. Most reports of the high incidence of TB in HIV positive IDUs and African heterosexuals come from Africa, Spain, Italy and New York - all areas with a higher incidence of TB among the general population than the UK.[88,124,156,157] Spain and Italy exemplify the European north/south divide with respect to HIV; in Southern Europe spread via IDU is more common,[47,63,72,124] whereas in Northern Europe most patients affected have been homosexual men. Edinburgh, which has a pattern of spread more akin to Southern Europe, is in a Northern European country with a low incidence of TB.

Another feature peculiar to the Edinburgh cohort is the social stability of the IDUs. In many other countries HIV infected IDUs are chaotic and often difficult to access because of their frequent changes of address (if they have one) both within towns and between different towns and countries.[159] The Edinburgh IDUs, by contrast, have mainly been born and brought up in the same area of Edinburgh - one of the reasons why it has been an ideal cohort to follow prospectively.[64] One other point of note is that almost all the Edinburgh HIV positive patients are white Caucasians and none are from the Indian subcontinent.

The UK has a programme of BCG in schools for all children aged between ten and 14.[160] The mass BCG immunisation programme is one reason why the UK has a low incidence of TB. Other reasons are effective chemotherapy, contact tracing and chemoprophylaxis.[160,161] The aim of this study was to assess the interaction between BCG and TB in the context of an HIV cohort which has a low incidence of TB.

Methods

Records of all BCGs given through the schools vaccination programme in Edinburgh since 1954 are kept in the Edinburgh Chest Clinic at Spittal Street. Records are kept in box files, filed alphabetically by date of birth. Information on each child's card includes name, date of birth, result of Heaf test, date of BCG, any reactions to BCG, reasons why any children had not received BCG, and follow up with chest X-ray results on children who were Heaf positive. Permission was given by the chest clinic to access these files.

A list was made of the names, dates of birth and risk factor of all patients attending the City Hospital HIV clinic. Maiden and other previous names were included where available. The data were obtained from the Chest clinic box files and matched with the City hospital list. Data therefore finally obtained and entered on to a database file were: identifier, date of birth, risk factor, sex, whether Chest clinic records had been found for that patient or not, whether BCG had ever been given and if not why not, result of Heaf test where recorded, and any follow up.

Results

By the time the study was carried out in 1991, 523 HIV positive patients had attended the City Hospital HIV clinic and another 24 year old male IDU had been admitted with TB, presenting with a pleural effusion. Risk factors of the 523 patients were IDU in 394 (66%), homosexual intercourse in 72 (14%), heterosexual intercourse in 53 (10%) and blood transfusion in 4; 350 were men and 173 were women. Dates of birth ranged from 1927 to 1973 but most were between 1955 and 1967.

Matching was achieved with chest clinic records for 310 (59%) of the City Hospital group. Records were found for 223 men and 87 women; 270 were

IDUs, 21 were heterosexual, 18 homosexual and one patient was infected from blood products.

Of the 310 patients whose records were available (figure 4.2), 243 had received BCG; 229 at age 11 in the schools programme and before this in 15 cases (one patient had BCG twice). The main reason for BCG prior to age 11 was because of contact with a case of TB. The children who were given BCG at age 11 included both patients who later developed TB. BCG was arranged for a further 46 children who did not receive the vaccine as planned for various reasons: absence from school, school exclusion, refusal by the child or their parents, and, in a minority, that the child had left school and moved away from the area. Of these 46 children, 43 were to become IDUs. This refusal rate therefore accounts for 15% of the 310 whose records were found. In 17 cases the child was Heaf positive without having received a previous BCG; follow up in all these cases, with at least one chest X-ray, was normal. None of these children developed active TB during their period of follow up by the chest clinic and none received later BCG. In a further four cases, BCG was not given for different reasons. In one case the child had developed TB when aged nine and was still under regular follow up, the chest X-ray showed calcified primary lesions in another, bad eczema was cited as the reason in a third and in the last the reason is not clear.

Discussion

Although the incidence of TB in the UK has been falling steadily over the past 100 years and is now at a very low level, there has been a slowing in the decline of notifications in the 1980s with a possible rise in cases since 1987.[125,162] Groups at risk for TB in the UK are immigrant populations (particularly from the Indian sub-continent), alcoholics and the homeless, the elderly, the poor and the immunosuppressed including those infected with HIV.[125,163-165] The reason for the slight rise in UK figures is not yet clear.

Although most UK cases are in Asians, there has been concern that the rise in cases may be directly related to HIV infection. But preliminary studies have suggested that areas with a rise in notifications are not those with higher numbers of HIV cases but rather areas with higher numbers of immigrants; and that the rise has not affected the age and sex groups associated with HIV infection but instead young females and older men and women.[125,163,166,167] This contrasts with the picture in the United States where the rise in reported cases has been particularly rapid amongst younger men, particularly black people and Hispanic populations, in which both poverty and HIV have a high prevalence.[163]

In this study 0.4% of the HIV positive clinic population (and 0.5% of the IDUs) had developed TB. By current reporting, 5% of AIDS patients in England and Wales develop tuberculosis.[168,169] This clearly may underestimate the size of the problem since by the CDC 1987 definition, TB was not an AIDS defining disease,[5] nor are all patients who present with TB tested for HIV infection. But even taking this into account, 5% is a low rate. Why is this so? One reason is that the overlap between the population with HIV infection in Britain (mainly young white men) and the population with previous tuberculous infection (mainly the elderly and people from the Indian sub-continent) is limited and that most UK HIV positive patients have never previously been infected with *M. tuberculosis*.[125,170] The other may be the effect of BCG immunisation.

Historically BCG has had a high and consistent efficacy in the UK.[126] A large randomised controlled trial of BCG in 14 year olds showed protective efficacy of 77% over 20 years of follow up.[171] The efficacy in a study of Edinburgh school children between 1970 and 1983 was over 60%.[172] Although controversy exists about the continuing value of the schools BCG immunisation programme in the face of the current low national incidence of TB,[164] the Joint Committee on Vaccination and Immunisation has advised continuation of the programme until at least 1995/1996 because of the

possibility of the HIV epidemic causing a future increase in cases of TB in the UK.[166]

BCG had been given to 243 of Edinburgh patients whilst they were children, i.e. to at least 46% of the 1991 HIV clinic population. Two hundred and eight of these were IDUs. Therefore at least 53% of the 1991 clinic (208/394) IDU population had received BCG, two of whom developed TB during the study period. Because the chest clinic records were complete, the only reason for not matching records was because of incorrect information of date of birth or name, or because the child did not attend school in Edinburgh. Many of these patients would have received BCG elsewhere. Matching was obtained with Chest clinic records for 59% of the City hospital group. The likelihood for matching was not equal for sex or risk group. Matching was obtained for 64% of the men but only 50% of the women; for 69% of the IDUs, 40% of the heterosexuals and 25% of the homosexuals. The lower rate of case finding for women was probably due to change of name on marriage and for homosexual men because they were on average older and more likely to belong to a more mobile population.

It is interesting that BCG uptake and refusal rate amongst IDUs, the group most likely to have been economically and socially disadvantaged as school children, was similar to that of the general population. BCG was given to at least 53% of the IDUs and 46% of the 1991 clinic population. Uptake rates of the school BCG programme have been documented at 75% over the past decade.[161] Uptake rate amongst this matched cohort was 78% and the refusal rate was 15%. Amongst IDUs the uptake rate was 77% and the refusal rate was 16%.

There is no published epidemiological evidence on whether BCG is effective in UK patients who later acquire HIV infection. BCG is contra-indicated in patients (both children and adults) already known to be HIV positive because of the risk of disseminated BCG infection.[164] But

theoretically BCG should be effective if given before HIV infection and before the first contact or infection with tuberculosis.[164] BCG has also been to shown to provide most protection in stopping haematogenous spread of mycobacteria and has generally provided high protection against TB meningitis.[172] These properties should be of particular value in HIV positive patients since TB is more often extrapulmonary and disseminated in HIV positive than in HIV negative patients.[174] The efficacy of BCG may reduce with time as the immune system becomes progressively impaired.[164] In a study from Tower Hamlets, an area in the east end of London with high levels of poverty, homelessness, immigrant populations and HIV infection, 10 (7%) of 150 HIV positive patients screened for TB were found to have active disease.[175] Five patients (four British whites and one African) had received BCG immunisation. Although this might suggest that BCG is not always protective, this paper does not state whether these patients had received BCG before or after acquisition of HIV infection. A paper from Austria has suggested that BCG immunisation before HIV infection could have untoward effects. In the case documented, disseminated BCG infection in an HIV positive patient was ascribed solely to BCG immunisation 30 years beforehand.[176]

In this Edinburgh study it is of note that the two patients who developed TB during the period of follow up had received BCG as schoolchildren only 12 years before. It is difficult to determine the efficacy of BCG in any population and even more so in an individual but further follow up of this cohort may give some intimation of the protective value of BCG to HIV positive patients.

None of the 19 children with evidence of previous tuberculous infection (17 Heaf positive and two with X-ray evidence of TB), developed TB during the study. The prevalence of previous tuberculous infection in this cohort was 6% (19/310), exactly the same as found in the study of all Edinburgh schoolchildren.[172] Applying this figure to the 523 clinic attenders or to the

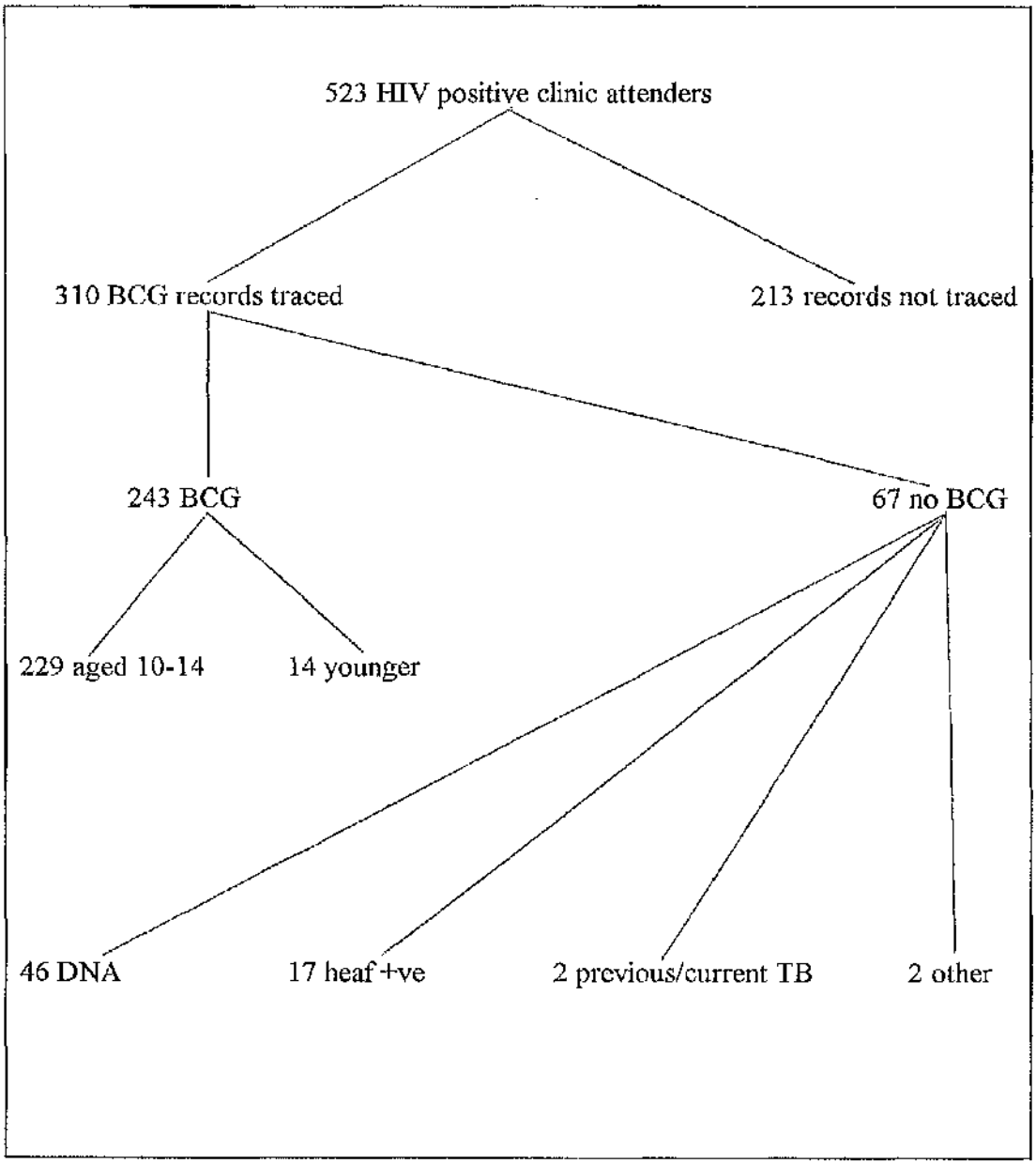
estimated 1000 HIV positive IDUs in Edinburgh[104] suggests that 31 to 60 might have dual infection with *M. tuberculosis* and HIV. Assuming that dual infection leads to active TB at a rate of about 10% per year,[88] then three to six cases of TB would be expected annually in this population. This is a rate considerably lower than the finding of less than one case a year and suggests that primary tuberculous infection may play an important role.

Some follow up of this study has already been performed (Dr AG Leitch, unpublished data). By 1994 none of the 19 tuberculin positive patients had developed TB. A further three patients had developed TB, two male IDUs and one homosexual man, none of whom had a scar, nor a history of BCG vaccination. By 1994 1030 cases of HIV infection in Edinburgh had been recorded, 60% of whom were IDUs. Five cases of TB among 1030 HIV infected patients, 60% of whom were IDUs, still represents a low rate compared with other cohorts.

In conclusion, the incidence of TB in HIV infected patients in Edinburgh is much lower than has been described in almost any other cohort. This is largely due to the low incidence in the UK, but even in those previously infected with *M. tuberculosis*, no cases of reactivation had been found. Primary tuberculous infection may therefore be important in cohorts with a high incidence of TB.[177] The protective value of BCG was not proven in this small study. Further long term follow up will be of the utmost importance.

Figure 4.2

BCG vaccination and tuberculin reactivity in Edinburgh HIV +ve patients



Study of bacteriological screening of urine samples from HIV infected patients.

Introduction

Urinary tract infections (UTIs) have been described as one of the manifestations of recurrent bacterial infections in HIV positive patients.[142,143] In the admission study only 13 admissions (in two men and 11 women) had a primary diagnosis of UTI. There were two admissions (in the same male IDU) for septicaemia secondary to a UTI. Perhaps more interestingly UTI was a second diagnosis in 15 patients suggesting that a larger spectrum of UTIs exists which may cause significant morbidity but not being life threatening is not deemed a primary diagnosis. It was thought that screening for these might be of value. Bacteriological examination of urine samples was part of the routine investigations carried out on all HIV positive patients admitted to the City Hospital and was thought to add significantly to the workload of the bacteriology department. A retrospective analysis of the results of bacteriological examination of all urine samples from adult HIV infected patients admitted to the City Hospital during the year from 1 April 1988 to 31 March 1989 was therefore carried out. The aims of this study were to assess the usefulness of this investigation in HIV positive patients without evidence of UTI and to document the prevalence of bacteriuria.

Methods

The results of urine samples received for bacteriological investigation from all HIV positive inpatients in the City Hospital between 1 April 1988 and 31 March 1989 were correlated with clinical information obtained from the medical casenotes.

Urine samples were considered to be "screening samples" in the absence of: (1) symptoms and signs of cystitis or pyelonephritis or (2) clinical "septic shock" or (3) pregnancy. If pyrexia was present without any of the above the samples were also considered "screening samples" but were analysed in a separate subcategory. All other samples were classified as "non-screening samples".

Results

During the year studied, 106 patients accounted for 181 admissions. One hundred and seven of the admissions were men aged 16-58 years (average 32 years) and 74 were women aged 22-41 years (average 27 years). Two pregnant women had five admissions between them. Sixty percent of the patients had CDC stage 4 disease, 50% of whom had AIDS, 31% had stage 3 and 9% had stage 2 disease. Altogether 30% of the 106 patients had AIDS.

Four hundred and forty samples were received during the study period. Of these, 279 were considered "screening samples" and were derived from 118 admissions (72 men and 46 women). There were two positive urinary cultures from the men and six from the women. The two men had CDC stage 4 disease. Two women had CDC stage 4 disease, two had stage 3 and two had stage 2 disease. Eighty one of the 279 samples were from patients with pyrexia and were derived from 36 admissions (26 men and ten women). There were two positive urinary cultures within this subgroup (one man and one woman). A positive culture was obtained with two or fewer samples in all but one patient. In the single exception the positive culture was the tenth sample and was almost certainly a hospital-acquired infection.

One hundred and sixty one "non-screening" samples were received from 63 admissions (35 men and 28 women). There were two positive urinary cultures from the men and 12 from the women, one of whom was pregnant.

One of the men had CDC stage 4 and the other had stage 3 disease. Nine of the 12 women had CDC stage 4, two had stage 3 and one had stage 2 disease. The number of samples required to obtain a positive culture ranged from one to five. The one episode which required five samples was probably due to a urinary tract infection acquired after admission to hospital.

The organisms isolated from both screening and non-screening urine samples were the common urinary tract pathogens. *Escherichia coli* was isolated in 11 of the 22 positive cultures, Enterococci were found in six and there was one episode each of UTI due to Enterobacter species, group B beta haemolytic streptococci, *Klebsiella oxytoca*, *Klebsiella pneumoniae* and mixed organisms.

Discussion

The prevalence of asymptomatic bacteriuria in this group of HIV positive patients was 13% in women and almost 3% in men, considerably higher than the normal figure of 3-5% in women and 0.5% in men.[178] In women this difference is statistically significant ($p < 0.05$ by chi-square test with Yates' correction). No significant differences were found between CDC stages. Of the non-screening samples, bacteriuria was detected in 6% of samples from men and 43% from women. The numbers involved are very small (14 positive samples in 63 admissions) but in ten of the 14 cases the patient had CDC stage 4 disease.

The prevalence of bacteriuria in HIV positive men in other reported studies is even higher.[142,143] There are two reasons for this. Firstly, the percentage of homosexual men among Edinburgh admissions is much lower than in many other studies. Bacteriuria was found in 17% of urine samples

from a Netherlands study of 98 men, 89 of whom were homosexual.[143] Although the authors did not find a correlation between the prevalence of UTI and specific sexual practices there was no non-homosexual group for comparison. In a study from Rio de Janeiro of 58 male patients without other local risk factors for UTIs, bacteriuria was found in 14%.[142]

Although the study did not find a significant association between risk factor and bacteriuria and the numbers were small, 75% of the patients were homosexual men. Secondly, the Edinburgh patients had less advanced disease than in other reported studies; during the year studied 40% of the admissions were in patients who had not reached CDC stage 4 disease. The Netherlands study correlated the presence of bacteriuria with a lower CD4 count: bacteriuria was significantly more common in men with a CD4 count of less than 200 cells/mm^3 compared with men who had a CD4 count between 200 and 500 cells/mm^3. In Pinho's Rio de Janeiro study all the men had CDC stage 4 disease.[142] In a later study by Pinho in which the prevalence of bacteriuria in a group of 245 HIV positive men was 9.4%, not only was the prevalence rate of bacteriuria much higher in patients with AIDS compared with those with asymptomatic infection, but the only patients with symptomatic UTI were those who had AIDS.[179]

All the asymptomatic bacteriurias in the Edinburgh study were detected in the first or second samples received. The high incidence of asymptomatic bacteriuria would suggest that screening urine samples should be sent in similar groups of asymptomatic HIV positive patients but that negative cultures from two specimens can reasonably exclude urinary tract infection. Following this policy would have reduced the number of urine samples in this study by 56 (13%). Screening urine samples should be sent only in patients who have been admitted. In many cases it may transpire that non-specific symptoms are secondary to a urinary tract infection. Because of the associated immune deficiency, even if at an early stage, and the

predisposition to bacteraemia, these patients should be treated with the appropriate antibiotic.

CHAPTER FIVE

DEATHS IN HIV POSITIVE EDINBURGH PATIENTS BEFORE NOVEMBER 1989

CHAPTER FIVE

DEATHS IN HIV POSITIVE EDINBURGH PATIENTS BEFORE NOVEMBER 1989

1. Introduction
2. Methods
3. Results

   Deaths due to hepatitis

   Deaths due to overdose
4. Discussion

Introduction

Studies of hospital admissions are at present one of the best methods of assessing the morbidity of HIV infection, even although they cannot give a full picture. Studies of mortality complement those on morbidity. Official figures of AIDS deaths might seem to be more accurate than any figures relating to morbidity but these figures are only available when a diagnosis of AIDS or HIV infection was made before death.[180] Additionally, deaths in HIV positive patients which are not specifically related to HIV infection are not always included in HIV statistics.[181,182] From the Edinburgh admissions study, fourteen patients died in the City Hospital and four patients died in other Edinburgh hospitals. Because patients with AIDS may choose to die at home and because deaths due to overdose are likely to be at home, the admissions study was unlikely to give a complete record of all deaths in the cohort. Therefore a separate study of all the deaths in the Edinburgh cohort before November 1989 was carried out. Particular attention was paid to post mortem results since deaths ascribed to overdose might be due to HIV disease.

Methods

The names of all patients who had attended the City Hospital outpatient clinic and who had died before November 1989 were obtained from the City Hospital computer files. Details were obtained from the City Hospital casenotes of date of death, place of death, postulated cause of death, whether post mortem was carried out and the results if so, CDC stage and CD4 count before death, previous hospital admissions and AIDS defining diagnoses, sex and risk factor. Since all post mortems performed may not have been recorded in the City Hospital notes, a list of names of sudden deaths at home where no post mortem was recorded was sent to the University of Edinburgh Forensic Medicine Unit, to the Procurator Fiscal for Edinburgh and to the

General Register Office for Scotland. Full details of four post mortems were obtained from the Forensic Medicine Unit. In addition, for two patients, the general practitioner's notes were checked.

Results

Thirty four deaths were recorded by November 1989. Thirteen patients were homosexual, 19 were IDUs and two heterosexual; 28 were male and six were female (five IDUs and one heterosexual). One death was recorded in 1984, four in 1986, seven in 1987, nine in 1988 and 13 in 1989. Of the 34 deaths, 19 were due to AIDS, two to liver disease and 13 were thought to be drug related.

Deaths due to AIDS

Of the 19 AIDS related deaths, 13 were homosexual men, four were IDUs and two were heterosexual. Only two of these deaths were in women (one IDU and one heterosexual). Fourteen of the patients died in the City Hospital, two died in other hospitals (both patients were transferred from the City Hospital to the two other hospitals, one of which was in Fife, during their terminal admission), one patient died in an Edinburgh hospice and two patients died at home (one in Edinburgh and one in Spain).

AIDS had been diagnosed between two days and 45 months before death and the average time alive with AIDS in these 19 patients was 11.7 months. Eleven patients had died within one year, and 17 within two years of their AIDS diagnosis. Two patients died during their initial HIV hospitalisation and a further two patients died during their admission for their AIDS defining illness. AIDS defining diagnoses for these 19 patients were PCP (six patients), oesophageal candidosis (two patients), KS (three patients),

cerebral toxoplasmosis (two patients), and, in one patient each, CMV encephalitis, AIDS dementia, cryptococcal meningitis, PCP with KS, toxoplasmosis with KS and PCP with cerebral lymphoma (table 5.1). Lifetime HIV related admissions per patient ranged from one to 20 (mean 5.7 admissions). The 19 AIDS patients had a total of 44 AIDS related conditions- 14 episodes of PCP, six of CMV, five of KS, five of mycobacteriosis, four of oesophageal candida, four lymphoma, four toxoplasmosis, one cryptococcal meningitis and one AIDS dementia. Average CD4 count at death was 41 cells/mm^3 in the 18 patients in whom it was recorded (range 0-255 cells/mm^3). The CD4 count was less than 30 cells/mm^3 in 14 patients, between 30 and 100 cells/mm^3 in two and between 100 and 300 cells/mm^3 in two patients (who died in 1986 and 1987).

It was often difficult to assess what was the principal cause of death. Dual (or multiple) pathology was found in at least seven cases. Disseminated CMV was implicated in six deaths, KS in five, PCP in four, cerebral toxoplasmosis in four, lymphoma in three and mycobacteriosis in two (table 5.1).

Post mortem studies were carried out in nine patients. Of the other ten, a refusal for post mortem was documented in three casenotes, no mention of post mortem was made in three casenotes and post mortem was not requested in the two patients who died at home, the patient who died in the hospice nor in the patient who died in the Fife hospital.

Post mortem revealed unexpected findings in eight of the nine cases (table 5.2). Multiple pathology was detected in all of them. Diagnoses which were made only at post mortem (and not suspected clinically ante mortem) were CMV disease in three, disseminated mycobacteriosis in two and lymphoma in one. In addition, one patient who had initially been treated for cerebral toxoplasmosis (which was his AIDS defining diagnosis) but whose ante

mortem brain biopsy showed evidence of cerebral lymphoma had no evidence of cerebral toxoplasmosis on post mortem.

Deaths due to hepatitis

Two men died of IDU related hepatitis which may have been exacerbated by concomitant HIV infection. One man died at home of a massive haematemesis. He was known to have chronic hepatitis B infection, cirrhosis, portal hypertension and oesophageal varices and had been admitted on six occasions to the City Hospital (for diagnoses including bacterial pneumonia, *Escherichia coli* septicaemia, urinary tract infection, haematemeses and ascites). His CD4 count just before death was 20 cells/mm^3 and he had CDC stage 3 disease. The other man with chronic liver disease was known to have chronic hepatitis B and D infections but was not admitted until the day of his death when he developed peritonitis. Post mortem revealed a primary *E. coli* peritonitis with subphrenic and pelvic collections, macronodular cirrhosis and a 4cm hepatoma. Hepatitis C was demonstrated by EIA in his stored serum in 1990. He had CDC stage 3 disease and a CD4 count of 221 cells/mm^3 at death.

Deaths due to overdose

Thirteen deaths were assumed to be due to overdose. Eleven patients were found dead at home and two died in hospital. Post mortem studies were performed on seven patients. In the six patients who did not have post mortems (four were reported to the Procurator Fiscal and were examined by the forensic doctor without a full post mortem), there was good circumstantial evidence of overdose which in all cases seemed accidental rather than deliberate. Three had CDC stage 2 or 3 disease, two had stage 4e and one had disease stage 4c2. Average CD4 count at death was 363

cells/mm³ (range 135-840 cells/mm³). One patient died from injecting Diconal (dipipanone and cyclizine) the day after his release from prison, one patient died in police custody, one patient was found dead in the bath with fresh needle marks, one patient had had three admissions for overdose and one other patient had had two previous IDU related admissions.

Of the seven IDUs who had post mortems carried out, five were in patients found dead at home. In four cases there was likely evidence of recent drug use and this was confirmed on post mortem when aspiration pneumonia was also found in three and acute pulmonary oedema in one (table 5.3). Significant lymphadenopathy was found in two patients, one of whom (who was known to have hereditary spherocytosis) also had marked splenomegaly with prominence of the white pulp. In these four cases the brain was not examined. The fifth death in this category was in an IDU who had had one previous admission for pneumococcal pneumonia, who was in CDC stage 4a and whose CD4 count was 155 cells/mm³. He was found dead at home, three days after being seen in the City Hospital out patient clinic and one day after being seen by his general practitioner. He had been assessed at both clinics as being in his usual state of health. When found dead at home he had fallen out of bed and petechial haemorrhages were seen on his buccal mucosa. The death was thought to be drug related but post mortem revealed a florid meningoencephalitis of uncertain aetiology and marked cerebral oedema. The pathologist remarked that he could not conceive how this patient had been walking around the day before his death.

The two other post mortems were carried out in IDUs who died in hospital. One was an IDU who was admitted unconscious and died after two days artificial ventilation in the Intensive Care Unit. The diagnosis on the death certificate was of self poisoning and bronchopneumonia. Post mortem revealed morphine in post mortem blood, a bilateral confluent pneumonia secondary to a viral pneumonitis, evidence of septicaemia and generalised lymphadenopathy. The other patient had been admitted for drainage and

packing of an IDU related antecubital abscess. He later had a respiratory arrest, ascribed to the effects of IDU, from which he died. A post mortem drugs screen was completely negative and death was due to acute pulmonary oedema. Splenomegaly was also found but the abdominal organs were only examined superficially and the cranium not at all.

Discussion

The most striking finding from this study was that although there were more deaths due to AIDS (19) there were almost as many deaths not due to AIDS (15). All 15 of these other deaths were in IDUs. Two of these deaths were due to chronic liver disease, one to a meningoencephalitis of unknown cause and the remaining 12 were likely to be related to drug use. Of these 12, six had post mortems carried out confirming overdose in four, overdose with bronchopneumonia in one and acute pulmonary oedema in one. Acute pulmonary oedema is a recognised complication of opiate use[81,183] although a toxicological screen was negative in one patient with this diagnosis. Bronchopneumonia is a recognised complication of both drug use[81] and HIV infection.[87,184] Chronic liver disease is also a recognised complication of drug use[81,86,185] with, in the case of hepatitis C, a synergistic effect with HIV infection.[132] Therefore of the 34 deaths, 19 were due to AIDS, one to meningoencephalitis, two to liver disease and 12 were principally due to the effects of drug use.

Was there an increase in non-AIDS deaths due to the impact of HIV? This phenomenon has been seen in some other countries. In Italy the mortality rate for non-AIDS related deaths was 1.7/100 person years for HIV seropositives compared with a rate of 0.8/100 person years for seronegatives.[186] Deaths from overdose and endocarditis were higher in these HIV seropositives than in the seronegatives. In this Edinburgh study there was a rise throughout the years studied for both AIDS and non AIDS deaths.

For AIDS deaths, after one death at the end of 1984, there were two deaths in the first year of the study (1986), two in the second, six in the third and eight in the final year. For non-AIDS deaths there was a virtually parallel rise at one death in the first year, four in the second, four in the third and six in the final year. These figures might suggest a rise in non-AIDS related deaths but it is probable that deaths due to overdose in IDUs in the early years of the study were in IDUs who had not been HIV tested either ante or post mortem. There is therefore a likely underestimate of deaths due to overdose in HIV positive patients in the early part of the study period. This underestimate would not have occurred in the later years because a policy of HIV screening all sudden deaths in patients with a history of drug use was instituted in Edinburgh in 1987.[187] None of the patients in this study were identified by this method - all IDUs had been known to be HIV positive before death.

The annual expected mortality for all causes in IDUs in the UK before the advent of HIV infection was calculated at 18.4/1000 in 1980.[84] This figure is taken from a study of deaths of notified drug addicts in the UK from 1967-81. Although this study included deaths from all causes (the causes were not specified but drugs were specifically implicated in 74%) it was a study of notified drug addicts and is therefore likely to be an underestimate of the true IDU related mortality. This study also showed a fall in mortality in drug addicts when compared with earlier studies, due to the decreased availability of barbiturates,[83] and that the mortality figures for the UK were much higher than for the US. Other estimates of the mortality in IDUs in the immediate pre AIDS era are of 13.3/1000 in 1984 in New York, half of these deaths being due to cirrhosis, overdose and trauma.[85] By November 1989, 319 HIV positive IDUs had attended the City Hospital clinic. Fourteen deaths in this cohort due to overdose and liver disease gives a death rate in this cohort of 43/1000 over the four year period, an annual death rate of 10.75/1000. If one assumes that 14 deaths over four years is the death rate of the estimated

1000 HIV positive IDUs in Edinburgh[104] then the annual death rate due to overdose and liver disease drops to 3.5/1000. These figures, although crude, suggest that the deaths due to overdose and liver disease in this study are those expected as the results of IDU and are not increased. This is in keeping with other studies where, although there is an excess of deaths in IDUs due to overdose, trauma and liver disease, the mortality due to these diseases has remained stable since the advent of HIV infection.[85,87]

What this Edinburgh study has not shown is a rise in non-AIDS mortality not specifically related to drug use. Studies from the US have shown a marked increase in deaths due to septicaemia, pneumonia, tuberculosis, endocarditis and suicide in HIV positive patients.[85,87,135,188] Studies from the UK of death entries at the Office of Population Censuses and Surveys have also suggested by inference that this is the case in the UK.[189] A substantial increase in deaths in HIV positive haemophiliacs without AIDS (including from pneumonia, cirrhosis, poisoning, suicide and drug abuse) has been shown in the UK study of haemophiliacs.[129] Whilst the Edinburgh deaths due to overdose could be ascribed to suicide there was absolutely no evidence to suggest that they were suicidal in nature. No deaths were due to endocarditis or tuberculosis. Although the final cause of death in some of the AIDS patients was ascribed to pneumonia, as were four of the overdose deaths, no deaths were recorded due to septicaemia or pneumonia in HIV positive patients without AIDS who did not have a likely underlying overdose. This seems in direct contrast to the marked morbidity found in the admissions study due to chest and other bacterial infections which concurs with US data.[85] This phenomenon of increasing morbidity without a rise in non-AIDS mortality has been described among IDUs in Amsterdam.[97] The authors of this paper suggest that the reason for this is the easy access to medical care and consequent early detection and treatment of bacterial pneumonias in Amsterdam. Access to medical care in Edinburgh is very similar to that in Amsterdam and the Amsterdam explanation is probably very relevant to the

Edinburgh findings. More UK data on deaths in HIV positive patients without AIDS should be available from the confidential reporting system which, since mid-1989 has asked doctors to report deaths in HIV positive patients without AIDS.[190]

This study has shown the importance of post mortem examinations in HIV positive patients. Clearly post mortems are important in patients dying of AIDS and will usually show multiple, often unexpected pathology. But post mortem studies are less often carried out in HIV infected patients who have not progressed to AIDS. In this study one IDU who was thought likely to have died of overdose was found to have a florid meningoencephalitis, a previously undiagnosed hepatoma was found post mortem and one patient who probably did die of an overdose was also found to have a post viral pneumonitis. In addition lymphadenopathy and splenomegaly were found. Post mortem studies are essential for a full description of the early natural history of HIV infection. In a German series of 53 post mortems in IDUs who died from drug related causes (20% were HIV positive), hepatitis was found in 40%, foreign body granulomas in 30% and myocarditis in 18%.[191] Although most of the patients whose death was ascribed to overdose in this study probably did overdose, this is not always the case. In a later case report from Edinburgh an HIV positive drug user was found dead in a room in which were discovered tablets of dihydrocodeine and amitryptiline.[192] She had had past episodes of drug overdose which was the suspected cause of death. However post mortem revealed a severe desquamative interstitial pneumonitis and HIV encephalitis, and toxicological screen was negative. The points made in Jones' Edinburgh paper[192] were that the sudden onset of illness (such as HIV encephalitis or a chest infection) might alter the tolerance of IDUs to their usual dose of prescribed or recreational drugs.

The brain was not examined in any of the patients with sudden non-AIDS related death except in the patient who turned out to have meningoencephalitis. It is clearly important to do this to assess whether

cerebral disease was a causative factor in the patient's death and to describe the early features of HIV related brain disease. This has since been done in Edinburgh.[187] Histological examination with polymerase chain reaction for HIV of the brain was done in 23 IDUs who died suddenly some years after seroconversion but while still in the presymptomatic stages of infection. The findings were that significant HIV infection of the brain does not occur in the presymptomatic stages of infection and that invasion of the central nervous system may be delayed until the transition to symptomatic AIDS. This is in contrast to an earlier similar study from Germany which suggested that invasion of the central nervous system was an early feature.[193]

So that full and relevant information can be sought at post mortem, HIV infection has to be recognised ante mortem. In Scotland 8.5% of all deaths come to medico-legal necropsy.[194] HIV testing of sudden or drug related deaths has been instituted in many centres.[187,194,195] This is primarily for epidemiological assessment of HIV seroprevalence in that community. Much more use could be made of this if more detailed post mortems were carried out. In one study from Dundee routine post mortem HIV serology was instituted on deaths selected for medico-legal examination.[194] If the patient was found to be seropositive, a post mortem was not carried out "except for compelling legal reasons".

In the AIDS patients, post mortem studies revealed additional multiple pathology to that diagnosed ante mortem. In particular, previously undiagnosed CMV disease was revealed in three patients and disseminated mycobacteriosis in two. Treatment of these infections would have been unlikely to have prolonged life or achieved symptomatic benefit, but the knowledge of their local prevalence would increase physicians' awareness when treating other patients. Neither the patient whose AIDS defining diagnosis was CMV encephalitis, nor the two patients who developed CMV retinitis had post mortems.

Survival differences in AIDS patients have been clearly linked to the initial AIDS defining diagnosis and some studies have found this to be the most important factor determining survival.[100,101] Age, sex and year of diagnosis of AIDS are also important predictors of survival.[25,100,101,196] Unfortunately the numbers in this Edinburgh study are too small to make any meaningful comparisons on survival with reference to AIDS defining diagnosis, year of AIDS diagnosis, sex, risk factor or age.

As patients are living longer and are less likely to die of their AIDS defining illnesses, they are developing and are dying of different and multiple diseases, many of which are refractory to current treatments.[196] In this study, three patients died with lymphoma, three with disseminated mycobacteriosis and six with probable disseminated CMV infection. It is important to have continuing surveillance on the prevalence of different AIDS related diseases as well as on AIDS defining diseases, and post mortem studies are one way of doing this. Eight five percent of AIDS patients die in hospital (although this figure may change with better community care) so higher post mortem rates should be achievable.[197] Clinicians caring for HIV positive patients should make every effort to obtain permission for post mortem examinations and should liaise closely with pathologists to ensure that all relevant information is obtained.

Table 5.1

AIDS defining diagnosis, survival time and cause of death in 19 patients

AIDS defining diagnosis	AIDS survival time	Cause of death
PCP	16 months	Disseminated mycobacteriosis + CMV
PCP	29 months	CMV
PCP	20 months	Toxoplasmosis + CMV
PCP	7 days	PCP + CMV pneumonitis
PCP	4 months	PCP
PCP	2 months	Toxoplasmosis
PCP + lymphoma	2 days	PCP + lymphoma
PCP + KS	18 months	KS
KS	11 months	KS
KS	15 months	KS + mycobacteriosis
KS	14 months	KS
KS + toxoplasmosis	8 months	KS + toxoplasmosis + CMV + mycobacteriosis
Toxoplasmosis	5 months	Cerebral lymphoma
Toxoplasmosis	1 month	Toxoplasmosis
Oesophageal candida	19 months	Disseminated mycobacteriosis
Oesophageal candida	45 months	Lymphoma
CMV encephalitis	11 months	CMV
AIDS dementia	3 months	AIDS dementia
Cryptococcal meningitis	2 months	PCP + lymphoma + cryptococcosis

Table 5.2

Ante mortem and post mortem causes of death in nine AIDS patients

Ante mortem	**Post mortem**
AIDS dementia + bronchopneumonia	AIDS dementia Bilateral bronchopneumonia
Atypical mycobacteriosis	*Mycobacterium avium* pneumonia Adrenocortical haemorrhage Micronodular cirrhosis Early HIV encephalitis
Cerebral lymphoma	Cerebral lymphoma Bronchopneumonia Prostatitis Splenomegaly
Viral encephalitis	Cerebral toxoplasmosis Bronchopneumonia
Cerebral toxoplasmosis	Cerebral toxoplasmosis Pulmonary microabscesses Disseminated CMV Disseminated mycobacteriosis Cutaneous KS
KS + bronchopneumonia	KS Rectal mycobacteriosis
Cerebral toxoplasmosis + bronchopneumonia	Cerebral toxoplasmosis Bronchopneumonia Disseminated CMV
PCP	PCP Cerebral lymphoma Leucoencephalopathy
PCP	PCP CMV pneumonitis

Table 5.3

Post mortem results in seven patients in whom death was thought to be due to overdose

Presumed cause of death	**Post mortem result**
Overdose	Temazepam + alcohol in post mortem blood Aspiration pneumonia Generalised lymphadenopathy
Overdose	Aspiration pneumonia
Overdose	Temazepam in post mortem blood
Overdose	Acute pulmonary oedema Aspiration pneumonia Splenomegaly Lymphadenopathy
? Overdose ? Head injury	Florid meningoencephalitis Marked cerebral oedema
Overdose Bronchopneumonia	Morphine in post mortem blood Bilateral confluent bronchopneumonia Post viral pneumonitis Septicaemia Generalised lymphadenopathy
Respiratory arrest ? Overdose	Acute pulmonary oedema Post mortem drugs screen negative Splenomegaly

CHAPTER SIX

DISCUSSION

The study of Edinburgh hospital admissions and of deaths in a cohort of HIV positive patients over a four year period must be one of the most comprehensive studies of morbidity, hospital use and mortality within the early years of an HIV epidemic. Apart from obstetrics, all hospital admissions in one city were studied, and different methods of case finding were used. It is therefore a complete record for the 409 patients attending the City Hospital out patient clinic and can be extrapolated to represent the 1000 drug users estimated to have been HIV infected in Edinburgh at that time. It is not confined to one hospital, one diagnostic category, one risk group nor one sex. It provides a complete picture of the early phase of an epidemic. The results have been used for planning resources within the city of Edinburgh and can used by other cities who are assessing health service resources required for an HIV epidemic. The results show that planning for AIDS related admissions five to ten years after the introduction of HIV infection into a population is not appropriate, and that extra resources are needed at all stages, particularly in a population of HIV infected IDUs, because of the early rise in morbidity and mortality.

Had the City Hospital admissions alone been studied, not only would details have been missed on 30% of the total admissions but the disease spectrum would have seemed very different. It would have been skewed towards admissions in patients with symptomatic disease and admissions for BCIs. None of the gynaecological admissions and only a very small proportion of the drug related and psychiatric admissions would have been analysed. Very few of these admissions were in homosexual men or AIDS patients. Therefore the early natural history of HIV disease in women, heterosexuals and IDUs and the large number of admissions in patients with CDC stage 2 and 3 disease would not have been so accurately documented. Also, a larger number of psychiatric admissions might have expected in this community, whereas only 38 occurred.

This thesis did not include obstetric admissions. The nature of these admissions is quite different from any medical, surgical or psychiatric admissions and they have already been extensively described.[198] No admissions outwith Edinburgh were analysed. Most of the admissions among the IDUs and heterosexual patients were likely to have occurred within Edinburgh since these patients are known to belong to a socially stable group.[199] A minority of the homosexual men attended for medical care in other cities before or after attending in Edinburgh. It was not necessary to study these admissions to provide a picture of the services used in Edinburgh.

There was a change in the disease spectrum over the years studied so that by the end of the study, although only six years after the introduction of HIV into the Edinburgh IDU community, more IDUs (and patients from all risk groups) were developing symptomatic disease and more admissions were AIDS related. By 1989 this was arguably no longer the "early natural history of HIV infection". But the advantage of studying up until 1990 was that it gave a clear picture of admissions within the first four years of the introduction of the City Hospital clinic and within the first six years of the Edinburgh epidemic. Even in late 1989 many of the admissions were in patients without CDC stage 4 disease. It also documents the changing face of an epidemic with the consequent change in services required.

Comparisons of different risk groups can give rise to criticism of this thesis. The nature of the patients from different risk groups are not directly comparable. The homosexual men are, as a group, older and the heterosexual patients younger than the IDUs. Older age is one of the most important cofactors for progression of HIV disease,[100,200,201] so progression of HIV in these Edinburgh patients from different risk groups cannot be directly compared. Furthermore, accurate dates of seroconversion are only known for the IDUs. Although the homosexual men as a group seroconverted earlier, and the heterosexual patients later than the IDUs, seroconversion

dates for these risk groups can only be surmised. Length of time since seroconversion and year of presentation with AIDS are also important predictors of survival.[14,18,24] But the primary aim of this thesis was not to investigate progression of, nor survival with, HIV infection. To have studied each risk group independently would not have produced a picture of the inpatient services required for a city with a large number of HIV infected patients, many of whom are at different stages of HIV disease and have differing needs for HIV care. Although comparisons are drawn between different risk groups, these are only with relation to different health care needs.

The thesis has obviously focused on IDUs because they are the largest group requiring medical and other care in Edinburgh. One of the most difficult problems facing the study was in assessing how much morbidity was due to the effects of HIV infection, how much was due to the effects of drug use per se and how much was additive. Unlike the US methadone maintenance programmes,[88,89] there was no clear comparison cohort of HIV negative IDUs. Many studies in Edinburgh are following up groups of IDUs regardless of HIV status.[93,116] But in these groups the IDUs who are not known to be HIV positive are not necessarily negative and may have chosen not to be HIV tested.[93] Projections of IDU-related HIV in Edinburgh would suggest that many of these IDUs are in fact HIV positive. Other IDUs in Edinburgh are therefore not a suitable comparison group. Additionally, no comprehensive data are available on admissions of these IDUs. There is no "flagging" system of these IDUs nor would a diagnosis of IDU always be recorded on discharge summaries and SMR-1 forms. Because of this problem, data were found on admissions in Edinburgh for BCIs from the immediate pre HIV era and from the first two years following the introduction of HIV into IDUs - when it was very unlikely that any admissions, even in patients already HIV positive, would be HIV related. This is the most suitable comparison group. Admissions for drug related

disease are compared with published data from Glasgow for the immediate pre HIV era (see below). A prospective study comparing HIV positive and negative IDUs in Edinburgh would be invaluable.

Most published studies on admissions and health care utilisation were not relevant to planning resources for IDUs and other HIV-infected patients in Edinburgh. This is not to say that comparisons between study groups are not valid, nor that this thesis is not applicable to any group out of Edinburgh. But comparisons are best drawn between similar groups of patients in similar health care environments. Most studies are from America where the health care system is quite different from that in the UK. This is borne out by numerous American studies which suggest inequalities within the American health care system such that women, IDUs and certain racial groups have more difficulty in accessing health care,[202] and that in-patient survival is better in hospitals more experienced in treating AIDS patients.[203] One major advantage of American studies is the large number of patients studied and the consequent validity of statistically significant results. CDC studied 43,000 admissions in 1988,[204] and 222,200 admissions from the National Hospital Discharge Survey between 1983 and 1988.[205] The 1987 US hospital AIDS survey reported on 14,145 patients, 22,088 admissions and 371,768 bed days. But the very size of these studies does limit detail.

Of necessity many studies on admissions have focused on bed utilisation and on costings of hospital services.[206] Widely different lengths of hospital stay for HIV positive patients have been reported (tables 6.1, 6.2). For 38 IDUs with AIDS in Brooklyn the annual number of admissions was 1.13, annual days in hospital was 38.5 and average length of stay was 34 days.[206] In Cleveland in 1987 and 1990 the average length of stay for a group of 50 homosexual AIDS patients was around 16 days.[207] In the Kaiser Permanente study, 863 Californian AIDS patients had a mean 40 lifetime inpatient days and 3.3 hospitalisations with average length of stay of 17 days in 1983, and 11 days in 1987.[208] The 1987 US hospital AIDS survey of 276 hospitals and

14,145 AIDS patients gave an average length of stay of 17 days.[204] Between 1984 and 1987 in San Francisco the average length of admission for an AIDS patient was 11.6 days.[209] From European data, mean lifetime bed use in AIDS patients in Geneva was 56 days in 2.4 admissions with an average length of stay of 22.5 days.[210] Johnson's 1985 study of 33 London AIDS patients gave a mean length of admission per AIDS patient of 17 days with a total of 50 hospital days whilst alive with AIDS.[211] In Dublin in 1987 the average length of stay for patients with CDC stage 2 or 3 disease was 8.5 days and 13.5 days for patients with stage 4 disease.[212] The average length of stay in Edinburgh was 9.6 days. This particularly low length of stay is due to a number of factors. Patients were included at all disease stages, all admissions (including overdose) were studied and there was a good system of out patient care, thereby relieving some burden from inpatient ward care. IDUs often lead such chaotic life styles that they tend to present in crisis. Community care and out patient services are often not able to accommodate this so that problems which might be resolved by earlier out patient attendance require admission in IDUs. Tailoring of out patient services to the needs of the local community is important and walk in and methadone clinics have been shown to reduce the number of crisis admissions in IDUs.[112,213-215] The availability of out patient services is therefore an important factor to take into account when assessing the literature on hospital admissions, and particularly when comparing European and US studies.[216]

Lengths of hospital stay have decreased since the early years of the epidemic,[204,208] partly due to physician familiarity and partly due to better out-patient, primary care and hospice services.[209,214] Despite this, lifetime bed days post AIDS may not have changed and may be a feature of longer life expectancy with more, albeit shorter, admissions.[208] A decrease in length of stay was clearly found in Edinburgh. Average length of stay in the City Hospital fell from 18.5 to 15.3 to 10.1 and then 10.8 days over the four years studied, while the length of admissions to the other hospitals (usually not

classically HIV related), stayed relatively stable. This fall in length of stay was despite a rising number and percentage of admissions in patients with symptomatic stage 4 disease and AIDS. Physician familiarity with HIV disease was an important factor but even more influential was the development of good out patient facilities and of home care support teams.[215] Out patient facilities which were "IDU friendly" decreased the percentage of admissions in IDUs over the years, the other factor being the decline in injecting in Edinburgh and admissions consequent to IDU.[93,115,116]

Some studies have found lengths of stay to vary between risk groups. In the US this may be due to different health care needs, and the longer admissions in IDUs have been related to housing problems.[206] No difference between risk groups was found in Geneva.[210] In Edinburgh there was a clear difference between risk groups with homosexual men having significantly longer admissions than any other risk group. This was partly because of the many short admissions for overdose by the IDUs and partly because most of the homosexual men were likely to have seroconverted some years before the IDUs and had more advanced disease.

Another problem when comparing admission studies is that most studies have focused on homosexual men,[208] and some studies have actively excluded women from analysis because of "marked differences in types and intensity of health care resource utilisation".[206]

That women were included in this Edinburgh study and that women comprised 39% of admissions is of epidemiological importance. The medical problems of HIV in women did not receive much attention until some years after the onset of the HIV epidemic. A flurry of studies in the late 1980s tried to redress this balance. These were mainly epidemiological studies, many of which suggested that the natural history of HIV infection showed much faster progression in women.[100,200] Of 5833 New York patients who developed AIDS before 1986 the poorest prognosis was found among

women.[101] Gender was an independent predictor of survival in this study (and only 9% of the study patients were women) but contributing factors were black race, that women did not present with KS and that more women than men had a zero survival (which accounted at that time for 11% of the cohort). There was concern that women presented with later stage disease,[217] had poorer access to medical care,[218] were less likely to be enrolled in clinical trials,[219] and received less zidovudine.[220] Physicians were less likely to consider an HIV related diagnosis in female patients.[221] In a study of gender difference in survival of 2,526 men and 544 women with first episode PCP, although analysis for gender alone revealed that women were not significantly more likely to die during the initial hospitalisation than men this was only when analysis was adjusted for the confounders of admission through the emergency room, not having private health insurance and receiving medical care in hospitals with less experience in treating PCP.[221] Women were significantly more likely to belong to all of these categories and were also more likely to be non-white. Women were also less likely to undergo bronchoscopy than men but were more likely to be intubated for respiratory failure suggesting that women with PCP may be treated less aggressively than men. Studies have since shown little difference in progression to AIDS and to death in women if adjustment is made for confounding factors.[201,222-225] The main confounders are underlying risk factor, ethnicity and socioeconomic status.[226]

An important indicator of survival is presenting illness at diagnosis of AIDS and this has implications for survival of women.[17,101] Women are less likely to present with KS, the most benign of the AIDS defining illnesses.[101,222,227] Women are more likely to present with oesophageal candidosis,[96,128,217,228] wasting syndrome,[217] and chronic muco-cutaneous herpes simplex.[96,217] Some studies have reported that women are also less likely to present with PCP.[228,229] Some recent studies have even suggested enhanced survival in women compared with men.[227] In the European study of 6578

patients diagnosed with AIDS before 1990, no significant difference in survival was found between men and women.[17]

This thesis has, almost uniquely, been able to compare very similar groups of men and women with HIV infection. Excluding the homosexual men, who as a group were on average older and more likely to be of a higher social class, the male and female IDUs came from very similar backgrounds. The heterosexual patients also came from very similar backgrounds since many of them had acquired their infection from Edinburgh IDUs.[230] The heterosexual group did differ, but only by route of infection, later date of seroconversion and younger age. By November 1989 only three heterosexually HIV infected African patients (two women and one man) had been admitted to Edinburgh hospitals. The rest of the patients were Caucasians with the same access to health care and, excluding the homosexual men, of the same social class. This makes this thesis very different from most American studies where women are more likely to be black or Hispanic and socio-economically disadvantaged. A study of women attending for out-patient follow-up in London hypothesised that women from sub-Saharan Africa may even have difficulty in accessing health care in the UK.[231] Some European studies have compared similar socioeconomic and racial groups of women and men but most of the patients are IDUs and comparison groups with heterosexuals are less valid. Although by November 1989 the numbers of progressions to AIDS and of deaths were too small in this study for valid statistical comparisons between men and women, different risk groups and different indicator diseases, further follow up of this cohort of 409 patients will be invaluable. Of the ten women who developed AIDS during the study, eight presented with PCP and two with oesophageal candidosis. One African heterosexual woman had KS (although this was not a reason for admission) and the 13 admissions for KS or lymphoma were all in homosexual men. Admissions among heterosexual women were significantly more likely to be for AIDS related conditions and,

since three of these four women (one was African) had acquired their infection from Edinburgh IDUs and had later dates of seroconversion, this would suggest faster progression among heterosexual women.

Studies of clinical disease in women have focused on AIDS defining diagnoses, the effect of pregnancy on progression and on women-specific diseases.[224,232,233] Edinburgh studies on pregnancy have shown a small increase in spontaneous abortion but otherwise no adverse effect on the outcome of the pregnancy in 50 seropositive women compared with 64 seronegative controls.[234] The same seropositive cohort has also been studied for progression to AIDS and, comparing women who became pregnant pre HIV seroconversion, women who became pregnant post HIV seroconversion and HIV positive women who had never been pregnant, found that intercurrent pregnancies did not affect progression.[235] Similar post AIDS survival has also been documented in Edinburgh among five women with AIDS who had been pregnant compared with 17 women who had not.[198]

Women-specific diseases reported in the literature are genital tract infections and malignancy. There is a significant association between HIV, cervical intraepithelial neoplasia (CIN) and cervical cancer. The summary odds ratio of five studies (of 628 women) on CIN indicated that the odds of HIV-infected women having CIN were five times that of matched HIV-negative women.[236] Cervical cancer is more rapidly invasive in HIV positive women.[232] Despite this, most women with HIV infection and cervical cancer are more likely to die of HIV related diseases than of cervical cancer. In Chu's study of 1157 death certificates in US women with any mention of HIV or AIDS, cervical cancer was listed as a cause of death in five.[237] But studies in this area are difficult to interpret because of confounding and because closer surveillance of HIV positive women may identify more pathology.[223] Pelvic inflammatory disease has also been studied, but to a lesser degree, and has been found to be more common in HIV positive women.[238] Chu's study reported that pelvic inflammatory disease was listed

as a certified cause of death in two HIV positive women.[237] A small study by Korn comparing 23 HIV-seropositive women with a control group of 108 sero-negative women admitted for pelvic inflammatory disease showed that the altered immune response in the HIV positive women affected their clinical presentation.[238] HIV positive women had significantly lower abdominal tenderness, lower white cell counts and required more surgical intervention and were less likely to have gonococcal infection.

In this thesis no women were admitted for cervical cancer and no deaths were due to this. The routine assessment of women attending the out-patient clinic included at least yearly cervical smears with colposcopy for any abnormalities. CIN is more likely to be an out-patient diagnosis but patients with cervical cancer would be admitted at some point in their illness and therefore the figure for cervical cancer is probably true. Pelvic inflammatory disease accounted for 26 admissions in ten women (and 100 days in hospital) and was a significantly more common reason for admission among heterosexual women. Many of the women may have been commercial sex workers and it is surprising that only 26 of 359 admissions in women should be for pelvic inflammatory disease and that, in general, these admissions should be short and uncomplicated. Gonococcus was cultured in two cases (8% of admissions) which is even lower than Korn's figure of 27%.

Few studies have assessed gender differences for other clinical presentations in HIV positive patients. A Rhode Island study of 200 women found recurrent vaginal candidiasis to be the most common initial manifestation of HIV infection (43 of 117 women) as well as the most frequently observed infection during the course of HIV infection, and bacterial pneumonia was the initial presentation in 15.[128] The authors comment that these sentinel diagnoses rarely prompted HIV testing, even if the patient had a history of IDU. Twenty patients died in this study including five from PCP, four from bacterial pneumonia, two from staphylococcal endocarditis, two from liver failure and one from sepsis of

unknown aetiology. Chu's study of causes of death due to HIV infection in US women identified that in addition to deaths related to "classical" HIV related conditions there was an increase in deaths due to chronic liver disease and cirrhosis, pneumonia, pulmonary tuberculosis and septicaemia.[237] From the US National Hospital Discharge Survey analysis of HIV related admissions, women were more often admitted with non-AIDS related illness than AIDS and were more likely to be admitted than men with non-opportunistic infections.[205]

This thesis differs importantly from other studies of women in that it examines all clinical presentations in women, not just diseases specific to women or AIDS defining diagnoses. Women-specific diseases (pelvic inflammatory disease, pregnancy, termination of pregnancy and other gynaecological conditions) accounted for only 56 of the 359 admissions by women in this study. The most common clinical presentation among this group (among both men and women) was with bacterial infection. Urinary tract infections were a more common reason for admission among women than men (11 women, two men) and appeared to be complicated in that the average length of admission was five days. It is interesting that published studies on urinary tract infections in HIV positive patients have focused on men.[142,143,179] Women were over-represented among admissions for bacterial chest infections but the difference did not reach statistical significance. Admissions for detoxification, overdose and investigation of fits, headaches and drop attacks were also more common amongst women.

This thesis has focused on another group, which like HIV infected women, has not been the subject of enough research attention - namely HIV infected patients without AIDS. Most published studies have only reported on AIDS patients.[204,208] Data are easier to obtain on AIDS patients but to focus solely on AIDS patients vastly understimates the total resources needed for HIV care. Forty percent of admissions to the Edinburgh City Hospital, accounting for 2586 bed days, were in patients with CDC disease stage 2 or

3. Some studies have described admissions in HIV infected patients without AIDS,[89] but few have described admissions in patients without "symptomatic disease". Since most of the admissions to the other Edinburgh hospitals were likely to have been in patients with "asymptomatic" HIV infection (only six AIDS exclusive diagnoses were recorded in the other hospitals) it is likely that over 50% of all Edinburgh admissions were in patients with asymptomatic disease. Clearly there were also many asymptomatic patients who did not require admission - both those already attending the clinic who were not admitted and those already infected who had not yet attended the clinic or learned of their HIV positivity. If the admissions in asymptomatic patients are extrapolated to represent all Edinburgh asymptomatic HIV positive patients then a figure of 20% may be more representative of the whole city. Although many of the admissions would have occurred regardless of the HIV status of the patient it is likely that there was a real rise in the number of IDUs admitted with overdoses and other conditions directly attributable to drug use. There was also a real increase in admissions due to bacterial infection in asymptomatic patients. HIV positive IDUs suffered an eight fold increase in the incidence of bacterial chest infections compared with figures in IDUs immediately before the Edinburgh epidemic. That these IDUs with BCIs required hospital admission (i.e. admissions were not due to increased hospital referral as a result of known HIV status) is shown by the long average hospital stay of ten days. Of all admissions to the City Hospital with bacterial infections, 62% were in patients who had not progressed to CDC stage 4 disease. The average length of admission was longer for the asymptomatic patients (12.9 days) compared with the symptomatic patients (10.7 days). Correlated with the analysis of admissions by CDC stage is the analysis by CD4 count. Eighteen percent of admissions to the City hospital were in patients with a CD4 count above 500 cells/mm^3 and 48% were in patients with a CD4 count above 200 cells/mm^3.

But the data from AIDS patients in this study must not be ignored. Thirty two percent of admissions were in patients with AIDS and 60% in patients with CDC stage 4 disease. These admissions were more common in homosexual men and in the last year of the study accounted for a larger percentage of bed days. PCP was the commonest AIDS defining diagnosis (in all risk groups) and principal diagnoses of KS and lymphoma were only found in the homosexual men. Nineteen patients died of AIDS, 17 of whom had died within two years of their diagnosis. Post mortem studies on nine patients revealed multiple pathology with unexpected findings in eight cases.

The AIDS related diagnoses highlight the main differences in clinical presentation between risk groups. Homosexual men were more likely to be admitted with AIDS and less likely to suffer bacterial infections. Heterosexual patients were also more likely to have AIDS and were also the group which suffered most episodes of pelvic inflammatory disease. IDUs were less likely to be admitted with AIDS and more likely to be admitted with chest infections, overdose and drug related conditions. Of the 34 deaths studied, all 15 which were not due to AIDS were in IDUs. Two were due to chronic liver disease, one to acute meningoencephalitis and 12 were likely to be due to drug use. Post mortem studies were particularly important in this group of patients to document the early natural history of HIV infection. Meningoencephalitis, hepatoma and pneumonitis were all diagnoses which were not suspected clinically ante mortem.

Some published studies have examined the whole spectrum of HIV related illnesses. One such is Rosenblum's study of 222,200 hospitalisations from the US National Hospital Discharge Survey.[205] Admissions were AIDS related in 69%, and 90% admissions were in men. Women were less likely to have an AIDS defining illness. For the AIDS related admissions 30% were for PCP, 20% for candidosis and 13% for KS although the proportion of admissions for PCP and KS declined from 34% to 28% and from 13% to 9% respectively over the five year period. Among non AIDS related

illnesses, infections accounted for 39% and drug abuse for 9%. Infections were more common among women, blacks and younger patients, most (28%) were bacterial and most (25%) were pneumonia. "Sepsis" accounted for 17%, enteritis for 16% and urinary tract infections for 8% of the infectious disease admissions. In another analysis of the US National Hospital Discharge Survey, HIV-infected patients had an average of 3.6 diagnoses in addition to their HIV diagnosis.[239] In the 1988 CDC survey of 43,000 admissions, patients with HIV related diagnoses other than AIDS accounted for one third of all HIV-related admissions and slightly less than one third of the hospital days.[240] The ALIVE study recruited 1881 Baltimore IDUs and estimated that the presence of two or more AIDS-related symptoms had the strongest influence on the use of both inpatient and outpatient health care services.[103] Neither HIV positive serostatus alone nor low CD4 counts in the absence of symptoms were associated with increased health service utilisation (i.e. asymptomatic HIV positive IDUs were no more likely to use services than their HIV negative counterparts). However even among individuals with symptoms, the absence of health insurance was associated with a lower probability of receiving inpatient treatment.

UK studies should be more comparable with the data from Edinburgh because of the same health care system. But most UK studies are from London where most patients are homosexual men and any women and heterosexually infected patients are likely to be African,[241,242] and most focus on AIDS patients.[211,242] In a study of admissions to a London hospital between 1983 and 1988, 84 men, 71 of whom had AIDS, accounted for 371 admissions.[241] Over two thirds of admissions were day cases and blood transfusions accounted for 43% of all admissions. Blood transfusions decreased by 25% in a follow-up study.[242,243] Median length of admission for AIDS patients, excluding day cases was 8.5 days. Pulmonary infections (37 due to PCP, nine due to pyogenic infections) accounted for 12% of all admissions. The follow-up study assessed 1541 admissions in 338 AIDS

patients and 121 HIV positive patients without AIDS.[243] Between 1983 and 1989 the number of day case admissions increased while the number of planned admissions decreased. This paper did not report on admission diagnoses. Admission diagnoses were recorded in a 1988 study from another London hospital.[127] Of the 221 admissions, blood transfusion accounted for 47, gastro-intestinal investigations for 24, AIDS related pneumonias for 20 (with an average length of stay of 15.4 days), terminal care for ten and social reasons for eight. The 20 patients admitted with pneumonia required the largest proportion of bed days (310). Approximately half of all the medical admissions stayed for less than a week.

Only two UK studies have been reported from outside London. One from Newcastle was an elaborate costing study of 24 patients.[244] The other from Oxford describes a predominantly haemophiliac cohort of 83 patients between 1986 and 1990.[245] Of the 2,446 days spent in hospital, 1,533 were by patients who did not have AIDS. The average length of hospital admission decreased from 16.8 days in 1986 to 8.6 days in 1989 although there was no significant difference in the median length of stay. Although this study did not include discharge diagnoses, the causes of death in 28 patients is documented. Eighteen deaths were due to AIDS, three to septicaemia, one each to bronchitis, suicide, lung cancer and a wasting disease and the cause was unknown for three.

Edinburgh studies are perhaps more comparable with studies from Ireland and Italy. In both countries the predominant mode of transmission is via IDU and both have a universal health care system.

Of 644 Italian AIDS patients, those diagnosed before 1986 spent about half of their life span in hospital compared with patients diagnosed between 1987 and 1988 who spent a quarter of their life in hospital.[246] This was due to an increased life span (from seven to 12 months) rather than due to a

decrease in lifetime hospital days (which declined only slightly from 109 to 91 days).

A very comparable study to the study of admissions in Edinburgh was published from Dublin in 1991.[212] Over a four year period between 1987 and 1990, 179 patients were admitted 409 times to St James's hospital (table 6.3). IDUs accounted for 74% of admissions, 23% were homosexual, 3% were heterosexual and overall 73% were male. The annual number of admissions increased tenfold over the four year period. One hundred and forty five admissions were for patients with CDC disease stage 2 or 3 and 263 for patients with stage 4 disease. Mean lengths of stay were 8.5 and 13.5 days respectively. Bacterial pneumonia accounted for 21% admissions, PCP for 11%, cellulitis for 7%, chronic hepatic disease for 4%, tuberculosis for eight admissions, drug overdose or withdrawal for eight, urinary tract infection for five and seizures for four admissions. The high percentage of admissions in patients with early stage disease was mainly attributed to the effects of IDU (cellulitis, skin abscesses, endocarditis, hepatitis, drug overdose and opiate withdrawal). The lower mean length of stay when compared with other studies was ascribed to the large number of admissions due to bacterial chest infections. It is not clear from this paper whether St James's is the only hospital which would admit HIV positive patients in Dublin and whether this is fully representative of the whole spectrum of admissions by HIV positive patients in Dublin. It is possible that there is another psychiatric institution or poisons unit which would admit IDUs with primary drug related problems. If not, then eight admissions for overdose or withdrawal is a very small number compared with the Edinburgh study.

A study of Accident and Emergency (A & E) department attendances published by the same group suggested that there is a much larger spectrum of IDU related disease in Dublin.[213] Two hundred and sixty of 600 known HIV positive patients attended the A & E department of St James's Hospital between 1990 and 1992. There were 709 visits with a mean annual

attendance rate of 2.7, twice that for the general A & E population. Bacterial respiratory tract infection was the single most common reason for attending A & E and for admission to hospital. BCIs (37%) and AIDS defining illnesses (31%) accounted for over two-thirds of all admissions. Only 12% of admissions by IDUs were for problems attributable to IDU but nearly 30% of A & E attendances by IDUs were directly related to drug use. Eighteen percent of these patients had infective conditions (abscesses and cellulitis) related to the site of a recent injection. These figures are lower than those from a 1986 study of IDUs presenting to a Glasgow A & E department where, of 488 attendances, 50% were for "surgical conditions" (mainly abscesses, cellulitis and trauma but also including acute abdominal pain, gynaecological and dental problems) and 30% were for "psychiatric conditions", mainly alcoholic and narcotic intoxication.[247] But this, like other studies of A & E attendances and admissions by IDUs,[90,248] was largely before the HIV era and so the Glasgow and Dublin studies are not directly comparable.

The usefulness now of these studies is in the background incidence of admissions directly related to drug use. The immediate pre HIV era is the best period for studying this, unless clear distinctions are drawn between HIV positive and negative patients as in the studies from methadone maintenance clinics in New York.[89] This Edinburgh study was not able to compare admissions by HIV positive IDUs with HIV negative IDU controls. The incidence of BCIs were compared with figures from the general age matched population and from IDUs from the pre HIV era giving a markedly increased incidence of BCIs in HIV positive IDUs compared not only with the general population but also, by extrapolation, with HIV negative IDUs. Figures for admissions for drug related disease in Edinburgh for the pre HIV era or for HIV negative IDUs are not available. This is because most patients admitted with overdose are not IDUs.[248] It is difficult to tell whether the figure of 220 admissions over a four year period is in excess of what

would be expected. Certainly, only one admission was in a patient with AIDS. But more admissions might be expected in patients with early HIV disease because of the psychological effects of an HIV diagnosis and the "crisis" response of IDUs. Also, HIV positive IDUs who had repeated BCIs and abnormal pulmonary function tests might be more susceptible to the adverse respiratory effects of their usual quantities of recreational drugs.[192] On the other hand, the HIV epidemic in Edinburgh has been associated with a decrease in injection drug use, and the number of drug related admissions decreased remarkably over the four year period.[93,115,116] More patients may request detoxification on learning of their seropositivity. In the Glasgow study of admissions by IDUs over a five year period between 1980 and 1984, 39 admissions were for overdose, 14 for thrombophlebitis and deep venous thrombosis and 35 for abscess and cellulitis.[90] Since only one admission was recorded in the first year of the study it is reasonable to discount the first year and consider 122 admissions in four years. Denominator data are not available from this paper other than that the hospital serves a population of 240,000. At least 5,000 drug users were estimated to be in Glasgow at that time, although not evenly distributed about the city and the catchment population of IDUs for the hospital concerned might be almost the 2,000 IDUs estimated in Edinburgh.[104] The Edinburgh figures of 102 admissions for overdose and 49 for abscesses and cellulitis are therefore far in excess of this. There are clear differences in IDU behaviour between Glasgow and Edinburgh,[105,249] but these figures suggest that there are more drug related admissions in Edinburgh patients who are HIV infected compared with those who are not. The 220 admissions directly related to drug use made this category the commonest during the four year period. The figure of 220 does not even include those for fits and black outs which were likely to be drug related. These could have caused some diagnostic confusion and used considerable resources. Fits and blackouts in HIV positive patients would normally require CT or MRI scanning and a lumbar puncture to exclude the diagnoses of cerebral toxoplasmosis, lymphoma or cryptococcal meningitis.

Therefore health service resources in the face of HIV infected IDUs need to consider not only admissions for classic AIDS related conditions, for symptomatic HIV positive patients without AIDS and for bacterial infections which can occur at early stage HIV infection, but also an increase in admissions for what appear to be unrelated conditions such as injection related injuries, overdose, detoxification and fits and blackouts. These patients often require inpatient and outpatient counselling. Trauma in an HIV positive patient will require more resources because of different surgical techniques, additional theatre time and the greater likelihood of an HIV positive patient developing infectious and other complications. Despite the apparent increase in admissions due to overdose and other complications of IDU, the 12 deaths directly attributable to drug use are unlikely to represent an increase due to HIV.

Although admissions for drug related diseases were the commonest, most bed days occupied were for respiratory conditions. PCP was the commonest AIDS defining diagnosis and required the most bed days (1065 total days, average length of admission 23 days) but the most striking finding in this study was the high number of admissions for bacterial chest infections. Not only was the incidence of these infections much increased compared with the general population, but it was also increased in HIV positive IDUs compared with other risk groups and in HIV positive IDUs compared with presumed negative IDUs. These were infections which, even given an increase in incidence, might be thought to have responded to out patient treatment yet required admission with an average length of admission of ten days. Some of this admission time may have been because of diagnostic confusion with PCP and therefore the algorithm was drawn up for clinical use. Another striking finding was that despite the increase in incidence and morbidity associated with BCIs, there was no associated mortality. This is in direct contrast to US studies but in keeping with Amsterdam studies where early

diagnosis and treatment may the reason for the lower BCI related mortality.[87,97,250]

Chest infections accounted for 51% of all the admissions for bacterial infections. A total of 189 admissions for bacterial infections were recorded and these accounted for 21% of all admissions. Urinary tract infections and pelvic inflammatory disease were the other common sites for bacterial infections. Admissions amongst IDUs were significantly more likely to be for bacterial infections when compared with homosexual men and admissions by women to the City Hospital were significantly more likely to be for bacterial chest and genito-urinary infections. What was also striking about bacterial infections in this study was that 62% of these admissions were in patients who did not have CDC stage 4 disease. Despite the high number of admissions due to bacterial infections and the reports from other IDU studies of the high incidence of TB,[124,251] only one case of TB was recorded during this study. From the study of BCG records, the low UK prevalence of TB is the most likely reason for this difference with other cohorts.

Bacterial infections have long been recognised to be a complication of IDU.[99] In papers from the pre AIDS era on the medical complications of heroin abuse, tetanus, abscesses, endocarditis, pneumonia and septicaemia were often quoted as major reasons for increase in mortality and morbidity among drug addicts.[81,83,185] Endocarditis was primarily right-sided with consequent problems of septic pulmonary emboli and tricuspid incompetence.[144] Pneumonia presented with typical symptoms, the predominant organism was the pneumococcus and it usually responded quickly to penicillin. It was also recognised to be a common sub-clinical finding and was partly thought to be responsible (along with foreign particle emboli) for the alterations in pulmonary function seen in IDUs - the most common being reduced carbon monoxide diffusing capacity.[140,141] In a Scottish review of admissions by IDUs to a district general hospital,

abscesses accounted for over half of the surgical admissions, most commonly in the groin due to repeated injection into the femoral vein.[90] This increase in bacterial infections in IDUs is due to poor dental hygiene, poor tracheobronchial clearance of bacteria during periods of intoxification, decreased cell-mediated immunity as a result of IDU and repeated injections of unsterile drugs with dirty needles and syringes by people who are often carriers of *Staphylococcus aureus*.[91]

HIV clearly has an additional effect. Selwyn's prospective study of 144 HIV positive and 289 HIV negative IDUs enrolled in a methadone maintenance programme estimated a cumulative yearly incidence of pneumococcal pneumonia of 35 per 1000 for seropositives and 3.5 per 1000 for seronegatives compared with 2.6 per 1000 for the general US population.[89] Morbidity and mortality were both increased in the seropositive group in which two patients died and average length of hospital stay was 10.4 days compared with 6.1 days for the seronegatives. In another New York study of IDUs attending a MMP, the prevalence and incidence of tuberculous infection (as measured by positive PPD skin testing) were found to be similar for HIV positive and negative IDUs but the risk of active tuberculosis was increased only for the positive subjects.[88] Likewise, endocarditis seems to have a greater than expected mortality in HIV positive IDUs, is associated with a greater diversity of organisms, prolonged duration of fever, more persistent bacteraemia and a higher rate of embolic abscesses.[98,186,252]

An increased risk of bacterial infections has been documented in patients from all risk groups. In 1984 Simberkoff reported a 26 fold increase in incidence of pneumococcal pneumonia in 35 hospitalised homosexual AIDS patients compared with other patients in the same hospital.[253] A population based study from San Francisco, where most cases of HIV infection are in homosexual men, found a 100 fold increase in incidence of pneumococcal bacteraemia following the onset of the AIDS epidemic.[254] Of 294 patients

with pneumococcal bacteraemia in the age group 20 to 55, 75 (26%) were known to be HIV positive. In patients with pneumococcal bacteraemia and AIDS, 24 (75%) were bacteraemic during the six months before or after the diagnosis of AIDS. Seven (22%) of these patients had concomitant PCP and readmissions for pneumonia occurred in 16% of HIV positive patients. In a similar study from the Bronx, New York (where there is a greater proportion of IDUs), pneumonia hospitalisations are thought to be a sentinel indicator for HIV infection.[255] Indeed such is the association between invasive pneumococcal disease and HIV infection (tables 6.4, 6.5, 6.6) that pneumococcal surveillance is now being used in some areas as a surrogate marker to assess the size of the HIV infected population.[256] The excess in pneumococcal infection is due to impairment of humoral immunity related to functional B cell defects. Although HIV positive patients characteristically mount a hypergammaglobulinaemia, low IgG2 levels have been found in patients with pyogenic infections.[257,258] Antibody to polysaccharide (the major component of most bacterial cell walls) is predominantly of the IgG2 subclass and appears to be essential for adequate opsonisation of encapsulated organisms. Another manifestation of B cell dysfunction is the poor response to pneumococcal vaccination in patients with AIDS who mount low post vaccination titres and in whom clinical vaccine failure has been reported.[253,259,260] But patients may mount a reasonable response to pneumococcal vaccine in the early stages of HIV infection.[259]

In some series, including in this Edinburgh study, *Haemophilus influenzae* chest infections are more prevalent than pneumococcal BCIs.[89,261] Presenting symptoms of pneumonia are usually similar to those of the immunocompetent population but fever may be absent even in the presence of bacteraemia, the diagnosis may be confused with PCP or the two infections may occur concomitantly.[262-264] Because of the considerable mortality and morbidity associated with recurrent pneumonia this was included as an AIDS indicator diagnosis in the 1993 CDC AIDS

definition.[6,87,265] HIV infected patients also have an increased incidence of sinusitis, skin infections, gingivitis and periodontitis, pelvic inflammatory disease, prostatitis and urinary tract infections.[252]

Some bacterial infections are associated with the T cell immunodeficiency. These include salmonella species, *Cryptococcus neoformans*, *Listeria monocytogenes* and *Histoplasma capsulatum*.[252,266,267] Recurrent salmonella bacteraemia and cryptococcal meningitis are AIDS defining conditions.[4,5,6] In a study from Nairobi, Kenya of 506 consecutive hospital admissions, 19% of whom were HIV positive, *Salmonella typhimurium* was the most common cause of bacteraemia.[268] This contrasted with the HIV negative patients in whom *S. typhi* was a more common cause of bacteraemia. *S. typhimurium* isolates exceeded those of *S. typhi* in HIV positive patients by a factor of ten. Mortality was significantly higher in the HIV positive patients with salmonella bacteraemia, despite treatment with appropriate intravenous antibiotics.

Neutropenic patients are at particular risk of nosocomial staphylococcal and pseudomonal infections and these have a high mortality.[263,266,269] Patients with neutropenias, central venous lines, nosocomial infections and infections associated with T cell deficiencies are more likely to have advanced HIV disease and AIDS: these infections are unlikely to present within the early natural history of HIV infection.[269] It is the infections associated with functional B cell defects, predominantly bacterial chest infections and pneumonias, which may present early in the course of the disease.

The importance of documenting admissions for bacterial infections lies not only in knowledge of the natural history of HIV infection, nor simply in the planning of resources. It is because this knowledge can be used in clinical decision making. Patients with early stage disease are unlikely to be suffering from a classic opportunistic disease and therefore early diagnosis of a likely bacterial infection and treatment with an appropriate antibiotic,

usually as an outpatient, can be instituted. On review, further investigations and hospital admission need be considered only if the patient fails to respond to this initial treatment. And it leads on to the question of prophylaxis. Antibiotics can afford prophylaxis against bacterial infections and a decline in bacterial infections has been seen with the use of antibiotic prophylaxis for PCP when compared with pentamidine.[270] Immunisation can be offered against *Streptococcus pneumoniae* and *Haemophilus influenzae*. Despite reports of clinical failure of pneumococcal vaccine,[253] of poor B cell function and low antibody levels both pre and post vaccination,[271-273] immunisation clearly has a role to play. It is likely to have greatest efficacy when given to patients as early as possible in their HIV infection but even late stage patients can mount some response to some of the antigens.[259,260,275] Pneumococcal vaccine has now been recommended for all HIV positive patients by the UK Joint Committee on Vaccination and Immunisation.[276]

In conclusion, this thesis has demonstrated the value of a study of hospital admissions in determining the morbidity associated with HIV infection. Data on admissions are available in the UK and can be collated to give a picture of a city wide HIV epidemic. That IDUs, a group usually described as chaotic and difficult to access, can be followed up and a picture drawn of the spectrum of IDU associated HIV infection has been shown. The study of IDUs especially has highlighted the morbidity associated with bacterial infections and the morbidity and mortality associated with drug use combined with HIV infection. The most important results are of high morbidity and mortality even within the early years of an epidemic as demonstrated by many admissions in patients otherwise classified as having "asymptomatic" HIV infection. These results are vital for allocating health care resources and for improving the remaining life of those infected with this lethal virus.

Table 6.1

Reported studies of the average length of hospital admission in AIDS patients

Country	1983	1984	1985	1986	1987	1988	1989	1990
California (Chen[209])	17		11					
San Francisco (Quesenbery[208])				11.6				
US (Andrulis[204])					17			
US (Andrulis[240])						17		
Cleveland (Sharp[207])								16
Brooklyn (Bennett[206])								34
London (Johnson[211])				17.5				
Geneva (Vanhems[210])					22.5			
Oxford (O'Brien[245])				10	13	9	6	12

Table 6.2

Reported studies of the average length of hospital admission in HIV positive patients without AIDS

Country	1983	1984	1985	1986	1987	1988	1989	1990
US (Andrulis[240])						14		
Dublin (Murphy[212])					8.5 13.5			
Oxford (O'Brien[245])				17	10	8	9	12
Edinburgh				18	15	10	11	

Table 6.3

Reasons for hospital admission in Dublin[212] and Edinburgh HIV positive patients

	Dublin 1987-90	**Edinburgh City Hospital 1985-89**	**All Edinburgh hospitals 1985-89**
Number of admissions	408	612	910
CDC stage 2/3	145 (36%)	246 (40%)	
CDC stage 4	263 (64%)	365 (60%)	
BCI	84 (21%)	97 (16%)	100 (11%)
PCP	46 (11%)	48 (8%)	49 (5%)
Cellulitis/abscess	27 (7%)	29 (5%)	49 (5%)
Bacterial endocarditis	8 (2%)	6 (1%)	6 (<1%)
Overdose/withdrawal	8 (2%)	31 (5%)	131 (1%)
Anaemia	24 (7%)	39 (6%)	39 (4%)
Chronic hepatitis	17 (4%)	11 (2%)	11 (1%)
Oesophageal candida	16 (4%)	6 (1%)	6 (<1%)
KS/lymphoma	19 (5%)		13 (1%)
Headaches	13 (3%)		8 (1%)
Tuberculosis	8 (2%)	2 (<1%)	2 (<1%)
Cerebral toxoplasmosis	8 (2%)		18 (2%)
Urinary tract infection	5 (1%)		13 (1%)
CMV retinitis	4 (1%)		5 (<1%)
Seizures	4 (1%)	11 (2%)	17 (2%)

Table 6.4

Published studies on the incidence of pneumococcal bacteraemia

Study period	Reference	Place	Population	Incidence pneumococcal bacteraemia
1/82-7/83	Selwyn[89]	New York	35 AIDS patients General medical patients	57/1000/year 3.5/1000/year
1/83-8/85	Witt[269]	Boston	59 AIDS/ARC pts Adult hospital patients	22.6/1000/year 2.67/1000/year
11/83-11/87	Redd[254]	San Francisco	San Francisco AIDS patients 3417 person years	9.4/1000/patient years
1986	Schuchat[256]	New Jersey	New Jersey AIDS patients age 25-44 only "pre AIDS" patients "pre AIDS" patients age 25-44 only General population General population age 25-44 only	11.2/1000/year 10.7/1000/year 4.5/1000/year 5.3/1000/year 0.176/1000/year 0.033/1000/year
1986-7 1974-6	Breiman[277]	South Carolina	All Charleston County residents (294,830)	0.187/1000/year 0.085/1000/year
1989	Winter[278]	Scotland	All 5m residents	0.0622/1000/year

Table 6.5

Published studies on the incidence of pneumococcal pneumonia

Study period	Reference	Place	Population	Incidence pneumococcal pneumonia
10/85-10/86	Selwyn[89]	New York	MMP IDUs 144 HIV+ve 289 HIV-ve	 35/1000/year 3.5/1000/year
1/80-4/85	Polsky[261]	New York	336 AIDS patients	17.9/1000/51 months
1/83-8/85	Witt[269]	Boston	59 AIDS/ARC patients	45.5/1000/year
1/88-4/90	Garcia-Leoni[279]	Madrid	HIV +ve General population	5.9/1000/?year 0.87/1000/?year
10/84-10/85	Woodhead[280]	Nottingham	General adult population (70,000)	1.2/1000/year

Table 6.6

Published studies on the incidence of bacterial pneumonia

Study period	Reference	Place	Population	Incidence bacterial pneumonia
10/85-10/86	Selwyn[89]	New York	MMP IDUs 144 HIV+ves 289 HIV-ves	 97/1000/year 21/1000/year
1/80-4/85	Polsky[261]	New York	336 AIDS pts	53.5/1000/51 months
11/85-11/89 1985-86 1985-86		Edinburgh	1000 HIV +ve IDUs 2000 IDUs pre HIV Edinburgh population aged 15-44	12/1000/year 1.4/1000/year 0.6/1000/year
10/84-10/85	Woodhead[280]	Nottingham	General adult population (70,000)	4.7/1000/year

REFERENCES

1. Department of Health. The Health of the Nation. A strategy for health in England. HMSO, 1992.

2. Centers for Disease Control. *Pneumocystis* pneumonia - Los Angeles. MMWR 1981;**30**:250-252.

3. Mann JN. AIDS-the second decade: a global perspective. J Infect Dis 1992;**165**:245-50.

4. Centers for Disease Control. Classification system for human T-lymphotropic virus type III/lymphadenopathy-associated virus infections. MMWR 1986;**35**:334-9.

5. Centers for Disease Control. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. MMWR 1987;**36**(suppl 1S):1S-15S.

6. Centers for Disease Control. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992;**41**(RR-17):1-19.

7. Lifson AR, Rutherford GW, Jaffe HW. The natural history of human immunodeficiency virus infection. J Infect Dis 1988;**158**:1360-7.

8. Lee CA, Webster A, Griffiths PD, Kernoff PBA. Symptomless HIV infection after more than ten years. Lancet 1990;**335**:425-6.

9. Learmont J, Tindall B, Evans L et al. Long-term symptomless HIV-1 infection in recipients of blood products from a single donor. Lancet 1992;**340**:863-67.

10. Moss AR, Bacchetti P. Natural history of HIV infection. AIDS 1989;**3**:55-61.

11. Lee CA, Phillips A, Elford J et al. The natural history of human immunodeficiency virus infection in a haemophiliac cohort. Br J Haematol 1989;**73**:228-234.

12. Cuthbert RJG, Ludlam CA, Tucker J et al. Five year prospective study of HIV infection in the Edinburgh haemophiliac cohort. BMJ 1990;**301**:956-61.

13. Phillips AN, Lee CA, Elford J et al. More rapid progression to AIDS in older HIV-infected people: the role of CD4 T-cell counts. J Acquir Immune Defic Syndr 1991;4:970-5.

14. Lee CA, Phillips AN, Elford J, Janossy G, Griffiths P, Kernoff P. Progression of HIV disease in a haemophiliac cohort followed for 11 years and the effect of treatment. BMJ 1991;**303**:1093-6.

15. Webster A, Lee CA, Cook DG et al. Cytomegalovirus infection and progression towards AIDS in haemophiliacs with human immunodeficiency virus infection. Lancet 1989;**ii**:63-6.

16. Webster A, Phillips AN, Lee CA, Janossy G, Kernoff PB, Griffiths PD. Cytomegalovirus (CMV) infection, CD4+ lymphocyte counts and the development of AIDS in HIV-1-infected haemophiliac patients. Clin Exp Immunol 1992;**88**:6-9.

17. Lundgren JD, Pederson C, Clumeck N et al. Survival differences in European patients with AIDS, 1979-1989. BMJ 1994;**308**:1068-73.

18. Whitmore-Overton SE, Tillett HE, Evans BG, Allardice GM. Improved survival from diagnosis of AIDS in adult cases in the United Kingdon and bias due to reporting delays. AIDS 1993;7:415-20.

19. Sabin C, Phillips A, Elford J, Griffiths P, Janossey G, Lee C. The progression of HIV disease in a haemophiliac cohort followed for 12 years. Br J Haematol 1993;**83**:330-3.

20. Simmonds P, Beatson D, Cuthbert RJG et al. Determinants of disease progression: six-year longitudinal study in the Edinburgh haemophilia/HIV cohort. Lancet 1991;**338**:1159-63.

21. Ward JW, Bush TJ, Perkins HA et al. The natural history of transfusion-associated infection with human immunodeficiency virus. N Engl J Med 1989;**321**:947-52.

22. Medley GF, Anderson RM, Cox DR, Billard L. Incubation period of AIDS in patients infected via blood transfusion. Nature 1987;**328**:719-721.

23. Aledort LM, Hilgartner MW, Pike MC et al. Variability in serial CD4 counts and relation to progression of HIV-1 infection to AIDS in haemophiliac patients. BMJ 1992;**304**:212-6.

24. Schinaia N, Ghirardini A, Chiarotti F, Gringeri A, Mannucci PM and the Italian Group. Progression to AIDS among Italian HIV-seropositive haemophiliacs. AIDS 1991;**5**:385-391.

25. Bindels PJ, Poos RMJ, Jong JT, Mulder JW, Jager HJC, Coutinho RA. Trends in mortality among AIDS patients in Amsterdam, 1982-1988.AIDS 1991;**5**:853-858.

26. Mariotto AB, Mariotti S, Pezzotti P, Rezza G, Verdecchia A. Estimation of the acquired immunodeficiency syndrome incubation period in intravenous drug users: a comparison with male homosexuals. Am J Epidemiol 1992;**135**:428-37.

27. Morris DJ. Cytomegalovirus infection and progression to AIDS. Lancet 1989;**ii**:335.

28. Barnass S, O'Toole C, Colvin B. Cytomegalovirus infection and progression to AIDS. Lancet 1989;**ii**:336.

29. Rugman FP, Mannion PT, Hay CRM, Bolton-Maggs P, Roberts D, Mutton KJ. Cytomegalovirus, serum B2-microglobulin, and progression to AIDS in HIV-seropositive haemophiliacs. Lancet 1989;ii:631.

30. Rutherford GW, Lifson AR, Hessol NA et al. Course of HIV-1 infection in a cohort of homosexual and bisexual men: an 11 year follow up study. BMJ 1990;**301**:1183-8.

31. Ronald PJM, Robertson JR, Elton RA. Continued drug use and other cofactors for progression to AIDS among injecting drug users. AIDS 1994;**8**:339-343.

32. Weber R, Ledergerber B, Opravil M, Siegenthaler W, Luthy R. Progression of HIV infection in misusers of injected drugs who stop injecting or follow a programme of maintenance treatment with methadone. BMJ 1990;**301**:1362-5.

33. Des Jarlais DC, Friedman SR, Marmor M et al. Development of AIDS, HIV seroconversion, and potential cofactors for T4 cell loss in a cohort of intravenous drug users. AIDS 1987;1:105-11.

34. Pederson C, Lindhart BO, Jensen BL et al. Clinical course of primary HIV infection: consequences for subsequent course of HIV infection. BMJ 1989;**299**:154-7.

35. Keet IPM, Krijnen P, Koot M et al. Predictors of rapid progression to AIDS in HIV-1 seroconverters. AIDS 1993;7 :51-57.

36. Kaslow RA, Phair JP, Friedman HB et al. Infection with the human immunodeficiency virus: clinical manifestations and their relationship to immune deficiency. Ann Int Med 1987;**107**:474-480.

37. Moss AR, Bacchetti P, Osmond D et al. Seropositivity for HIV and the development of AIDS or AIDS related condition: three year follow up of the San Francisco General Hospital cohort. BMJ 1988;**296**:745-750.

38. Moss AR. Predicting who will progress to AIDS. BMJ 1988;**297**: 1067-8.

39. Schechter MT, Craib KJP, Le TN et al. Propression to AIDS and predictors of AIDS in seroprevalent and seroincident cohorts of homosexual men. AIDS 1989;**3**:347-353.

40. Flegg PJ, Brettle RP, Robertson JR, Clarkson RC, Bird AG. ß2-microglobulin levels in drug users: the influence of risk behaviour. AIDS 1991;**5**:1021-1024.

41. Yarchoan R, Venzon DJ, Pluda JM et al. CD4 count and the risk for death in patients infected with HIV receiving antiretroviral therapy. Ann Intern Med 1991;**115**:184-9.

42. Jacobson MA, Bacchetti P, Kolokathis A et al. Surrogate markers for survival in patients with AIDS and AIDS related complex treated with zidovudine. BMJ 1991;**302**:73-8.

43. Ellenberg SS. Surrogate end points in clinical trials. BMJ 1991;**302**:63-4.

44. Phillips A, Lee CA, Elford J et al. Prediction of progression to AIDS by analysis of CD4 lymphocyte counts in a haemophiliac cohort. AIDS 1989;**3**:737-741.

45. Phillips AN, Lee CA, Elford J et al. Serial CD4 lymphocyte counts and development of AIDS. Lancet 1991;**337**:389-92.

46. CD4 Collaborative Group. Use of monitored CD4 cell counts: predictions of the AIDS epidemic in Scotland. AIDS 1992;6:213-222.

47. Girardi E, Antonucci G, Armignacco O, Salmaso S, Ippolito G and the Italian group for the study of tuberculosis and AIDS. Tuberculosis and AIDS: a retrospective, longitudinal, multicentre study of Italian AIDS patients. J Infect 1994;**28**:261-9.

48. Girard PM, Pocidalo JJ, Murray JF. Primary prophylaxis against common infectious diseases in persons with human immunodeficiency virus infection. Am Rev Respir Dis 1991;**143**:447-450.

49. Hopewell PC. Prevention of lung infections associated with human immunodeficiency virus infection. Thorax 1989;44:1038-1044.

50. Centers for Disease Control. Guidelines for prophylaxis against *Pneumocystis carinii* pneumonia for persons infected with human immunodeficiency virus. MMWR 1989;**38**(Suppl):1-9.

51. Volberding PA, Lagakos SW, Koch MA et al. Zidovudine in asymptomatic human immunodeficiency virus infection. N Engl J Med 1990;**322**:941-9.

52. Fischl MA, Richman DD, Grieco MH et al. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. N Engl J Med 1987;**317**:185-91.

53. Fischl MA, Richman DD, Hansen N et al. The safety and efficacy of zidovudine (AZT) in the treatment of subjects with mildly symptomatic human immunodeficiency virus type 1 (HIV) infection. Ann Int Med 1990;**112**:727-737.

54. Fischl MA, Parker CB, Pettinelli C et al. A randomized controlled trial of a reduced daily dose of zidovudine in patients with the acquired immunodeficiency syndrome. N Engl J Med 1990;**323**:1009-14.

55. Gazzard BG. When should asymptomatic patients with HIV infection be treated with zidovudine? BMJ 1992;**304**:456-7.

56. Swart AM, Weller I, Darbyshire JH. Early HIV infection: to treat or not to treat? BMJ 1990;**301**:825-6.

57. Concorde Coordinating Committee. Concorde:MRC/ANRS randomised double-blind controlled trial of immediate and deferred zidovudine in symptom-free HIV infection. Lancet 1994;**343**:871-81.

58. Richman DD, Fischl MA, Gricco MH et al. The toxicity of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. N Engl J Med 1987;**317**:192-7.

59. Daniels DG, McCormack SMG, McLean KA, Davies PTG, Lane RJM. Zidovudine-related myopathy. Lancet 1990;**ii**:1256.

60. Des Jarlais DC, Friedman SR, Novick DM et al. HIV-1 infection among intravenous drug users in Manhattan, New York City, from 1977 through 1987. JAMA 1989;**261**:1008-1012.

61. Friedman SR, Des Jarlais DC. HIV among drug injectors: the epidemic and the response. AIDS Care 1991;**3**:239-50.

62. Des Jarlais DC, Friedman SR, Choopanya K, Vanichseni S, Ward TP. International epidemiology of HIV and AIDS among injecting drug users. AIDS 1992;**6**:1053-1068.

63. Angarano G, Pastore G, Monno L, Santantonio T, Luchena N, Schiraldi O. Rapid spread of HTLV-III infection among drug addicts in Italy. Lancet 1985;**ii**:1302.

64. Robertson JR, Bucknall ABV, Welsby PD et al. Epidemic of AIDS related virus (HTLV-III/LAV) infection among intravenous drug abusers. BMJ 1986;**292**:527-529.

65. Follett EAC, McIntyre A, O'Donnell B, Clements GB, Desselberger U. HTLV-III antibody in drug abusers in the west of Scotland: the Edinburgh connection. Lancet 1986;**i**:446-7.

66. Webb G, Wells B, Morgan JR, McManus TJ. Epidemic of AIDS related virus infection among intravenous drug abusers. BMJ 1986;**292**:1202.

67. Marks JA. The north wind and the sun. Proceed RCPEd 1991;**21**:319-27.

68. Brettle RP. Epidemic of AIDS related virus infection among intravenous drug abusers. BMJ 1986;**292**:1671.

69. Marmor M, des Jarlais DC, Cohen H et al. Risk factors for infection with human immunodeficiency virus among intravenous drug abusers in New York City. AIDS 1987;**1**:39-44.

70. Schoenbaum ES, Hartel D, Selwyn PA et al. Risk factors for human immunodeficiency virus infection in intravenous drug users. N Engl J Med 1989;**321**:874-9.

71. Rezza G, Titti F, Tempesta E et al. Needle sharing and other behaviours related to HIV spread among intravenous drug users. AIDS 1989;**3**:247-8.

72. Rodrigo JM, Serra MA, Aguilar E, del Olmo JA, Gimeno V, Aparisi L. HTLV-III antibodies in drug addicts in Spain. Lancet 1985;**ii**:156-7.

73. Des Jarlais DC. The first and second decades of AIDS among injecting drug users. Br J Addiction 1992;**87**:347-353.

74. Brettle RP. HIV and harm reduction for injection drug users. AIDS 1991;**5**:125-136.

75. Buning EC, Coutinho RA, van Brussel GHA, van Santen GW, van Zadelhof AW. Preventing AIDS in drug addicts in Amsterdam. Lancet 1986;**i**:1435.

76. Engelsman EL. Drug misuse and the Dutch. BMJ 1991;**302**:484-5.

77. Cooper JR. Methadone treatment and acquired immunodeficiency syndrome. JAMA 1989;**262**:1664-1668.

78. Des Jarlais DC, Friedman SR. HIV infection among intravenous drug users: epidemiology and risk reduction. AIDS 1987;**1**:67-76.

79. van den Hoek JAR, van Haastrecht HJA, Coutinho RA. Risk reduction among intravenous drug users in Amsterdam under the influence of AIDS. Am J Public Health 1989;**79**:1355-1357.

80. Stimson GV, Alldritt L, Dolan K, Donoghoe M. Syringe exchange schemes for drug users in England and Scotland. BMJ 1988;**296**:1717-9.

81. Louria DB, Hensle T, Rose J. The major medical complications of heroin addiction. Ann Int Med 1967;**67**:1-22.

82. Cherubin CE. The medical sequelae of narcotic addiction. Ann Intern Med 1967;**67**:23-33.

83. Bewley TH, Ben-Arie O, James IP. Morbidity and mortality from heroin dependence. BMJ 1968;**i**:725-732.

84. Ghodse AH, Sheehan M, Taylor C, Edwards G. Deaths of drug addicts in the United Kingdom 1967-81. BMJ 1985;**290**:425-428.

85. Selwyn PA, Hartel D, Wasserman W, Drucker E. Impact of the AIDS epidemic on morbidity and mortality among intravenous drug users in a New York City methadone maintenance programme. Am J Public Health 1989;**79**:1358-1362.

86. Perucci CA, Davoli M, Rapiti E, Abeni DD, Forastiere F. Mortality of intravenous drug users in Rome: a cohort study. Am J Public Health 1991;**81**:1307-1310.

87. Stoneburner RL, des Jarlais DC, Benezra D et al. A larger spectrum of severe HIV-1 related disease in intravenous drug users in New York City. Science 1988;**242**:916-919.

88. Selwyn PA, Hartel D, Lewis VA et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N Engl J Med 1989;**320**:545-50.

89. Selwyn PA, Feingold AR, Hartel D et al. Increased risk of bacterial pneumonia in HIV-infected intravenous drug users without AIDS. AIDS 1988;**2**:267-272.

90. Horn EH, Henderson HR, Forrest JAH. Admissions of drug addicts to a general hospital: a retrospective study in the Northern District of Glasgow. Scot Med J 1987;**32**:41-5.

91. Scheidegger C, Zimmerli W. Infectious complications in drug addicts: seven-year review of 269 hospitalised narcotics abusers in Switzerland. Rev Infect Dis 1989;**11**:486-493.

92. Hudson MT, Edmonds M, Watkins PJ. Misuse of temazepam. BMJ 1991;**303**:993.

93. Skidmore CA, Robertson JR, Robertson AA, Elton RA. After the epidemic: follow up study of HIV seroprevalence and changing patterns of drug use. BMJ 1990;**300**:219-23.

94. Swadi H, Wells B, Power R. Misuse of dihydrocodeine tartrate (DF118) among opiate addicts. BMJ 1990;**300**:1313.

95. Robertson JR, Witcomb JC, Roberts JJK, Egan J. Misuse of dihydrocodeine tartrate (DF118) among opiate addicts. BMJ 1990;**301**:119.

96. Selik RM, Starcher T, Curran JW. Opportunistic diseases reported in AIDS patients: Frequencies, associations and trends. AIDS 1987;**1**:175-182.

97. Mientjes GH, van Amcijden EJ, van den Hoek AJAR, Coutinho RA. Increasing morbidity without rise in non-AIDS mortality among HIV-infected intravenous drug users in Amsterdam. AIDS 1992;**6**:207-212.

98. Nahass RG, Weinstein MP, Bartels J, Gocke DJ. Infective endocarditis in intravenous drug users: a comparison of human immunodeficiency virus type 1-negative and -positive patients. J Infect Dis 1990;**162**:967-970.

99. Brettle RP. Infection and injection drug use. J Infect 1992;**25**:121-131.

100. Friedland GH, Saltzman B, Vileno J, Freeman K, Schrager LK, Klein RS. Survival differences in patients with AIDS. J Acquir Immune Defic Syndr 1991;**4**:144-153.

101. Rothenberg R, Woelfel M, Stoneburner R, Milberg J, Parker R, Truman B. Survival with the acquired immunodeficiency syndrome. N Engl J Med 1987;**317**:1297-1302.

102. Zangerle R, Fuchs D, Reibnegger G, Fritsch P, Wachter H. Markers for disease progression in intravenous drug users infected with HIV-1. AIDS 1991;**5**:985-991.

103. Solomon L, Frank R, Vlahov D, Astemborski J. Utilisation of health services in a cohort of intravenous drug users with known HIV-1 serostatus. Am J Public Health 1991;**81**:1285-1290.

104. Haw S, Liddell D. Drug problems in Edinburgh district. Report of the SCODA (Standing Conference on Drug Abuse) Fieldwork Survey 1987. SCODA, 1-4 Hatton Place, London EC1N 8ND.

105. Green S, Willocks L, Leen C. The appearance of HIV among Edinburgh and Glasgow injecting drug users: why do the HIV dissemination patterns differ so much between the two cities? ANSWER 1991;**A188**:1-4.

106. Peutherer JF, Edmond E, Simmonds P, Dickson JD, Bath GE. HTLV-III antibodies in Edinburgh drug addicts. Lancet 1985;**ii**:1129-30.

107. Mortimer PP, Vandervelde EM, Jesson WJ, Pereira MS, Burkhardt F. HTLV-III antibody in Swiss and English intravenous drug abusers. Lancet 1985;**ii**:449-450.

108. Haw S. Drug problems in Greater Glasgow. SCODA (Standing Conference on Drug Abuse) Report 1985. SCODA, 1-4 Hatton Place, London EC1N 8ND.

109. Robertson JR, Bucknall ABV, Wiggins P. Regional variations in HIV antibody seropositivity in British intravenous drug users. Lancet 1986;**i**:1435-6.

110. Brettle RP, Davidson J, Davidson SJ et al. HTLV-III antibodies in an Edinburgh clinic. Lancet 1986;**i**:1099.

111. Brettle RP, Bisset K, Burns S et al. Human immunodeficiency virus and drug misuse: the Edinburgh experience. BMJ 1987;**295**:421-424.

112. Brettle RP, Gore SM, McNeil A. Outpatient medical care of injection drug use related HIV. Int J STD AIDS 1992;**3**:96-100.

113. Hague RA, Burns S, Mok J, Yap PL. Diagnosis of *Pneumocystis carinii* pneumonia from non-invasive sampling of respiratory secretions. Arch Dis Child 1990;**65**:1364-5.

114. Terragna A, Mazzarello G, Anselmo M, Canessa A, Ross E. Suicidal attempts with zidovudine. AIDS 1990;4:88.

115. Griffin S, Peters A, Reid M. Drug misusers in Lothian: changes in injecting habits 1988-90. BMJ 1993;**306**:693.

116. Peters AD, Reid M, Griffin SG. Edinburgh drug users: are they injecting and sharing less? AIDS 1994;**8**:521-8.

117. Scott RN, Woodburn KR, Reid DB et al. Intra-arterial temazepam. BMJ 1992;**304**:1630.

118. Adiseshiah M, Jones DA, Round JM. Intra-arterial temazepam. BMJ 1992;**304**:1630.

119. Fox R, Beeching NJ, Morrison C, Ruben S, Garvey T. Misuse of temazepam. BMJ 1992;**305**:253.

120. Launchbury AP, Drake J, Seager H. Misuse of temazepam. BMJ 1992;**305**:252-3.

121. Davidson C, Leach R, O'Doherty, et al. Non invasive management in the out patient department of fever and breathlessness in HIV positive patients. Sixth International Conference on AIDS, 1990.

122. Pitkin AD, Grant AD, Foley NM, Miller RF. Changing patterns of respiratory disease in HIV positive patients in a referral centre in the United Kingdom between 1986-7 and 1990-1. Thorax 1993;**48**:204-7.

123. MacFarlane JT, Finch RG, Ward MJ, MacRae AD. Hospital study of adult community-acquired pneumonia. Lancet 1982;**ii**:255-258.

124. Antonucci G, Girardi E, Armignacco O, Salmaso S, Ippolito G and the Gruppo Italiano di Studio Tubercolosi e AIDS. Tuberculosis in HIV-infected subjects in Italy: a multi-centre study. AIDS 1992;**6**:1007-13.

125. Watson JM. Tuberculosis in Britain today. BMJ 1993;**306**:221-2.

126. Citron KM. BCG vaccination against tuberculosis:international perspectives. BMJ 1993;**306**:222-3.

127. Singh S, Hawkins D, Connolly M, Gazzard B. Model of care for the hospital treatment of individuals with HIV infection. Health Trends 1991;**23**:55-9.

128. Carpenter CCJ, Mayer KH, Stein MD, Leibman BD, Fisher A, Fiore T.Human immunodeficiency virus infection in North American women: experience with 200 cases and a review of the literature. Medicine 1991;**70**:307-325.

129. Darby SC, Rizza CR, Doll R, Spooner RJD, Stratton IM, Thakrar B. Incidence of AIDS and excess of mortality associated with HIV in haemophiliacs in the United Kingdom: report on behalf of the directors of haemophilia centres in the United Kingdom. BMJ 1989;**298**:1064-8.

130. Ross HE, Glaser FB, Germanson T. The prevalence of psychiatric disorders in patients with alcohol and other drug problems. Arch Gen Psychiatry 1988;**45**:1023-31.

131. Gruer LD, Peedle M, Carrington D, Clements GB, Follett EA. Distribution of HIV and acute hepatitis B infection among drug injectors in Glasgow. Int J STD AIDS 1991;**2**:356-8.

132. Soriano V, Garcia-Samaniego J, Gutierrez M, Bravo R, Gonzalez-Lahoz J. High morbidity and mortality of chronic viral liver disease in HIV-infected individuals in Spain. J Infect 1994;**28**:100-1.

133. Puschel K. Drug-related death - an update. Forensic Sci Int 1993;**62**:121-8.

134. Baer JW. Study of 60 patients with AIDS or AIDS-related complex requiring psychiatric hospitalisation. Am J Psychiatry 1989;**146**:1285-88.

135. Marzuk PM, Tierney H, Tardiff K et al. Increased risk of suicide in persons with AIDS. JAMA 1988;**259**:1333-1337.

136. Batki SL. Drug abuse, psychiatric disorders, and AIDS - dual and triple diagnosis. West J Med 1990;**152**:547-552.

137. Holland JC, Tross S. The psychosocial and neuropsychiatric sequelae of the acquired immunodeficiency syndrome and related disorders. Ann Int Med 1985;**103**:760-764.

138. Perry S, Jacobsen P. Neuropsychiatric manifestations of AIDS-spectrum disorders. Hosp Community Psychiatry 1986;**37**:135-142.

139. Greenwood J. Creating a new drug service in Edinburgh. BMJ 1990;**300**:587-9.

140. Camargo G, Colp C. Pulmonary function studies in ex-heroin users. Chest 1975;**67**:331-334.

141. Overland ES, Nolan AJ, Hopewell PC. Alterations of pulmonary function in intravenous drug abusers. Am J Med 1980;**68**:231-237.

142. Pinho AMF, Maranconi DV, Moreira BM et al. Bacteriuria in patients with CDC group IV manifestations: A prospective study. AIDS 1991;**5**:342.

143. Hoepelman AIM, van Buren M, van den Broek J, Borleffs JCC. Bacteriuria in men infected with HIV-1 is related to their immune status (CD4+ cell count). AIDS 1992;6:179-184.

144. Hind CRK. Pulmonary complications of intravenous drug misuse. Infective and HIV related complications. Thorax 1990;**45**:957-961.

145. Murray JF, Felton CP, Hopewell PC et al. Pulmonary complications of the acquired immunodeficiency syndrome. N Engl J Med 1984;**310**:1682-8.

146. Miller RF, Leigh TR, Collins JV, Mitchell DM. Tests giving an aetiological diagnosis in pulmonary disease in patients infected with the human immunodeficiency virus. Thorax 1991;**45**:62-65.

147. Luce JM. Sputum induction in the acquired immunodeficiency syndrome. Am Rev Respir Dis 1986;**133**:513-514.

148. Bigby TD, Margolskee D, Curtis JL et al. The usefulness of induced sputum in the diagnosis of *Pneumocystis carinii* pneumonia in patients with the acquired immunodeficiency syndrome. Am Rev Respir Dis 1986;**133**:515-518.

149. Russell WC, Newman C, Williamson DH. A simple cytochemical technique for demonstration of DNA in cells infected with mycoplasmas and viruses. Nature 1975;**253**:461-462.

150. Gosey LL, Howard RM, Witebsky FG et al. Advantages of a modified toluidine blue O stain and bronchoalveolar lavage for the diagnosis of *Pneumocystis carinii* pneumonia. J Clin Micro 1985;**22**:803-807.

151. Miller RF, Kocjan G, Buckland J, Holton J, Malin A, Semple SJG. Sputum induction for the diagnosis of pulmonary disease in HIV positive patients. J Infect 1991;**23**:5-15.

152. Miller RF, Buckland J, Semple SJG. Arterial desaturation in HIV positive patients undergoing sputum induction. Thorax 1991;**46**:449-451.

153. Miller RF, Semple SJG, Kocjan G. Difficulties with sputum induction for diagnosis of *Pneumocystis carinii* pneumonia. Lancet 1991;i:112.

154. Nelson M, Bower M, Smith D, Gazzard BG. Life-threatening complication of sputum induction. Lancet 1990;**335**:112-113.

155. Pitchenik AE, Fertel D, Bloch AB. Mycobacterial disease: epidemiology, diagnosis, treatment and prevention. Clin Chest Med 1988;**9**:425-41.

156. de Cock KM, Selik RM, Soro B, Gayle H, Colebunders RL. AIDS surveillance in Africa: a reappraisal of case definitions. BMJ 1991;**303**:1185-8.

157. Greenberg AE, Thomas PA, Landesman SH et al. The spectrum of HIV-1 related disease among outpatients in New York City. AIDS 1992;**6**:849-859.

158. Mukadi Y, Perriens JH, St Louis ME et al. Spectrum of immunodeficiency in HIV-1 infected patients with pulmonary tuberculosis in Zaire. Lancet 1993;**342**:143-6.

159. Bisset C, Jones G, Davidson J et al. Mobility of injection drug users and transmission of HIV. Lancet 1989;ii:44.

160. Subcommittee of the Joint Tuberculosis Committee of the British Thoracic Society. Control and prevention of tuberculosis in Britain: an updated code of practice. BMJ 1990;**300**:995-9.

161. Conway SP. BCG vaccination in children. BMJ 1990;**301**:1059-60.

162. Joseph CA, Watson JM, Fern KJ. BCG immunisation in England and Wales: a survey of policy and practice in schoolchildren and neonates. BMJ 1992;**305**:495-8.

163. Spence DPS, Hotchkiss J, Williams CSD, Davies PDO. Tuberculosis and poverty. BMJ 1993;**307**:759-61.

164. Subcommittee of the Joint Tuberculosis Committee of the British Thoracic Society. Guidelines on the management of tuberculosis and HIV infection in the United Kingdom. BMJ 1992;**304**:1231-3.

165. Ramsden SS, Baur S, El Kabir DJ. Tuberculosis among the central London single homeless. J R Coll Physicians Lond 1988;**22**:16-17.

166. Watson JM. Tuberculosis in perspective. CDR 1991;**1**:R129-132.

167. Watson JM, Fern KJ, Porter JDH, Whitmore SE. Notifications of tuberculosis in England and Wales, 1982-1989. CDR 1991;**1**:R13-116.

168. Yates MD, Pozniak A, Grange JM. Isolation of mycobacteria from patients seropositive for the human immunodeficiency virus (HIV) in south east England: 1984-92. Thorax 1993;**48**:990-995.

169. Hayward C. Re-emergence of tuberculosis. BMJ 1993;**306**:515.

170. Springett VH, Watson JM. Re-emergence of tuberculosis. BMJ 1993;**306**:932.

171. Hart P d'A, Sutherland I. BCG and vole bacillus vaccines in the prevention of tuberculosis in adolescence and early adult life. BMJ 1977;**ii**:293-5.

172. Capewell S, France AJ, Uzel N, Leitch AG. The current value of tuberculin testing and BCG vaccination in school children. Br J Dis Chest 1986;**80**:254-264.

173. Fine PEM, Rodrigues L. Mycobacterial diseases. Lancet 1990;**335**:1016-20.

174. Watson JM, Gill ON. HIV infection and tuberculosis. BMJ 1990;**300**:63-4.

175. Theodore CM, Forster GE, Goh BT. Re-emergence of tuberculosis. BMJ 1993;**306**:514-5.

176. Armbruster C, Junker W, Vetter N, Jaksch G. Disseminated Bacille Calmette-Guerin infection in an AIDS patient 30 years after BCG vaccination. J Infect Dis 1990;**162**:1216.

177. Daley CL, Small PM, Schechter G et al. An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus. N Engl J Med 1992;**326**:231-5.

178. Kass EH, Savage W, Santamarina BAG. The significance of bacteriuria in preventative medicine. In: Kass EH, ed. Progress in pyelonephritis. Philadelphia: FA Davis, 1965:3.

179. Pinho AMF, Lopes GS, Ramos Filho CF et al. Urinary tract infection in men with AIDS. Genitourin Med 1994;**70**:30-34.

180. Riley A. HIV infection and certification of death. BMJ 1992;**305**:647.

181. Aldous J, Hickman M, Ellam A, Gazzard B, Hargreaves S. Impact of HIV infection on mortality in young men in a London health authority. BMJ 1992;**305**:219-221.

182. van Haastrecht HJA, van den Hoek AJAR, Coutinho RA. High mortality among HIV-infected injecting drug users without AIDS diagnosis: implications for HIV infection epidemic modellers? AIDS 1994;**8**:363-366.

183. Hind CRK. Pulmonary complications of intravenous drug misuse. Epidemiology and non-infective complications. Thorax 1990;**45**:891-898.

184. Selwyn PA. Injection drug use, mortality, and the AIDS epidemic. Am J Public Health 1991;**81**:1247-1249.

185. Cherubin CE. Infectious disease problems of narcotic addicts. Arch Intern Med 1971;**128**:309-313.

186. Zaccarelli M, Gattari P, Rezza G et al. Impact of HIV infection on non-AIDS mortality among Italian injecting drug users. AIDS 1994;**8**:345-350.

187. Bell JE, Busuttil A, Ironside JW et al. Human immunodeficiency virus and the brain: investigation of virus load and neuropathologic changes in pre-AIDS subjects. J Infect Dis 1993;**168**:818-24.

188. Buehler JW, Devine OJ, Berkelman RL, Chevarley FM. Impact of the human immunodeficiency virus epidemic on mortality trends in young men, United States. Am J Public Health 1990;**80**:1080-86.

189. McCormick A. Excess mortality associated with the HIV epidemic in England and Wales. BMJ 1991;**302**:1375-6.

190. Evans BG, Gill ON, Emslie JAN. Completeness of reporting of AIDS cases. BMJ 1991;**302**:1351-2.

191. Keul HG, Schafer V, Lorcher U, Schneider M, Lutz FU, Reuhl J. Preliminary results of an interdisciplinary survey of drug victims. Forensic Sci Int 1993;**62**:147-9.

192. Jones ME, Brettle RP, Busuttil A, Inglis MH, Bell JE, Willocks L. Sudden death in HIV-infected drug users. Presumptive overdose in an HIV-positive narcotic addict. J Infect 1993;**27**:79-81.

193. Gosztonyi G, Schmidt V, Nickel R et al. Neuropathologic analysis of postmortal brain samples of HIV-seropositive and -seronegative iv drug addicts. Forensic Sci Int 1993;**62**:101-5.

194. Sadler DW, Pounder DJ, Urquhart GED, Porter-Boveri M. Prevalence of HIV antibody in forensic cases. BMJ 1992;**304**:1027-8.

195. Puschel K, Lockemann U, Schneider V et al. HIV-1 prevalence among drug deaths in major cities of central and northern Europe. Forensic Sci Int 1992;**57**:57-62.

196. Peters BS, Beck EJ, Coleman DG et al. Changing disease patterns in patients with AIDS in a referral centre in the United Kingdom: the changing face of AIDS. BMJ 1991;**302**:203-7.

197. McCormick A. Unrecognised HIV related deaths. BMJ 1991;**302**:1365-7.

198. Johnstone FD, Willox L, Brettle RP. Survival time after AIDS in pregnancy. Br J Obstet Gynaecol 1992;**99**:633-636.

199. Chiswick A, Egan V, Brettle RP, Goodwin GM. The Edinburgh cohort of HIV-positive drug users: who are they and who cares for them? AIDS Care 1992;**4**:421-4.

200. Whyte BM, Swanson CE, Cooper DA. Survival of patients with the acquired immunodeficiency syndrome in Australia. Med J Aust 1989;**150**:358-362.

201. The Italian Seroconversion Study. Disease progression and early predictors of AIDS in HIV-seroconverted injecting drug users. AIDS 1992;**6**:421-6.

202. Fahs MC, Fulop G, Strain J et al. The inpatient AIDS unit: a preliminary empirical investigation of access, economic, and outcome issues. Am J Public Health 1992;**82**:576-578.

203. Stone VE, Seage GR, Hertz T, Epstein AM. The relation between hospital experience and mortality for patients with AIDS. JAMA 1992;**268**:2655-2661.

204. Andrulis DP, Weslowski VB, Gage LS. The 1987 US hospital AIDS survey. JAMA 1989;**262**:784-794.

205. Rosenblum LS, Buehler JW, Morgan M, Moien M. Increasing impact of HIV infection on hospitalizations in the United States, 1983-1988. J Acquir Immune Defic Syndr 1992;**5**:497-504.

206. Bennett CL, Pascal A, Cvitanic M, Graham V, Kitchens A, DeHovitz JA. Medical costs of intravenous drug users with AIDS in Brooklyn. J Acquir Immune Defic Syndr 1992;**5**:1-6.

207. Sharp JW, Coleman E, Starling N, Cline J, Rehm SJ. Hospital utilization for AIDS: are all hospital days necessary? QRB 1991; 17:113-9.

208. Quesenberry CP, Fireman B, Hiatt RA, Selby JV. A survival analysis of hospitalization among patients with AIDS. Am J Public Health 1989;**79**:1643-7.

209. Chen RT, Rutherford GW, Payne SF, Barnhart JL, Lemp GF, Baskett LH. Use of hospitals by patients with AIDS in San Francisco. N Engl J Med 1988;**319**:1671-2.

210. Vanhems P, Wintsch J, Paradisi S, Hirschel B. Hospital care for patients with AIDS compared to other patients in Geneva, 1981-1968. AIDS 1991;**5**:469-470.

211. Johnson AM, Adler MW, Crown JM. The acquired immune deficiency syndrome and epidemic of infection with HIV: costs of care and prevention in an inner London district. BMJ 1986;293:489-492.

212. Murphy M, Misquito N, Pomeroy L, Mulcahy F. Admissions for HIV-1 related disease in a Dublin hospital 1987-1990. Int J STD AIDS 1991;2:436-439.

213. Desmond N, Murphy M, Plunkett P, Mulcahy F. Use of a Dublin inner city A & E department by patients with known HIV-1 infection. Int J STD AIDS 1993;4:222-5.

214. Selwyn PA, Feingold AR, Iezza A et al. Primary care for patients with human immunodeficiency virus (HIV) infection in a methadone maintenance treatment program. Ann Int Med 1989;111:761-3.

215. Brettle RP, Willocks L, Hamilton BA et al. Out-patient medical care in Edinburgh for IDU-related HIV. AIDS Care 1994;6:49-58.

216. Brettle RP. Hospital health care for HIV infection with particular reference to injecting drug users. AIDS Care 1990;2:171-181.

217. Hankins CA, Handley MA. HIV disease and AIDS in women: current knowledge and a research agenda. J Acquir Immune Defic Syndr 1992;5:957-971.

218. Hogan AJ, Solomon DJ, Bouknight RR, Solomon CT. Under-utilisation of medical care services by HIV-infected women? Some preliminary results from the Michigan Medicaid Program. AIDS 1991;5:338-9.

219. Kinney EL, Trautman J, Gold JA, Vesell ES, Zelis R. Underrepresentation of women in new drug trials. Ann Int Med 1981;95:495-499.

220. Moore RD, Hidalgo J, Sugland BW, Chaisson RE. Zidovudine and the natural history of the acquired immunodeficiency syndrome. N Engl J Med 1991;**324**:1412-6.

221. Bastian L, Bennett CL, Adams J, Waskin H, Divine G, Edlin BR. Differences between men and women with HIV-related *Pneumocystis carinii* pneumonia: experience from 3,070 cases in New York City in 1987. J Acquir Immune Defic Syndr 1993;**6**:617-623.

222. Ellerbrock TV, Bush TJ, Chamberland ME, Oxtoby MJ. Epidemiology of women with AIDS in the United States, 1981 through 1990. A comparison with heterosexual men with AIDS. JAMA 1991;**265**:2971-2975.

223. Keenlyside RA, Johnson AM, Mabey DCW. The epidemiology of HIV-1 infection and AIDS in women. AIDS 1993;7(suppl 1):S83-S90.

224. Brettle RP, Leen CLS. The natural history of HIV and AIDS in women. AIDS 1991;**5**:1283-1292.

225. Phillips AN, Antunes F, Stergious G et al. A sex comparison of rates of new AIDS-defining disease and death in 2554 AIDS cases. AIDS 1994;**8**:831-835.

226. Seage GR, Hertz T, Stone VE, Epstein AM. The effects of intravenous drug use and gender on the cost of hospitalisation for patients with AIDS. J Acquir Immune Defic Syndr 1993;**6**:831-9.

227. Morlat P, Parneix P, Douard D et al. Women and HIV infection: a cohort study of 483 HIV-infected women in Bordeaux, France, 1985-1991. AIDS 1992;**6**:1187-1193.

228. Mulcahy F, Kelly G, Tynan M. The natural history of HIV infection in women attending a sexually transmitted disease clinic in Dublin. Genitourin Med 1994;**70**:81-83.

229. Carpenter CCJ, Mayer K, Fisher A, Desai MB, Durano L. Natural history of acquired immunodeficiency syndrome in women in Rhode Island. Am J Med 1989;**86**:771-775.

230. France AJ, Skidmore CA, Robertson JR et al. Heterosexual spread of human immunodeficiency virus in Edinburgh. BMJ 1988;**296**:526-9.

231. Horner PJ, McBride M, Coker RJ. Outpatient follow-up in women with HIV infection in Parkside Health Authority (UK). Genitourin Med 1993;**69**:370-2.

232. Minkoff HL, DeHovitz JA. Care of women infected with the human immunodeficiency virus. JAMA 1991;**266**:2253-2258.

233. Bradbeer C. Human immunodeficiency virus and its relationship to women. Int J STD AIDS 1990;**1**:233-238.

234. Johnstone FD, MacCallum L, Brettle R, Inglis JM, Peutherer JF. Does infection with HIV affect the outcome of pregnancy? BMJ 1988;**296**:467.

235. Johnstone FD. HIV and pregnancy. Int J STD AIDS 1992;**3**:79-86.

236. Mandelblatt JS, Fahs M, Garibaldi K, Senie RT, Peterson HB. Association between HIV infection and cervical neoplasia: implications for clinical care of women at risk for both conditions. AIDS 1992;**6**:173-178.

237. Chu SY, Buehler JW, Berkelman RL. Impact of the human immunodeficiency virus epidemic on mortality in women of reproductive age, United States. JAMA 1990;**264**:225-229.

238. Korn AP, Landers DV, Green JR, Sweet RL. Pelvic inflammatory disease in human immunodeficiency virus-infected women. Obstet Gynaecol 1993;**82**:765-8.

239. Kozak LJ, McCarthy E, Moien M. Patterns of hospital use by patients with diagnoses related to HIV infection. Public Health Rep 1993;**108**:571-581.

240. Andrulis DP, Weslowski VB, Hintz E, Spolarich AW. Comparisons of hospital care for patients with AIDS and other HIV-related conditions. JAMA 1992;**267**:2482-2486.

241. Lau RKW, Pinching AJ. Analysing the workload from HIV inpatients: a 10-month retrospective study. Int J STD AIDS 1991;**2**:97-101.

242. Beck EJ, Whitaker L, Kennelly J et al. Changing presentation and survival, service utilization and costs for AIDS patients: insights from a London referral centre. AIDS 1994;**8**:379-384.

243. Beck EJ, Kennelly J, McKevitt C et al. Changing use of hospital services and costs at a London AIDS referral centre, 1983-1989. AIDS 1994;**8**:367-377.

244. Morton A, McCallum AK, Parkin DW, Bhopal RS. The patient profile approach to assessing the cost of AIDS and HIV infection. J Public Health Med 1993;**15**:235-242.

245. O'Brien SJ, Burch J, Mayon-White RT. Hospital bed usage by people with HIV disease: experience in a provincial setting. Public Health 1993;**107**:355-362.

246. Greco D, Declich S, Pezzotti P, Bellomi G, Visco G, and National Study Group on HIV-related Hospital Use. Hospital use by HIV patients in Italy: a retrospective longitudinal study. J Acquir Immune Defic Syndr 1991;**4**:471-9.

247. Stone MH, Stone DH, MacGreggor HAR. Intravenous drug misusers presenting to the accident and emergency department of a large teaching hospital: a failure of clinical management? Scot Med J 1989;**34**:428-30.

248. Ghodse AH. Drug problems dealt with by 62 London casualty departments; a preliminary report. Brit J prev soc Med 1976;**30**:251-6.

249. Haw S, Taylor A. Can prescribing policy influence patterns of drug taking and methods of drug administration? AIDS 1993;7:598-600.

250. Centers for Disease Control. Increase in pneumonia mortality among young adults and the HIV epidemic - New York City, United States. MMWR 1988;**37**:593-6.

251. Bouza E, Martin-Scapa C, de Quiros BJC et al. High prevalence of tuberculosis in AIDS patients in Spain. Eur J Clin Microbiol Infect Dis 1988;**7**:785-8.

252. Schrager LK. Bacterial infections in AIDS patients. AIDS 1988;**2** (suppl 1):S183-S189.

253. Simberkoff MS, Sadr WE, Schiffman G, Rahal JJ. *Streptococcus pneumoniae* infections and bacteraemia in patients with acquired immune deficiency syndrome, with report of pneumococcal vaccine failure. Am Rev Respir Dis 1984;**130**:1174-1176.

254. Redd SC, Rutherford GW, Sande MA et al. The role of human immunodeficiency virus infection in pneumococcal bacteraemia in San Francisco residents. J Infect Dis 1990;**162**:1012-1017.

255. Drucker E, Webber MP, McMaster P, Vermund SH. Increasing rate of pneumonia hospitalisations in the Bronx: a sentinel indicator for human immunodeficiency virus. Int J Epidemiol 1989;**18**:926-933.

256. Schuchat A, Broome CV, Hightower A, Costa SJ, Parkin W. Use of surveillance for invasive pneumococcal disease to estimate the size of the immunosuppressed HIV-infected population. JAMA 1991;**265**:3275-3279.

257. Parkin JM, Helbert M, Hughes CL, Pinching AJ. Immunoglobulin G subclass deficiency and susceptibilty to pyogenic infections in patients with AIDS-related complex and AIDS. AIDS 1989;**3**:37-39.

258. Unsworth DJ, Rowen D, Carne C, Sonnex C, Baglin T, Brown DL. Defective IgG2 response to *Pneumovax* in HIV seropositive patients. Genitourin Med 1993;**69**:373-6.

259. Huang KL, Ruben FL, Rinaldo CR, Kingsley L, Lyter DW, Ho M. Antibody responses after influenza and pneumococcal immunisation in HIV-infected homosexual men. JAMA 1987;**257**:2047-2050.

260. Klein RS, Selwyn PA, Maude D, Pollard C, Freeman K, Schiffman G. Response to pneumococcal vaccine among asymptomatic heterosexual partners of persons with AIDS and intravenous drug users infected with the human immunodeficiency virus. J Infect Dis 1989;**160**:826-831.

261. Polsky B, Gold JWM, Whimbey E et al. Bacterial pneumonia in patients with the acquired immunodeficiency syndrome. Ann Intern Med 1986;**104**:38-41.

262. Schlamm HT, Yancovitz SR. *Haemophilus influenzae* pneumonia in young adults with AIDS, ARC, or at risk of AIDS. Am J Med 1989;**86**:11-14.

263. Krumholtz HM, Sande MA, Lo B. Community-acquired bacteraemia in patients with acquired immunodeficiency syndrome: clinical presentation, bacteriology, and outcome. Am J Med 1989;**86**:776-779.

264. Moreno S, Martinez R, Barros C, Gonzales-Lahoz J, Garcia-Delgado E, Bouza E. Latent *Haemophilus influenzae* pneumonia in patients infected with HIV. AIDS 1991;**5**:967-970.

265. Caiaffa WT, Graham NMH, Vlahov D. Bacterial pneumonia in adult populations with human immunodeficiency virus (HIV) infection. Am J Epidemiol 1993;**138**:909-22.

266. Whimbey E, Gold JWM, Polsky B et al. Bacteraemia and fungaemia in patients with the acquired immunodeficiency syndrome. Ann Intern Med 1986;**104**:511-514.

267. Gold JWM. Infectious complications in patients with HIV infection. AIDS 1988;**2**:327-334.

268. Gilks CF, Brindle RJ, Otieno LS et al. Life-threatening bacteraemia in HIV-1 seropositive adults admitted to hospital in Nairobi, Kenya. Lancet 1990;**336**:545-49.

269. Witt DJ, Craven DE, McCabe WR. Bacterial infections in adult patients with the acquired immune deficiency syndrome (AIDS) and AIDS-related complex. Am J Med 1987;**82**:900-906.

270. Mayer HB, Rose DN, Cohen S, Gurtman AC, Cheung TW, Szabo S. The effect of *Pneumocystis carinii* prophylaxis regimens on the incidence of bacterial infections in HIV-infected patients. AIDS 1993;7:1687-8.

271. Ammann AJ, Schiffman G, Abrams D, Volberding P, Ziegler J, Conant M. B-cell immunodeficiency in AIDS. JAMA 1984;**251**:1447-9.

272. Rodriguez-Barradas MC, Musher DM, Lahart C et al. Antibody to capsular polysaccharides of *Streptococcus pneumoniae* after vaccination of HIV-infected subjects with 23-valent pneumococcal vaccine. J Infect Dis 1992;**165**:553-6.

273. Janoff EN, Douglas JM, Gabriel M et al. Class-specific antibody response to pneumococcal capsular polysaccharides in men infected with HIV-1. J Infect Dis 1988;**158**:983-90.

274. Rose DN, Schechter CB, Sacks HS. Influenza and pneumococcal vaccination of HIV-infected patients: a policy analysis. Am J Med 1993;**94**:160-8.

275. Kroon FP, van Dissel JT, de Jong JC, van Furth R. Antibody responses to influenza, tetanus and pneumococcal vaccines in HIV-seropositive individuals in relation to the number of CD4+ lymphocytes. AIDS 1994;**8**:469-476.

276. Joint Committee on Vaccination and Immunisation. Immunisation against infectious disease. HMSO 1992 edition, p101.

277. Breiman R, Spika J, Navarro V, Darden P, Darby C. Pneumococcal bacteraemia in Charleston county, South Carolina. Arch Intern Med 1990;**150**:1401-5.

278. Winter JH, Winter AEL. Human immunodeficiency virus infection and pneumococcal bacteraemia in Scotland. J Infect 1991;**22**:301-2.

279. Garcia-Leoni ME, Moreno S, Rodeno P, Cercenado E, Vicente T, Bouza E. Pneumococcal pneumonia in adult hospitalized patients infected with the human immunodeficiency virus. Arch Intern Med 1992;**152**:1808-1812.

280. Woodhead MA, MacFarlane JT, McCracken JS, Rose DH, Finch RG. Prospective study of the aetiology and outcome of pneumonia in the community. Lancet 1987;i:671-4.

ABBREVIATIONS

HIV	Human immunodeficiency virus
AIDS	Acquired immunodeficiency syndrome
OI	Opportunistic infection
PCP	*Pneumocystis carinii* pneumonia
KS	Kaposi's sarcoma
CMV	Cytomegalovirus
TB	Tuberculosis
CDC	Centers for Disease Control
MMP	Methadone maintenance programme
IDU	Injection drug use/user
BCI	Bacterial chest infection
UTI	Urinary tract infection
PID	Pelvic inflammatory disease
GI	Gastro-intestinal
GU	Genito-urinary
Heterosexual	HIV infected via heterosexual intercourse
Homosexual	HIV infected via homosexual intercourse
CD4 count	CD4 positive lymphocyte count