# A Modified Mathematical Model for HIV Transmission, AIDS and Intervention Strategies in Ireland

**Mary T. Dunne, B.A., H. Dip. Ed.**

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Dublin City University
Professor A.D. Wood and Dr. H. J. Ruskin, (supervisors).
Faculty of Computing and Mathematical Sciences.

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I hereby certify that this material, which I now submit for assessment on the programme of study leading to the award of Master of Science in Applied Mathematical Sciences is entirely my own work and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my work.

Signed _____ ID No .____

Date._____

Dedicated to Karen and Saorla, and to the memory of Pat

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# A Modified Mathematical Model for HIV Transmission, AIDS and Intervention Strategies in Ireland.

**Mary Dunne**

## Abstract

The aim of this project was to modify transmission models previously developed to describe HIV transmission in Ireland through more precise estimates of parameters delineating sexual and needle sharing behaviour and AIDS related mortality, with a view to examining the extent of spread from IVDUs to the general heterosexual population To provide predictions on HIV transmission and AIDS cases up to the year 2010 and to examine the sensitivity of the predictions to changes in the key parameters under different assumptions on intervention strategies

Essential data of relevance to HIV transmission were acquired (through the co-operation of the Department of Health, the AIDS Resource Centre, the Drug Treatment Centre, the Ana Liffey Drug Project, and St James's Hospital, Dublin) and analysed The parameters obtained from the descriptive and survival analyses were used in a refined deterministic model of HIV transmission which was solved numerically An attempt at a solution using perturbation methods was undertaken

Results provided a plausible range of projected new HIV infections and AIDS cases up to the year 2010. The model projects that if present behaviour continues, approximately 1009 new infections may be expected in Dublin by the year 2000, and 1496 new infections by 2010 Small changes in the values of key parameters induce significant changes in projected trends, particularly in the longer term However all projections point to the fact that

- Non-IVDU women are particularly susceptible to HIV infection
- Early introduction of behaviour change makes a significant difference to the growth of the epidemic
- Expanding the Drug Treatment System could help to significantly reduce the spread of HIV
- Central collation of data is essential if rational implementation of intervention plans is to be achieved

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# Abbreviated Terms

| | |
|---|---|
| AIDS | Acquired Immune Deficiency Syndrome |
| DTC | Drug Treatment Centre |
| HIV | Human Immunodeficiency Virus |
| IVDU | Intravenous Drug User |

# Chapter 1

# AIDS in Ireland

*'The HIV/AIDS pandemic is entering a new, more dangerous phase As the global threat increases, there are many signs of growing complacency, persistent denial, and resurgent discrimination '*

(Mann, Tarantola, and Netter, 1992)

## 1.1 Introduction

### 1.1.1 The HIV/AIDS pandemic

In 1981, a new syndrome, the acquired immunodeficiency syndrome (AIDS), was first recognised among homosexual men in the USA (Centres for Disease Control 1981) By 1982 the features of the disease had been attributed to a deficiency of the immune system, its transmissibility had been recognised and its viral origin was suspected This was confirmed through the identification of the aetiological agent — the human immunodeficiency virus (HIV) — in 1983 (Barre-Sinoussi et al , 1983 and Gallo et al , 1983) and a serological test for antibodies was available shortly afterwards Since that time, HIV- disease has been defined primarily on the criterion of the presence of antibodies to the antigenic components of the virus By the mid 1980s it became clear that the virus had spread, largely unnoticed and unsuspected, throughout the world since the mid- to late 1970s and that its effects had reached truly global — or 'pandemic' — proportions A comprehensive understanding of the disease-process, expressed in review articles (Curran et al and Wong-Staal et al ) was available by 1985

The HIV/AIDS pandemic consists of thousands of smaller, complicated epidemics, both separate and interdependent (in many cases there are many epidemics even within a single country) Each epidemic has its own distinct origin, in terms of geography and specific populations affected, each has its own rate of spread, intensity, and special characteristics, and each involves

different types and frequencies of risk behaviours and practices — for example, having unprotected sex with multiple partners or sharing intravenous drug injection equipment

The virus is being transmitted on all continents and is spreading to new communities all the time As of mid 1994, more than 17 million HIV infections (over 1/2 million of which are in Western Europe) are estimated to have occurred since the beginning of the pandemic, with over 16 million of them in adults (WHO July 1994) The WHO estimates and projections of HIV infection and AIDS should furthermore be viewed as very conservative since they use the lower value of the possible range of estimates

The HIV/AIDS pandemic was initially centred in urban locations but in most countries is now thought to be present in rural areas as well The precise nature and extent of HIV spread in rural areas varies between, and even within, individual countries In Ireland for example, the situation outside Dublin varies considerably, with most seropositive individuals living in the Southern Health Board Area, (see Table 1) No community or country in the world already affected by AIDS can claim that HIV spread has stopped In Europe alone, 75,000 to 100, 000 new HIV infections are estimated to have occurred in 1991, (Mann et al , 1992)

There is increasing evidence that women are more at risk of HIV infection when considered either on a *per contact* or *per partnership* level Initially, in developed countries, men were more exposed to HIV than women, primarily as a result of homosexual intercourse or IV drug injecting, but the difference in the numbers of men and women infected with HIV has gradually narrowed as heterosexual transmission has become more common Between 1990 and 1993 there was a significant increase (from 40 9% to 45 4%) in the proportion of female cases in the European heterosexual contact group, (European Centre for the Epidemiological Monitoring of AIDS, March 1994) In Western Europe, the sex ratio among all HIV-infected adults was 5 7 1 in 1993, (WHO, 1993)

In other parts of the world, where heterosexual transmission predominated from the outset, the difference between the sexes is even less World-wide, with heterosexual transmission being the most common mode of HIV dissemination, there are 3 men already infected for every 2 women and by the year 2000 the number of new infections among women is expected to approach that among men (Chin 1990) The rising infection rates in women are accompanied by a corresponding rise in the number of children born with HIV infection To date, it is estimated that about 1 million children have been infected with HIV through mother-to-child transmission Most of these children

rapidly develop AIDS and die — usually before the age of 5 (WHO 1993) By April 1994 in Ireland for example, 101 children at risk had been confirmed seropositive, 10 of these have developed AIDS, of whom 6 have already died

Mirroring the trend for women, upward seroprevalence trends have been noted in IVDUs in several countries, particularly those in Southern Europe, wheras a decline in HIV incidence has generally been noted in men who have sex with men

The interval between infection with HIV and the onset of clinical symptoms is unusually long compared with other communicable diseases, and varies considerably between individuals Reporting of AIDS was initially based on the clinical case definition established by the Centres for Disease Control in 1982 (Centers for Disease Control, 1982) In 1985 the Walter Reed Staging Classification of HIV was introduced (Redfield et al , 1986), dividing HIV infection into a hierarchy of stages of clinical immunological dysfunction In 1986 the CDC introduced an alternative classification system (Centers for Disease Control, 1986) which includes pathological confirmation of the presence of opportunistic disease and which was revised in 1987 (Centers for Disease Control, 1987) The CDC classifies those with the HIV virus into four groups Group I, seroconversion, Group II, asymptomatic, Group III, progressive generalised lymphadenopathy and Group IV, patients with clinical manifestations of HIV infection designated by assignment to one or more subgroups (A-E) Subgroup IV B, C1, and D defines an AIDS case Included are patients with symptomatic or invasive disease due to one of a number of specified secondary infectious diseases, patients with neurological disease such as dementia and patients with secondary cancers such as Kaposi's sarcoma Approximately 50% of those infected become ill within ten years of initial infection Current evidence suggests that, in the absence of other causes of death, almost all HIV-infected people will ultimately die of AIDS Once an individual develops AIDS, the average survival time appears to be between one and three years (WHO 1993)

The spread of HIV and the occurrence of AIDS are therefore separated by years, and so, at any specific moment in any area, these two epidemics may be evolving in very different ways

From 1992 to 1995, it is estimated that a total of 3 8 million people will develop AIDS, which is 150 percent more than have developed AIDS during the entire history of the pandemic through January 1, 1992, ( Mann et al 1992) As of 30 June 1994, 985, 119 AIDS cases have been reported to the World Health Organisation Global Programme on AIDS since the onset of the pandemic

This represents a 37% increase since 30 June 1993 However WHO estimates that as of mid 1994, allowing for under-diagnosis, under-reporting, and delays in reporting, and based on the available data on HIV infections around the world, there have been around 4 million AIDS cases world-wide since the pandemic began This represents a 60% increase over the estimated 2 5 million cases as of July 1993, (WHO 1994) By the end of June 1994, a cumulative total of 122,059 AIDS cases have been reported in the WHO European region, (European Centre for the Epidemiological Monitoring of AIDS, June 1994) In Ireland, as of mid 1994, there have been 408 cases reported to the Department of Health since the epidemic began, (official Department of Health figures) This represents a 19% increase over the reported 344 cases as of mid 1993

### 1.1.2 Modes of HIV transmission

An understanding of the ways in which HIV can be transmitted is central to an understanding of the epidemiology of the pandemic It has now been established, as a result of laboratory and epidemiological investigations, that HIV is transmitted in three ways through sexual intercourse, through blood and from mother-to-child There are however individual differences in the ability to transmit and acquire HIV that remain unexplained (Padian et al 1991)

HIV transmission as a result of sexual intercourse accounts for about three-quarters of all HIV infection world-wide (WHO 1993) HIV is therefore a sexually transmitted disease (STD) Although transmission through intercourse between men occurs in most parts of the world, the majority of the world's infections have been acquired through intercourse between men and women (heterosexual transmission) Studies have shown that the likelihood of being infected increases statistically with the number of sexual partners and with anal receptive intercourse (European Study Group, 1989, Padian et al , 1987 and 1991, Goedert et al , 1984, De Vincenzi, 1988) Heterosexual transmission continues to grow in importance world-wide (WHO 1993)

As with some other STDs, HIV infection can also be transmitted through blood, for example as a result of the medical transfusion of infected blood or blood products or from the use of contaminated injection equipment by intravenous drug users

The transmission of HIV from mother to child includes transmission during pregnancy, during delivery and through breast-feeding

## 1.2 Methods of estimating and projecting HIV/AIDS

### 1.2.1 Models in current use

Despite considerable advances in understanding the basic biology of HIV, the human immune deficiency virus, which is the aetiological agent of the acquired immune deficiency syndrome (AIDS), medical, public health and health education planning is still inevitably subject to uncertainties The problems are world-wide and many questions of an epidemiological nature currently remain to be answered, e g the likely magnitude of the epidemic, the period of peak incidence, the extent of the spread in the heterosexual community, the necessary behaviour changes required to affect the magnitude of the epidemic, the sexual and drug sharing habits of intravenous drug users (IVDUs), the inter-relationships of at risk populations, and the effects of intervention policies

An obvious way to predict the future course of any epidemic is to fit a smooth curve through the disease incidence (or cumulative AIDS case) data and *extrapolate* this line into the future on the supposition that previous trends will continue (Gail and Brookmeyer, 1988) Such empirical predictions are useful only up to two or three years into the future, after which they become too imprecise since they assume no change in observed trends and do not incorporate knowledge about disease progression or transmission dynamics or intervention policies where these exist In addition the extrapolations assume that the number of AIDS cases has been reported with the same accuracy over time Projections of HIV prevalence or incidence are not possible with this method AIDS incidence is also subject to a number of uncertainties, including delays in reporting cases, under reporting, and changes in the surveillance definition

*Back-calculation* methods also have been used to project new cases based on AIDS case data in a semi -empirical way and to obtain estimates of the incubation period (Brookmeyer and Damiano, 1989, Brookmeyer, 1991, Rosenberg et al , 1991, Comiskey & Ruskin, 1992) However back-calculation projects AIDS cases **only** from infections that have already occurred and AIDS is notoriously under-reported (Rosenberg and Gail, 1990, Mann et al , 1992) The methods therefore yield some information on the incidence of infection more than 2 or 3 years in the past, very little information on the incidence within the last 2 years, and **no** information on the future incidence of infection In addition, back-calculation is increasingly difficult to use because of the evident need to stratify by risk, age, treatment etc , and the complications that this

stratification involves The principal aim of epidemic models must be to learn about the underlying course of new infections in order to provide adequate resources taking these factors into account

As a third approach *dynamic* models, which use information required by back-calculation methods and information about modes of transmission, transmission probabilities, and behaviour associated with the spread of HIV, have been used Given the availability of data, these models should be preferred to back-calculation In the medium term, mathematical models of the dynamics of HIV transmission and its progression to AIDS can facilitate the indirect assessment of the essential epidemiological parameters and clarify relations between them Furthermore, such models can indicate gaps in our knowledge, clarify what data must be collected in order that better predictions can be obtained, assess the effects of future intervention policies, eliminate hypotheses put forward to explain observed trends, and importantly, provide predictions for several decades ahead In general mathematical models can provide a framework to guide the interpretation of observed trends ( May and Anderson, 1987, Anderson et al , 1986)

There are other methods also in use, e g the more recently developed Automata network *SIR* models for modelling the spread of AIDS in populations of moving individuals (Boccara and Cheong, 1992) Automata networks are discrete dynamical systems which consist of graphs with a discrete variable at each vertex Each vertex variable evolves in discrete time steps according to a definite rule involving the value of neighbouring vertex variables The vertex variables may be updated from the application of a local rule of automation, which consists of a number of subrules One of these subrules might describe e g the different types of *sequential* moves that an individual may perform Another might determine which susceptibles become infectives and which infectives are removed in a *synchronous* manner These are flexible models and may be applied to both closed and open populations to include births, deaths by other causes, immigrations, or emigrations.

Research on mathematical models of HIV transmission has to date concentrated mainly on the homosexual population In many parts of Western Europe and North America the majority of early cases of the virus were identified within this group and survey analyses to date have reflected this situation However, current work employs the insights gained from these more restricted models to model the spread of the disease within the heterosexual population Intravenous drug users have been recognised as a significant risk group for HIV and play a major role in transmission of the virus in many parts

of the world in particular for the heterosexual epidemic in the United States and Europe (Friedland & Klein, 1987, Moss, 1987, Curran et al , 1988; France et al , 1988, des Jarlais et al , 1989) In southern Europe, particularly Spain and Italy, IVDUs make up 66% of reported AIDS cases (European Centre for the Epidemiological Monitoring of AIDS, 1994) Understanding long term trends in the spread of HIV among intravenous drug users is therefore critical to controlling the AIDS epidemic

From the beginning of the AIDS epidemic in Ireland it was observed that we are unlike most of the rest of Western Europe in that the major spread is through drug users rather than homosexuals We therefore found it necessary to proceed directly to the difficult problem of modelling the spread of the HIV virus from within the IVDU group (Comiskey, 1991) Seropositive IVDUs can transmit HIV to non-seropositive intravenous drug users through sharing injecting equipment, and to both non-seropositive IVDUs and non-IVDU sex partners through sexual intercourse In addition seropositive female IVDUs are a source for perinatal transmission

In Ireland to date, there has been little analysis of the rate of spread of HIV, or attempts to model the future course of the disease at a national level (see however, Comiskey, 1991) It is the aim of this work to develop a deterministic mathematical model of HIV transmission from IVDUs to the general population under different assumptions of social and sexual mixing A survey of intravenous drug users is used to provide detailed information on the extent of needle use and sharing, the rate of change of sexual partners (both IVDUs and non-IVDUs) and the extent of spread to non-IVDU partners In conjunction with the mathematical models, we hope to provide more precise estimates of the incidence of HIV infection and AIDS in the heterosexual population of Dublin

### 1.2.2 Global estimates and projections of HIV/AIDS

Uncertainties about the potential spread of HIV and the ultimate dimensions of the HIV/AIDS pandemic have existed since the initial recognition of AIDS in the early 1980s The major uncertainties include

- when, and at what level, HIV prevalence will peak in different populations at risk in the various geographical areas

- the rate at which HIV-infected children and adults will ultimately develop AIDS and die

Despite these uncertainties, a variety of methods and models have been developed for making future projections of the pandemic

The first step in making future projections is to gauge the current magnitude of the HIV pandemic Here, the major problem is that HIV infection is largely silent — AIDS cases are the only visible part of the epidemic Attempting to estimate the number of HIV infections from the number of AIDS cases has several major disadvantages with several problems inherent to such data, (Jager et al , 1993) Firstly the number of AIDS cases is never complete and may be seriously underestimated in some countries because of inadequate diagnostic facilities and poor reporting mechanisms Even in countries with relatively complete reporting, delays between AIDS diagnoses and case reports are inevitable. In Europe it is estimated that reporting is only 60 to 90 percent complete (Mann et al , 1992) Indeed even if the **true** number of AIDS cases were known, estimating the number of HIV infections from this number is fraught with difficulty because of the long and variable time (asymptotic) between initial HIV infection and the onset of AIDS symptoms Moreover, because of the long interval between infection and illness, AIDS cases at best reflect the level and distribution of HIV infection 5-10 years **earlier** HIV infection is also silent because the assessment of HIV infection by available test procedures is complicated for social reasons

In making estimates of the current magnitude of HIV spread, WHO therefore draws on other sources of information, such as studies of HIV prevalence in specific population groups and areas, the estimated size of such groups, prevalence in neighbouring areas, and trends over time, for example the changes in prevalence from year to year in a given group

The ultimate long-term dimensions of the HIV/AIDS pandemic cannot yet be forecast with any degree of confidence However, on the basis of available data on the current global status of the pandemic and recent trends in its spread, WHO has generated a plausible range of projected new HIV infections during the 1990s In making projections of the future magnitude of the pandemic, WHO uses the lower limits of its estimated regional ranges of HIV prevalence The results of HIV/AIDS forecasting by WHO should thus be considered conservative During this decade, WHO projects that around 10-15 million new HIV infections may be expected in adults, mostly in developing countries During the same period, WHO projects that as many as 5-10 million children will be HIV- infected at birth or through breast-feeding, the majority of them in sub-Saharan Africa By the year 2000, the cumulative number of HIV-related deaths in adults is predicted to rise to more than 8 million from its mid

1993 total of 2 million, (WHO 1993) Therefore the number of AIDS deaths projected between 1993 and 2000 is four times the number that occurred during the entire pandemic through mid-1993

For the year 2000, the current WHO projection is that there will be a cumulative total of 30-40 million HIV infections in men, women and children, of which more than 90% will be in developing countries The projected cumulative total of adult AIDS cases is close to 10 million (WHO 1993) The impact of the AIDS pandemic goes far beyond these statistics however AIDS principally affects young and middle-aged adults The cost of medical care for each infected person — roughly estimated as equal to or greater than the annual per capita gross national product — overwhelms individuals and households, (Mann et al 1992)

## 1.3 The Irish situation

### 1.3.1 Background

The first case of AIDS in Ireland was identified in the homosexual/bisexual group in 1982 The first case of AIDS in an IVDU was not found until the second half of 1985 By the end of June 1994, 408 cases of AIDS had been reported Most cases occurred among IVDUs (177) and homosexual men (136) Heterosexual cases make up only 11% of all AIDS cases in Ireland, but they account for 31% of female AIDS cases indicating that heterosexual transmission is a particularly high risk acquisition route for females 49 per cent of all AIDS cases attributed to heterosexual transmission are women Heterosexual acquired AIDS increased from 29% of all women with AIDS in 1993 to 31% in 1994 The proportion of cases due to heterosexual sex is rising far more rapidly than any other route of transmission The number of reported cases of people infected through heterosexual sex rose by 80% in the past 2 years (June 1992-June 1994), (Department of Health Statistics) Many of these heterosexual cases were the sexual partners of HIV-infected IVDUs

A number of studies have shown that between 60% and 100% of heterosexually acquired HIV in the western world is related to intravenous drug use and that at least 40% of IVDUs are in relationships with non-users, (France et al , 1988) It has indeed been suggested by a previous Minister for Health (O'Hanlon 1988) that Ireland's most serious problems with AIDS may result from IVDUs acting as a 'bridge' for the virus into the non-drug using heterosexual population

The greatest percentage (57 8%) of Irish cases occur in the 25-34 year age group with 82 6% in males and 17 4% in females of all age groups This gives an overall male female ratio of 4 7 1

Up to the end of June 1994, 86,701 tests for antibodies to the human immunodeficiency virus had been carried out by the National Virus Reference Laboratory (NVRL) and 1494 individuals had been found to be seropositive (National Virus Reference Laboratory, June 1994) The 86,701 are not necessarily 86,701 individuals since some persons may have been tested more than once It should be noted that many other centres are also carrying out tests but when a positive result is identified it is sent to the NVRL to be confirmed There are **no** available statistics on the total number of tests carried out nationally A large proportion (46%) of the tests that the NVRL carry out are for insurance/visa purposes whereas other centres carry out the majority of their tests for a particular risk behaviour such as intravenous drug use

Figure 1 1 shows the cumulative number of HIV infections diagnosed at the Virus Reference Laboratory from 1985 (when the first tests were performed) to the end of 1993

The graph shows an almost linear increase in the numbers testing HIV antibody positive The highest number of positive tests occurred in 1992 with 157 individuals testing positive

It is impossible to obtain the exact number of people who are infected with the virus as the above statistics refer only to those who have been tested Conservative estimates put the number of people with HIV at four to five times the official figure


*Figure 1 1 Cumulative HIV cases 1985-1993*

### 1.3.2 The situation in Dublin

The majority (90%) of HIV seropositive individuals in Ireland are located in the Dublin metropolitan area (National AIDS Strategy Committee, 1992) Although appearing initially among homosexuals and intravenous drug users, HIV infection is now spreading to the general heterosexual population HIV infection here follows a pattern which is dissimilar to that of the U K but closely resembles that of Spain and Italy (the only other European countries to have a higher proportion of AIDS cases in the IVDU risk group (66%) than in the Homosexual risk group (15-16%), European Centre for the Epidemiological Monitoring of AIDS, March, 1994) 50 2% of those who are known to be infected with HIV in Ireland have been exposed to it through the intravenous use of drugs, 13 4% have acquired their status through heterosexual transmission, and 19 5% have been infected through homosexual intercourse The other 16 9% is made up of children, persons with haemophilia and others, (National Virus Reference Laboratory, June 1994) In contrast, unprotected homosexual intercourse accounts for the majority (60 5%) of those who are HIV seropositive in the U K (Communicable Disease Report, 1994)

Recent studies have however indicated that **sexually**-transmitted HIV infection may be the commonest mode of transmission outside Dublin (Department of Health, 1993), (see Dublin versus the Regions, below)

The male female ratio of HIV infections attributed to IVDU is approximately 3 1 (National Virus Reference Laboratory, June 1994) Infected drug users provide one of the major driving forces for heterosexual transmission of HIV in Ireland Their significance as a high risk group lies in the large number of young people, particularly in Dublin, who have used intravenous drugs since heroin became widely available in the late 1970s and early 1980s (Dean et al , 1983) Estimates of the total number of intravenous drug users are varied and impossible to confirm, they range from a low estimate of 3000 people to a high one of 15,000 (Bury 1989) The true number is probably somewhere between these figures but certainly involves thousands of people who have used drugs intravenously at some stage Ireland's drug problem is concentrated in Dublin and there is little evidence of a serious problem outside the city (Department of Health, 1991) Information on HIV positive IVDUs is essential to our understanding of the spread of the virus, and to the construction of any mathematical model for the transmission dynamics of the disease

Drug addiction and treatment services in Dublin are shared by the Drug Treatment Centre (whose emphasis is on abstinence), the AIDS Resource Centre in Baggot Street and its satellite clinics (emphasis is on harm reduction), and a number of non statutory/voluntary agencies like the Coolmine Therapeutic Community (based on abstinence), and those which include harm reduction treatments like the Ballymun Youth Action Project, the Ana Liffey Drug Project and the Merchants' Quay Project Co-operation between services can be rather intermittent, partly because of the different philosophies guiding the different services Primary care or satellite clinics of the Baggot St centre have been established in three locations (with plans for a further two) in the Dublin area The services available in these centres include methadone maintenance, condom distribution, and needle exchange

Our national statistics state that while 50 2% of Ireland's seropositive population have been infected through intravenous drug use, only 9 6% of all tests carried out by the NVRL with IVDU named as a risk factor are seropositive (see earlier note on NVRL, section 1 3) However Bury (1989) suggests that many people who have tested positive or negative in the past have had the test repeated using other names or identifying numbers, and that therefore the apparent total number of IVDUs tested is inflated and thus the proportion of

IVDUs who have tested seropositive is an underestimate In addition many drug users who have tested positive outside the country and have returned to Ireland will not be included in the statistics It is generally accepted too that a large number of potential HIV seropositive individuals have not been tested, for psychological, social and legal reasons In their study of 'Admissions for HIV-1 related disease in a Dublin Hospital 1987-1990', Murphy et al (1991), found that 27 4% of patients were admitted with advanced disease (CDC4) who had not been previously diagnosed HIV seropositive These findings suggest a sizeable reserve of undetected disease in the population The reasons for this are varied as pointed out by Murphy et al In Dublin, intravenous drug use is more common and more detectable in the lower socio-economic groups and IVDUs tend to be poorly motivated to seek medical attention Secondly, many socially disadvantaged IVDUs have spent time in prison where it has been the policy since 1985 to segregate HIV seropositive prisoners, and IVDUs were therefore reluctant to be tested for HIV (Harding, 1987, Dept of Justice, 1993) Thirdly, in the early years of the epidemic, many homosexuals were encouraged by various voluntary agencies not to have the HIV antibody test, and this advice may have filtered through to IVDUs Because of these reasons and others (such as fear of learning the result), it is probable that many individuals who are in high risk categories have still not been tested

Data published by the Department of Health in 1986 showed that 30 per cent of selected samples of IVDUs had tested positive for HIV (Department of Health, 1986) Indeed others have suggested seroprevalence levels of 27% (Dean et al , 1987), 28 2% (Richardson et al , 1993), and even as high as 39% (Bury, 1989) A survey of 120 clients of the Merchants' Quay drugs/HIV service found that 58 of the 107 (54%) clients who were tested were seropositive (McKeown et al , 1993) In a study conducted in Edinburgh where the IV drug using situation is similar to that in Dublin it was found that 52% of IVDUs tested were seropositive (Brettle et al 1987) Estimating the prevalence of HIV infection among IVDUs is methodologically difficult because true random samples of the general population of drug injectors are not obtainable Studies have found that drug injectors with no experience of treatment had significantly lower rates of HIV-antibody testing, and significantly higher levels of HIV prevalence and of unreported HIV positivity than those previously or currently in treatment, (McKeown et al , 1993, Donoghoe et al 1993, Rhodes et al ,1993b) It was pointed out by Robertson et al (1986) that young drug users are particularly at risk of AIDS because they rarely have their own equipment and have little contact with the medical services or access to health education

These studies suggest that previous studies of HIV prevalence among drug users may be biased by drawing on samples primarily from treatment settings (see section 4 2)

Intravenous drug users are therefore a critical group in the AIDS epidemic in Ireland, and control of the AIDS epidemic here will thus require control of HIV infection among IVDUs An underestimate now of the total numbers infected by IVDU will lead to under resourcing of the services needed to cope with AIDS Accurate predictions and estimates of the level of HIV infection and spread are essential to enable planning by government authorities and health care personnel working within a system that is already overstretched

The first phase of an anonymous, unlinked HIV surveillance programme commenced in October 1992 in Maternity Hospitals and Maternity Units in General Hospitals throughout Ireland Pregnant women are especially important since they are by definition sexually active, and they represent one of the routes by which the epidemic can spread outwards from the high risk groups The government propose to extend this programme initially to hospital out-patients and then to hospital admissions during 1994 (Department of Health, Annual Report, 1993) With this in place we should have a more comprehensive and accurate estimate of the prevalence of HIV infection in the population and a reduction in some of the uncertainty surrounding heterosexual contact transmission However, since HIV infection is not uniformly distributed within the population, and those persons attending maternity and other hospitals do not constitute a strictly representative sample of the general population, the seroprevalence of HIV antibody found in these samples may provide biased estimates However, if such a bias exists, it may not vary much over time and, thus, inferences on rates of change of HIV prevalence, regional differences, etc should be highly informative

### 1.3.3 Dublin versus the Regions

In November 1993, the Department of Health introduced a more comprehensive Notification Form for Cases of AIDS This requires details of the Postal District (Dublin) and the County (elsewhere) of residence of the person This will allow more focused monitoring of AIDS Under the revised Notification System cases of AIDS will now be reported first to the Regional AIDS Co-ordinator in a health board and then to the Department of Health (Department of Health, Annual Report, 1993) Figure 2 shows a map of Ireland detailing the Health Board Areas

THE HEALTH BOARD AREAS

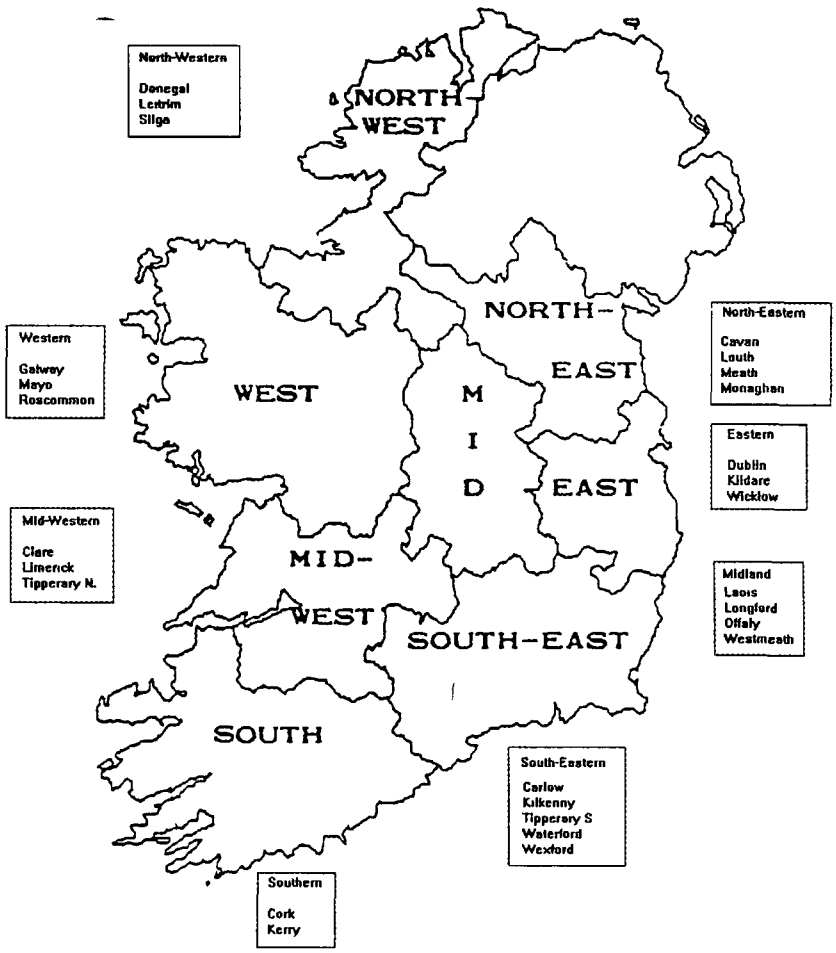



*Fig 1 2 Map of Ireland detailing the Health Board Areas*

The Virus Reference Laboratory only began to classify HIV antibody tests into regions in June 1992, and therefore their statistics do not provide an adequate picture of the situation in Ireland outside Dublin Figures for the prevalence of HIV outside Dublin can currently only be arrived at by combining the results of personal communication with the AIDS co-ordinators from each of the Health Board areas with the results of a few limited studies These have included a retrospective study conducted by the Department of Genito-Urinary Medicine, St James's Hospital, Dublin (Foreman et al , 1994), on the profile of 109 seropositive patients residing outside Dublin city, and a survey of Irish general practitioners, on contact with HIV positive patients (Bradley et al , 1993) Information which we have obtained from the AIDS co-ordinators includes only those cases known to them up to June 1993 The St James's Hospital study used data up to March 1994 and the Bradley study was conducted in June 1992 The following table shows the distribution of HIV positive individuals from outside Dublin city, obtained from a crude synthesis of the above information

**Table 1.1 Distribution of HIV seropositive individuals outside Dublin City.**

| Health Board Area | Number |
|---|---|
| Eastern | 45 |
| Midland | 17 |
| Mid Western | 9 |
| North Eastern | 7 |
| North Western | 4 |
| South Eastern | 14 |
| Southern | 100 |
| Western | 12 |
| Total | 208 |

The St James's Hospital study suggests that the transmission of HIV outside of Dublin city is primarily through sexual intercourse 69% of their cohort were infected through this route and 55% were infected through homosexual transmission This proportion differs substantially from that in the national statistics and that in the Department of G U M in St James's, where the majority of those who are seropositive, are or were IVDUs However it is

still likely to be an underestimate of the true proportion of persons infected through sexual intercourse, since the St James's Hospital study included patients in the Dublin area but outside Dublin city Thus the 31% of seropositive subjects found by the study who were IVDUs, have probably biased the overall figure, since there is a higher proportion of IVDUs on Dublin's periphery than in any of the other health board areas Supporting this view we note that the Virus Reference Laboratory have recorded the same number of seropositive tests from Co Dublin for IVDUs and bi/homosexual men since June 1994 (National Virus Reference Laboratory Statistics) Further, the AIDS co-ordinators, and the microbiologists from the regional hospitals in Cork and Galway (personal communication 1993), also agree that the vast majority of HIV infections have been acquired sexually and that up to 1993 most of these were homosexually transmitted However, it should be noted that the overall numbers involved at present are small, although these undoubtedly omit a percentage who have not yet been tested

An indicator of this last point lies in the fact that 40% of the patients in the St James's Hospital study (Foreman et al , 1994) were CDC stage IV when they first presented to the hospital This is worrying and suggests a reservoir of undetected disease in rural Ireland

There is a need for a comprehensive linked picture of the situation regarding HIV infection, and its geographical distribution, which could be arrived at through conducting similar studies to those mentioned above in Dublin and the regions

## 1.4 The history of mathematical modelling/epidemiology

The application of mathematics to the study of infectious disease appears to have been initiated by the mathematician and physician Daniel Bernoulli in 1760 He developed a method to calculate the gain in life expectancy if smallpox were eliminated as a cause of death The research of Henle (1809-85), Pasteur (1827-1875) and Koch (1843-1910) in the science of bacteriology gave a solid and important basis to epidemiology Hamer (1906), using post-germ-theory thinking suggested that the course of an epidemic depends on the number of susceptibles and the contact rate between the susceptibles and infectious individuals This set the stage for all future deterministic studies

The people who pioneered work in this area were epidemiologists with an interest in mathematics which they used to study the transmission dynamics of

epidemics The foundation was firmly laid by Sir Ronald Ross, who received the second Nobel prize in medicine in 1902 for his discovery that the mosquito is the vector of malaria Ross (1911) produced a deterministic mathematical model for the transmission of malaria This model predicts the future state of the epidemic given the initial numbers of susceptible and infectious individuals, together with the attack, recovery, birth and death rates Mathematical theory had made its debut as a research tool in epidemiology

Kermack and McKendrick (1927-39) developed this work further and Bailey's book "The Mathematical Theory of Infectious Diseases" (1957) became the handbook of epidemiologists and mathematicians working in the area

Ross and McKendnck (1912) noted that their equations for the prevalence of the malaria infection in the human and in the vector host could also be applied to females and males with respect to a sexually transmitted disease Bailey (1979) and Hethcote and Yorke (1984) provide an extensive list of references on modelling sexually transmitted diseases in general and for gonorrhoea in particular

In recent years there has been a great upsurge of interest in models for epidemics, partly generated by concern over the AIDS epidemic In fact the AIDS epidemic has tremendously stimulated the development of mathematical models of infectious diseases Much of the work on building mathematical models for the transmission dynamics of HIV infection is deterministic Anderson et al (1986) published the first comprehensive study of the transmission dynamics of HIV in 1986 and many more studies have followed since then The models are almost always described in stochastic terms even when a deterministic analysis is envisaged A deterministic model for the state of a system consists of a set of differential equations which, given assumed parameter values, can be solved numerically if not analytically to give a fixed temporal evolution of the system As Isham (1993) points out different realisations of a corresponding stochastic model can be simulated and results will, in general, exhibit considerable variability depending on the conditions involved Explicit solutions are not usually possible

## 1.5 Scope of thesis

The aim of this work is to develop a mathematical model for the transmission of HIV from intravenous drug users to the general heterosexual population in Dublin which has been identified as being a problem of particular relevance (see section 1 3) We derive the parameters of the model using data collected in Ireland as far as possible To achieve our aim a system of non-linear differential equations first proposed by Anderson et al (1986), and developed by Comiskey (1991), and Comiskey et al (1992), is adopted and adjusted to suit the present model In addition we explore the possibility of adopting other modelling approaches to this work

In Chapter 2 we review the literature on various deterministic models of the transmission dynamics of HIV and their numerical solutions

Chapter 3 looks at the role of statistical studies in providing parameter estimates Details of parameter choice in other studies are examined This chapter concentrates on HIV prevalence and incidence A Retrospective Survey of persons attending needle exchange centres, and a retrospective HIV Transmission Survey carried out in conjunction with the Drug Treatment Centre and the Ana Liffey Drug Project provide further input on the parameters of the sexual and drug using behaviour of intravenous drug users in Dublin

Chapter 4 examines current statistics of AIDS incidence, prevalence and deaths It includes a detailed survival analysis of AIDS patients which is used to estimate the survival parameter for the models

Chapter 5 uses a perturbation method to attempt an analytical solution of the system of non-linear differential equations which describe a deterministic model of HIV transmission, and describes the work to date on this method

Chapter 6 applies the new parameters derived from studies described in chapters 3 and 4 to a deterministic mathematical model of HIV transmission It describes the construction and numerical evaluation of a predictive model under various assumptions covering model structure and parameter values, which are based in part on the results of our various studies It examines the sensitivity of the model to changes in parameters and evaluates potential intervention steps The model, which works in discrete annual time steps, is deterministic and provides predictions on the spread of HIV and AIDS from the IVDU population to the general male and female population of Ireland

Chapter 7 details the results, conclusions and recommendations based on the findings of the thesis

# Chapter 2

# The Mathematical Modelling of AIDS

*I have yet to see any problem, however complicated, which, when you look at it in the right way, did not become still more complicated*

Poul Anderson (Science-fiction writer)

## 2.1 A definition of transmission models

Epidemiology is the study of the distribution of disease in human populations and of the search for determinants of disease encountered in different groups The study of epidemic models of various types is currently highly topical in a number of different disciplines Epidemiological mathematical models of HIV transmission consist of sets of simultaneous differential equations which are formulated based upon specific assumptions about the transmission dynamics of the virus

Numerous particular models have been introduced in recent years to explain various specific aspects of the dynamics associated with the spread of AIDS (see section 1 2 1) These provide useful results by a variety of means including analytical approaches, numerical approximation methods and simulation For example mathematical models based on the theory of Markov chains have been used to predict the spread of HIV/AIDS These models define a population's state at a particular point in time in terms of the states of the individuals in the population at that time The success of these models is dependent only on the availability of adequate data about the states of individuals in the population However data such as dates of diagnosis of AIDS disease stages in individuals are generally **not** known and impossible to determine precisely Fuzzy Arithmetic Techniques have been used to estimate such dates (Bielefeld, 1992)

Back-calculation methods have also been widely studied because they require few assumptions about the shape of the infection curve and require

only AIDS incidence data and an estimate of the incubation period distribution However they provide no information on the future incidence of infection Automata network *SIR* models are a relatively recent development, which put the emphasis on the evolution of the disease

A detailed review of mathematical approaches to modelling HIV/AIDS can be found in Anderson (1989), Castillo-Chavez (1989) and Isham (1988) In what follows, we give the principal outlines of models we have used, indicating obvious limitations and desirable extensions

### 2.1.1 Stages in the course of HIV infection and AIDS

Figure 2 1 provides an illustration of the stages relating to the course of AIDS in a susceptible individual

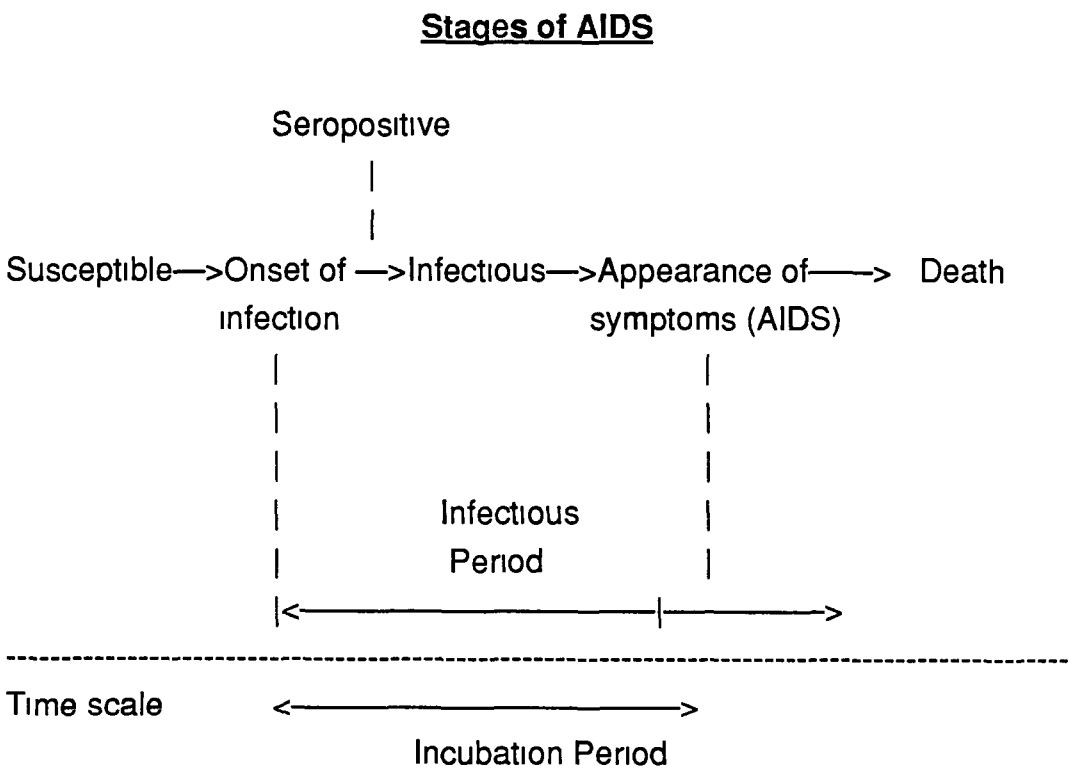



*Figure 2 1 Stages of AIDS*

Individuals infected with HIV pass through a series of progressive irreversible stages (at least 4), from infected but antibody negative to acquired immune deficiency syndrome diagnosis (Redfield et al , 1986) The onset of infection is followed by an infectiousness period during which the individual is

an infective and can pass on the disease to susceptibles A few weeks after infection (6-10, with an average of approx 65 days) (Anderson & May, 1991), antibodies to the virus are normally detectable in the blood and at this stage the individual is termed seropositive The time from infection until symptoms of disease occur is the incubation period It is thought that the incubation period can be described by three stages These correspond to an initial period of high HIV antigen concentration shortly after infection, the longer asymptomatic stage, and the final symptomatic stage with high levels of antigenaemia (an antigen is a substance capable of stimulating the formation of an antibody), before the individual reaches fully developed AIDS (see section 1.1 1)

Studies suggest that infectiousness varies with disease stage, beginning with a highly infectious period immediately after becoming infected, followed by a longer period of low infectiousness and reaching a maximum shortly before the onset of AIDS (Pederson et al , 1987, Goedert et al , 1987 and 1988, Anderson & May, 1988) This could imply that the infectious period is much less than the incubation period In the absence of conclusive data, most published models assume that the infectious period is equal to the incubation period (e g Anderson et al , 1986)

In modelling the epidemic it is usually assumed that all those infected with the virus will ultimately progress to AIDS and that, after AIDS is diagnosed, the individual concerned is effectively isolated (e g sexually inactive) and unable to infect further susceptibles This means that the infectious period is contained within the incubation period

## 2.2 Deterministic models of HIV transmission

Deterministic models involve the representation of individual risk behaviours, HIV transmission from infected to previously uninfected persons, and the development of the disease (AIDS) among those infected with HIV In this way the spread of HIV infection is modelled and future AIDS cases are projected These models incorporate principles of epidemic theory such as the distributed incubation and infectious periods, estimates of the transmission probabilities of HIV infection, an estimate of the initial HIV prevalence, and estimates of the numbers of susceptibles recruited to the sexually active and drug using population They include features like heterogeneity in drug using and sexual activity (defined as the rate of needle sharing or sexual partner change per unit of time, or the percentage of non-drug-using heterosexuals

who have sexual contact with IVDUs) and the effect of changes in sexual or needle-sharing habits

A complete model of the spread of the AIDS virus in the sexually active and IVDU community must account for the complicated interactions between people such as patterns of sexual mixing However, one must begin by understanding the behaviour of simple models with main features like incubation period, contact rates and transmission probabilities before going on to explore more complex ones Two different approaches to the modelling of sexually transmitted diseases have been developed

The first considers the behaviour of individuals as they form and break partnerships In this approach, paired individuals become infected when one partner is infected, but remain uninfected for the duration of the partnership if both are uninfected (Dietz & Hadeler, 1987) The second approach considers the risk to the individual and stratifies the population according to the amount of risk that individuals incur We will concentrate on the latter approach since we are primarily concerned with the models proposed for the spread of HIV in and from high-risk populations (Bailey, 1957, Anderson et al , 1986)

### 2.2.1 Deterministic epidemic transmission models: basic approach

A deterministic model consists of a set of differential equations which, given assumed parameter values, can be solved numerically if not analytically to give a fixed temporal evolution of the system

In most countries in the developed world, spread of HIV infection was initially among the male homosexual population and this was the first situation to be modelled

A basic deterministic epidemic model divides a closed population of male homosexuals into three categories susceptible, infected and AIDS case individuals This is based on a *SIR* model where *S* represents the class of susceptible individuals, *I* the class of infected individuals, and *R* the class of removed (e g sexually inactive) or recovered individuals Suppose that at time *t*, a fixed population, of size *n*, can be separated into a group of X(*t*) susceptibles, Y(*t*) infectives and A(*t*) AIDS cases, where

$$X(t) + Y(t) + A(t) = n,$$

the latent period of the infection being regarded as negligible Suppose that each susceptible acquires new sexual partners at a rate *s*, that the population mixes homogeneously so that at time *t* the probability that such a partner is an

infective is $Y(t)/n$ (strictly $Y(t)/(n-1)$ but $n$ is assumed large), that $\beta$ is the probability of infection from a sexual contact with an infected individual and that $\alpha$ is the rate of developing AIDS for infected individuals Then in a small time interval $(t, t+\delta)$ there will be on average $\beta s X(t) Y(t) \delta / n$ new infectives A deterministic approximation to this stochastic process is therefore that $X(t)$ satisfies

$$\frac{dX(t)}{dt} = -\beta s X(t) Y(t)/n \qquad (2\ 1)$$

Infected individuals are assumed to go on to develop AIDS with $\alpha$ per infective being the mean rate of withdrawal from the infective class Therefore a second equation

$$\frac{dY(t)}{dt} = \beta s X(t) Y(t)/n(t) - \alpha Y(t) \qquad (2\ 2)$$

must be included in the deterministic model and $n$ must be replaced by $n(t)$ in (1) The appropriate form for $n(t)$ depends on the assumptions made about the pool of possible sexual partners It could be the whole population so that $n(t) = n$, or one could assume that each withdrawn individual ceases to belong to the pool of possible sexual partners, and plays no further part in the spread of infection, in which case

$$n(t) = X(t) + Y(t)$$

Anderson et al (1986) proposed that on withdrawal from the class of infectives, each individual enters the class of AIDS patients In this case the incubation period for AIDS, $\alpha$, is the same as the infectious period for HIV, and has expectation $1/\alpha$ (i e $1/\alpha$ denotes the average incubation period) We now have our third equation

$$\frac{dA(t)}{dt} = \alpha Y(t) \qquad (2\ 3)$$

Thus an infective in an otherwise wholly susceptible population will pass on the infection to an average of $R = \beta s/\alpha$ susceptibles, where R is the reproductive rate of the infection

### 2.2.2 The reproductive rate of infection

The potential for the spread of an epidemic such as HIV depends on the magnitude of the reproductive rate of the infection This rate denoted as $R_0$ defines the average number of secondary cases of infections generated by one typical primary case in a population where almost everyone is susceptible to infection — as in the early stages of the epidemic Using data from the U K on rates of partner change, Anderson and May (1988), suggest that $R_0$ may be just above or below 1 If $R_0$ is just above 1 then the doubling time of the heterosexual epidemic would be in the order of 8-14 years, much longer than in the homosexual community Thus, viral spread may increase very slowly and, at the low prevalence outside high-risk populations, require large seroprevalence surveys to detect changes of a small magnitude With a deterministic model, if $R_0$ is greater than one, each infection generates more than one secondary case and the result is a chain reaction or an epidemic If on the other hand $R_0$ is less than one, the infection cannot develop or sustain itself The larger the value of $R_0$ the shorter the time it takes for the number of cases to double

For HIV, $R_0$ is a product of 3 factors the average probability that an infected person will infect a sexual or drug using partner over the period of the partnership, the average number of partners acquired per unit time and the average duration of infectiousness (as noted earlier in section 2 1 1 infectiousness probably does not remain constant, but is often taken to be so for the sake of simplicity)

The reproductive rate of the infection can, however, differ between risk groups and can change over time as behaviour changes Much recent work, for example, has concentrated on the estimation of $R_0$ for the heterosexual population (Dietz, 1993) The nature of $R_0$ suggests that the importance of the timing of behaviour changes cannot be underestimated Changes introduced early in the course of the epidemic have a disproportionately greater effect than similar changes introduced later (Peterson et al , 1990)

### 2.2.3 Model for a population that is not closed

The basic model described above has assumed a closed population and has concentrated on the initial stages of the spread of infection For longer time periods it is necessary to allow immigration at rate $\lambda$, to the class of susceptibles, and migration by all competing causes from all classes Suppose that migration, including deaths unrelated to AIDS occur in all classes at the same rate $\mu$ (to include the natural mortality rate) and that deaths due to AIDS

occur within the class of AIDS patients at an additional rate ν (where $1/\nu \approx$ the average survival time), ν being large relative to μ Then the differential equations in section 2 2 1 are modified as follows

$$\frac{dX(t)}{dt} = \lambda - \beta s X(t) Y(t)/n(t) - \mu X(t) \qquad (2\ 4)$$

$$\frac{dY(t)}{dt} = \beta s X(t) Y(t)/n(t) - (\alpha + \mu) Y(t) \qquad (2\ 5)$$

$$\frac{dA(t)}{dt} = \alpha Y(t) - (\mu + \nu) A(t) \qquad (2\ 6)$$

Anderson et al (1986) describe numerical studies of the deterministic model described above, based on analyses of the available quantitative epidemiological data which assesses how various processes influence the course of the initial epidemic following the introduction of the epidemic

### 2.2.4 Heterogeneity

There are two broad types of heterogeneity which affect the spread of epidemics population heterogeneity (i e that due to differences between individuals, whether intrinsic or behavioural) and heterogeneity of mixing (contact patterns) So far the model described has assumed that the population under consideration is homogeneous, and the parameter *s* represents the constant rate at which individual members of the population acquire new sexual partners However this is an unrealistic assumption since individuals vary considerably in their levels of sexual activity The model can be modified to allow for this variation

May and Anderson (1987), describe one such modified model where it is assumed that the infection probability per partner does not depend on the number of contacts per partner They justify this assumption by reference to data by Peterman et al (1988) where no relationship could be found between the risk of HIV transmission and the number of contacts at risk

This modification is usually done by means of three types of matrices *contact matries, mixing or contact fraction matrices and transmission parameter matrices* A *contact matrix*, gives the number of contacts that persons in group *i* make with persons in group *j* per unit of time (i e the *rate* of making contacts between different groups) The *mixing matrix*, gives the fraction of the contacts of persons in group *i* that are made with persons in *j* per unit of time The *transmission parameter matrix* includes the effects of the probability of

transmission per contact, and so, it gives the transmission rate to susceptibles in *i* resulting from contacts with infectious individuals in *j*

The coefficients within the matrices determine the links within and between the subgroups, these coefficients specify the probability that an individual in subgroup *i* 'mixes' (has sex or shares injecting equipment) with an individual in subgroup *j* Therefore, the mixing matrices serve to allocate partnerships, they specify who has sex with whom and who shares needles with whom Transmission models can be used to determine such variables as which mixing pattern, sex or equipment- sharing, is the most crucial in determining the magnitude of the epidemic, and which parts of the mixing patterns (i e which links between which subgroups) are the most important to HIV epidemiology

There are two main lines of development in the attempts to take into account the effects on heterogeneity on disease transmission One line is empirical, the other is based on a model of mixing in the population

The empirical approach is to try to fill in the elements of a contact matrix directly from data The difficulty with this approach is that such information is not always available, particularly so with regard to sexually transmitted diseases

There are somewhat different approaches to the development of mixing models The most common type of contact matrix in epidemic models of sexually transmitted diseases is built upon the assumption that individuals from different sub-groups mix randomly This leads to a *proportionate mixing model* in which the probability of contact between individuals from different groups is proportional to the size or amount of activity of the groups involved Hethcote and Yorke (1984) have developed a mathematical model for the transmission dynamics of Gonorrhoea to allow for the influence of population structure and a proportional mixing assumption, with sexual partners being weighted by their activity They have thus shown the importance of the existence of so-called core groups of individuals with much higher rates of partner change than the majority of the population

Anderson et al (1986) have explored numerically the properties of the course of the AIDS epidemic using such a modified model

Peto (1986) describes a simulation study using a simple AIDS transmission model in which he classifies the sexual activity parameter *s* into two groups, with a small minority of individuals having a very high activity rate while the majority of the population has a low rate

Another possibility is that of *restricted* mixing, where individuals choose partners only from within their own sub-groups

However because the *proportional* and *restricted* mixing assumptions are not very realistic, especially for sexually transmitted diseases, Sattenspiel et al (1990), have relaxed some of the constraints on mixing patterns and developed a model based on a particular form of non-random mixing which they term *preferred mixing* In this form of mixing a certain proportion, $p_i$ of contacts are made between persons within the same group, while the remaining contacts, $(1-p_i)$ occur between individuals from different groups and are made in proportion to the amount of sexual activity of the groups Sattenspiel et al explore the effects of varying the proportion of contacts restricted to within the group and show conclusively that lack of randomness in the choice of sexual partner can profoundly affect the course of the epidemic and is an important confounding factor to the levels of sexual activity

In contrast, Castillo-Chavez (1991), shows that preferred mixing (a convex combination of two mixing functions), contrary to the suggestions of some researchers, does not contain all reasonable possibilities

Jacquez et al (1989) and Koopman et al (1989) devised a mixing scheme (*structured mixing*) which allows the proportions of choices to be specified over all the subgroups In this scheme, choices are made in "contact classes" which can be thought of as locations (e g , geographical or social) in which the partner choices take place Alternatively, they could be determined by type of sexual activity or age group

With a heterogeneous model, the early exponential increase in the incidence of seropositivity or of AIDS will soon be replaced by a more slowly increasing function This is because after the initial period of rapid spread of infection through the highly active individuals, during which a large proportion of them will become infected, most of the subsequent infections will be of the less active individuals amongst whom the epidemic will progress at a slower rate Therefore a slowing of the rate of increase in the incidence curve is an inevitable consequence of heterogeneity in sexual activity and not necessarily a consequence of individuals changing their behaviour (Blower et al , 1990, DeGruttola & Lagakos, 1989, May and Anderson, 1987) In such a situation the observed slowing may be only temporary and the seroprevalence/incidence level may soon begin to rise again

### 2.2.5 The incubation period distribution

Attempts have been made to relate the number of reported cases of AIDS in a defined population to the proportion of that population infected with the virus as a specified point in time (Anderson et al , 1986, May & Anderson, 1987) Non-parametric methods use only the information available from the observed data, but cannot therefore provide estimates of the progression to AIDS at durations greater than have been observed Parametric methods, which provide estimates of rates of progression to AIDS at durations greater than have yet been observed, require assumptions to be made about the form of the distribution of the incubation period of the disease Proper analysis of the distribution of incubation times for people infected with HIV can only be carried out by studying groups where the date of infection is known, or can be accurately estimated, and observing them over a long period, probably for 20 years or more

Because we are presently in the relatively early stages of the HIV epidemic knowledge of the shape of the incubation time distribution is limited Medley et al (1987, 1988 a, b) analysed 297 cases of transfusion-associated AIDS known to have been diagnosed in the U S A before 1986 and for whom date of diagnosis and date of AIDS were known Assuming exponential growth (because it fitted the data better than linear growth) in the number of infected individuals and a Weibull distribution (because it best described the data) for the incubation time, Medley et al estimated a mean incubation time of 8 23 years for adults The Weibull distribution, which is widely used in survival studies, is equivalent to supposing that some power of incubation time is exponentially distributed

The simple model described in section 2 2 3 assumes that the infectives who develop AIDS are withdrawn into the class of AIDS patients at a constant rate $\alpha$ However it is more probable that the chance of withdrawal depends on the time since infection A simple deterministic model describing the incubation of AIDS is as follows Let $a(t)$ denote the proportion of a cohort of patients (all of whom were infected with HIV at time $t = 0$) who have AIDS at time $t$ If we assume that the rate of conversion from seropositivity to 'full blown' AIDS is $\alpha(t)$ at time $t$ from the point of infection, then the rates of change of $a(t)$ and $y(t)$ (the proportion who do not have AIDS, $y+a=1$) are given by

$$\frac{dy}{dt} = -\alpha(t)y(t), \qquad (2\ 7)$$

$$\frac{da}{dt} = \alpha(t)y(t) \qquad (2\ 8)$$

The initial condition is, of course, $y(0) = 1$ and $a(0) = 0$ We assume for simplicity that all infected members of the cohort eventually develop AIDS Because the progressive impairment of the patient's immune system through time from the point of infection with HIV results in a linear rise with time in the probability that an opportunistic infection or cancer develops in that patient, a simple assumption concerning the form of the function $\alpha(t)$ is that it is linear with an intercept at zero ($\alpha(t) = ct$) The solutions of equations (2 7) and (2 8) are

$$y(t) = \exp\left(-\frac{1}{2}ct^2\right), \qquad (2\ 9)$$

$$a(t) = 1 - y(t) \qquad (2\ 10)$$

Equation (9) is identical to the 'hazard function' of the Weibull distribution The incubation period for AIDS should have an increasing hazard function, representing progressive deterioration of the infective's immune system In order to take this into account one must subdivide the class of infecteds at time $t$ by time of infection and by sexual activity Anderson et al (1986) describe numerical studies of a model modified to include the incubation period distribution

It seems clear, however that the incubation periods for men and women may differ as may those for different age groups (see Medley et al , 1987 and 1988, Longini et al , 1991, Mientjes et al , 1993, and references therein)

### 2.2.6 Stages of infectiousness

In order to differentiate between stages of infectiousness, Billard and Zhen Zhao (1994), have established a mathematical framework for a multiple stage Markov model in which a population of fixed size $N$ is divided into five categories susceptible, infected seronegative, seropositive asymptomatic, pre-AIDS and AIDS case individuals This division of overall infectiousness into these different stages was first proposed in the Walter Reed study (Redfield et al , 1986), which divided the infective stage into six different components This was developed by Longini et al (1989) who partitioned the infective period into

four progressive stages and distinguish between individuals diagnosed with AIDS who are alive and those who have died

Blythe and Anderson (1988a, b), proposed a deterministic model to account for the effect of varying infectivity by allowing the transmission probability to vary from stage to stage Their model is simplified by assuming that the rate of infection in the second stage of infection is 0 In their models in which the incubation parameter values reflect two peaks in infectiousness, Blythe and Anderson show how temporal variation in infectivity (the contact transmission probability) can influence the qualitative shape of the epidemic, and suggest that infectiousness is of shorter duration but of greater intensity than has previously been envisaged In this model no allowance is made for variable susceptibility of individuals to infection by an infected partner

Isham (1993) has shown that predictions depend crucially on the actual levels over time of the infectiousness

## 2.3 The heterosexual epidemic

The models described in section 2 2 have concentrated on a male homosexual population For transmission between heterosexuals the model has to be made more complicated, since there are two groups of individuals with the infectives in one group spreading the infection to the susceptibles in the other If we denote the numbers of female susceptibles, infectives and AIDS cases at time $t$ by $X_f(t), Y_f(t)$ and $A_f(t)$, with $X_m(t), Y_m(t)$ and $A_m(t)$ being the corresponding numbers for males, then a two group model corresponding to the simple homogeneous mixing model (see equations 4, 5 and 6) can be described by the following equations

$$\frac{dX_f(t)}{dt} = \lambda_f - \beta_{mSf} X_f(t) Y_m(t)/n_m(t) - \mu_f X_f(t) \qquad (2\ 11)$$

$$\frac{dX_m(t)}{dt} = \lambda_m - \beta_{fSm} X_m(t) Y_f(t)/n_f(t) - \mu_m X_m(t) \qquad (2\ 12)$$

$$\frac{dY_f(t)}{dt} = \beta_{mSf} X_f(t) Y_m(t)/n_m(t) - (\alpha + \mu_f) Y_f(t) \qquad (2\ 13)$$

$$\frac{dY_m(t)}{dt} = \beta_{fSm} X_m(t) Y_f(t)/n_f(t) - (\alpha + \mu_m) Y_m(t) \qquad (2\ 14)$$

$$\frac{dA_f(t)}{dt} = \alpha Y_f(t) - (\mu_f + \nu) A_f(t) \qquad (2\ 15)$$

$$\frac{dA_m(t)}{dt} = \alpha Y_m(t) - (\mu_m + \nu) A_m(t) \qquad (2\ 16)$$

where $X_f(t) + Y_f(t) + A_f(t) = n_f(t)$ and $X_m(t) + Y_m(t) + A_m(t) = n_m(t)$ the total number of females and males in the sexually active age groups The mean incubation period and the rate of deaths due to AIDS is assumed to be the same for females and males but the transmission coefficients $\beta_f, \beta_m$ for spread of infection from female to male and from male to female are not assumed to be the same May and Anderson (1987) suggest that $\beta_f < \beta_m < \beta,$, where $\beta$ is the corresponding coefficient for homosexual males Similarly, the rates for partner change $s_f, s_m$ of females and males are probably not the same, and are likely to be substantially smaller than the male homosexual rate, and the rates of migration (to include natural mortality) are assumed to be different for females and males

In equations 11-16, the spread of HIV infection and the incidence of AIDS in a heterosexual population is modelled However it is of particular interest to us to investigate the effect on the heterosexual population of the current epidemic in male and female IVDUs as IVDUs may also be expected to transfer the infection to their non-IVDU sexual partners (see section 1 1), and for this the model must be extended still further Comiskey et al (1992) describes a numerical study of such an extended model in which the migration rate (to include mortality) and the rate of change of sexual partners are assumed to be constant

Comiskey (1992) denotes the four different groups within the population by the subscripts 1, 2, 3 and 4 for male and female drug users and male and female non drug users respectively Hence the population of male drug users at time $t$ is denoted by $P_1(t)$, the population of female drug users at time t is denoted, $P_2(t)$ and so on The nonlinear differential equation model to describe the rate of change in the number of susceptible, infectious and AIDS patients in the male and female intravenous drug using and non IV drug using populations is given by

$$\frac{dX_i(t)}{dt} = \lambda_i - \sum_{j=1}^{4} \frac{\beta_{ij} s_{ij} X_i(t) Y_j(t)}{P_j(t)} - \sum_{j=1}^{4} \frac{\hat{\beta}_{ij} \eta_{ij} X_i(t) Y_j(t)}{P_j(t)} - \mu_i X_i(t) \qquad (2\ 17)$$

$$\frac{dY_i(t)}{dt} = \sum_{j=1}^{4} \frac{\beta_{ij} s_{ij} X_i(t) Y_j(t)}{P_j(t)} + \sum_{j=1}^{4} \frac{\hat{\beta}_{ij} \eta_{ij} X_i(t) Y_j(t)}{P_j(t)} - (\alpha + \mu_i) Y_i(t) \quad (2\ 18)$$

$$\frac{dA_i(t)}{dt} = \alpha Y_i(t) - (\mu_i + \nu) A_i(t) \quad (2\ 19)$$

where

$$X_i(t) + Y_i(t) + A_i(t) = P_i(t)$$

$\hat{\beta}_{ij}$ is the probability of transmission during a single needle sharing act from an infectious in group $j$ to a susceptible in group $i$ The rate of needle sharing for members in group $i$ with members in group $j$ is $\eta_{ij}$ per unit time

Williams and Anderson (1994) describe a model for England and Wales which mimics transmission within and between different sexual activity classes (or needle sharing classes in the case of intravenous drug users) and within and between different risk groups such as male homosexuals, intravenous drug users and heterosexuals However they make no distinction between males and females and so fail to allow for differing probabilities of the transmission of HIV from males to females and vice versa

A factor that plays an important role in HIV transmission, especially in the initial phase of the epidemic, is the phenonomen of pair formation Pair formation markedly decreases the number of contacts involved in general transmission by concentrating the contacts within pairs Dietz (1988) and Dietz and Hadeler (1988) have developed models of the transmission of HIV infection for populations in which long-lasting partnerships are common In these models the population is divided into single males, single females and female-male pairs These models introduce explicitly a pairing rate and a separation rate The infection transmission dynamics depends on the contact rate within a pair and the duration of a partnership Dietz and Hadeler assuming that a new partnership can only start after the termination of the previous one, found that endemic equilibria can only exist if the separation rate is sufficiently large in order to ensure the necessary number of sexual partners The classical models are recovered if one lets the separation rate tend to infinity This approach highlights the importance of sexual pair formation, but, some of these models can prove quite complicated as can be seen from that of Dietz (1988) Dietz has 29 variables, the equations for which involve 42 parameters Reliable information does not in fact exist for many of the parameter values

The model would become even more complicated if it was extended to consider the progression of infectives to AIDS Daykin (1990) and Wiley et al (1989) furthermore note recent studies which indicate variation in the infectivity of HIV among heterosexual couples ($\beta$) Wiley et al represent this heterogeneity by modelling $\beta$ as a random variable

Blower et al (1991) used a transmission model as an explanatory tool to clarify the relationship between heterosexual and IVDU transmission They used a computer simulation to examine the gender-specific risks of heterosexual transmission in IVDUs Their results showed that the effect of the heterosexual transmission risk factor on increasing the risk of HIV infection depends upon the level of risk of drug injecting behaviour They also demonstrated that the addition of the heterosexual transmission risk factor to an individual with a very risky drug-injecting behaviour does not increase the individual's risk of HIV infection, whereas the addition of the same risk factor to an individual with a less risky drug injecting behaviour can significantly increase the individual's risk of HIV infection Another variation of a transmission model has been used as an explanatory tool by Kaplan (1989), to identify which factors determine the transmission speed of the virus among a community of needle-sharers

### 2.3.1 Demographic factors

Age structured models have also been proposed These may allow for more realism since it is known that the length of the incubation period tends to decrease with increasing age in adults Bongaarts (1989) proposed a staged computer simulation model in which he divides the infectious period into four infectious substates He stratifies his population by age, sex, sexual behaviour, marital status and infection/disease status

Anderson and May (1991) developed a series of age structured models and concluded that three realistic refinements, concerning sexual behaviour and the likelihood of transmission between the two sexes, produced a higher likelihood of the disease AIDS inducing a severe demographic impact These are age dependency in sexual activity (from high to low as people age), male preference for female sexual partners younger than themselves, and a higher likelihood of transmission from males to females and vice versa The reasons for the increased severity of the epidemic with these refinements are that all three factors enhance the chance that females are infected and die from AIDS during their years of high fertility. They modelled the situation when each of the three factors were taken independently and when all three were taken

together The most severe independent impact results when the effective rate of sexual partner change is highest in young men and women

### 2.3.2 Changes in behaviour

Changes in behaviour can be incorporated into the model by letting individuals move from one sexual/drug-using activity subgroup to another Another sort of behaviour change is the adoption of safer sexual/needle-sharing practices as the epidemic progresses or publicity campaigns are mounted In the models for AIDS described so far, it has been assumed that infected individuals will take steps not to transmit HIV infection once they have progressed to full AIDS However, it is possible that many individuals who are aware of their infected status will cease transmission of infection at an earlier stage

This change could be introduced to the model by taking the transmission probability $\beta$ to be a function of real time $t$ (as well as the time $\tau$ since infection) Alternatively, in a staged model one could suppose that the mean period of the third infectious stage is cut short even though full AIDS will not develop for the number of years by which it is shortened

A discrete-time model such as that for AIDS incidence, developed by Pickering et al (1986) would be appropriate to model such changing behaviour In a similar vein it will be necessary to allow for the temporal evolution of the model by incorporating treatment effects (Schechter et al , 1989)

## 2.4 Summary

The major goal of modelling the AIDS epidemic is to gain insight into its dynamics which in turn will assist policy decisions This insight can best be gained by first using simple models and then developing these by the gradual inclusion of more complex features However the penalty attached to models incorporating greater realism is clearly the increased number of parameters about whose values and distributions there is considerable uncertainty As stated by Davis and Hersh (1981) a model is "a 'sometime thing', a convenient approximation to a state of affairs rather than an expression of eternal truth" The essence of modelling is to capture the main processes at work

We need to understand how the dynamics of a model depend on its basic components, and how sensitive they are to the way in which these are incorporated into the model Numerical studies of the models described in this

chapter have been made to judge the effects of changes in assumptions and parameter values, and to gauge which of these have a critical influence on the course of the epidemic and conversely to identify those to which it is reasonably robust Many of these studies have used estimates of parameter values based on observational or survey data for particular populations (see e g Comiskey, 1991, Comiskey et al , 1992)

However one must be careful here, since, as the epidemic progresses and attracts publicity, the underlying parameter values relating to sexual or drug using behaviour may change (see for example Noone et al , 1993)

By identifying critical points in the transmission chains it may also be possible to identify places for intervention in the process that would not otherwise be obvious Therefore, mathematical models could be used to identify which subgroup and /or type of behaviour it is most important to target for behavioural change or for treatment In addition, by investigating the effectiveness of particular strategies in model form one can examine the impact on the total epidemic (Peterson et al , 1990)

The use of mathematical models to provide reliable predictions on the future course of the AIDS epidemic requires the collection and analysis of many more data sets than are currently available In Ireland there is a particularly strong need for data regarding IVDUs and for data that will clarify the parameters involved in heterosexual spread Nevertheless, by critical consideration of the assumptions made in the modelling process, by using such data as are available and, in particular, by exploring the effects of alternative assumptions, mathematical models have a crucial role to play in predicting the future course of the disease

# Chapter 3

# Revised Parameter Estimates: HIV Prevalence

## 3.1. Introduction

In this chapter we looks at the role of statistical studies in providing parameter estimates We also review the available literature on HIV transmission to determine plausible ranges for the parameters which we use in the deterministic model described in chapter 6, which is used to provide future projections

Sources of parameter estimates of the sexual and drug using behaviour of intravenous drug users, are drawn primarily from studies conducted in Western Europe, in particular from studies conducted in Scotland and Italy where patterns may be expected to be similar to those in Ireland Previous Irish sources include retrospective studies of persons attending needle exchange centres, persons being maintained on Methadone, and HIV-infected prisoners We have also obtained refined estimates, particularly for example, of intervention parameters, through our own retrospective studies carried out in conjunction with the AIDS Resource Centre, the Drug Treatment Centre and the Ana Liffey Drug Project (Dunne et al , 1993, Dunne et al , 1995)

The collection of statistics is not only an end in itself It is a means of providing information on which the development of plans and strategies are based The aim of our studies is to provide the basis (i e the parameters or a reasonable range of estimates of these) to refine the models which seek to determine the development of the epidemic

The key parameters in determining the rate of growth of the AIDS epidemic are (1) rate of contact between individuals in different sub populations and different populations, (2) risk of transmission per contact, (3) risk of developing AIDS given infection with HIV, and (4) risk of infectivity (i e , capability of transmitting HIV) over time, given infection has occurred These can be categorised under three headings demographic, behavioural and biological

## 3.2. Demographic data

### 3.2.1 Size of the IVDU population

Current estimates of the size of the IVDU population in Dublin are generally informed guesses rather than estimates Several attempts to estimate the size of IVDU populations in discrete locations have been attempted Frischer et al (1993) point out that ecological techniques used to estimate animal populations can be applied to IVDU populations In particular, the capture-recapture method (CRM) has been applied to drug-user populations Frischer (1992), applied this method to estimate the number of drug injectors in Glasgow (see also Frischer & Leyland, 1992 and Brancato et al , 1992)

Prior to 1990, the most reliable indicator of general trends in the incidence of drug use in Dublin was the number of new cases seen in the Drug Treatment Centre (DTC) Ireland's major treatment centre for drug users, (later to be named the National Drug Advisory and Treatment Centre and, later still the DTC), was established in Jervis Street Hospital in Dublin in 1969 The Centre treats drug users from all parts of Ireland although 90% of their cases are from the Eastern Health Board Area and the vast majority of these in turn are from the Greater Dublin Area

There was a dramatic increase in the number of new cases seen by the DTC from 1979 on, with a peak number of new cases (892) in 1982 Most of this increase was attributable to opiate users, particularly heroin addicts Indeed it was commonly thought that there was an opiate epidemic in Dublin during the years 1980-1985 (Butler, 1991) With the advent of heroin, intravenous drug use became the norm A prevalence study, commissioned by the Minister for Health, which investigated a north inner-city community during the period 1982-1983, revealed that 10 per cent of those in the 15-24 age group had used heroin in the year prior to the study Since 1982 the number of new cases has fallen, and the situation stabilised during the years 1983-1990 In 1991 the DTC saw 424 new cases However, this fall off in the number of new clients seen by the DTC does not necessarily reflect a fall off in the incidence of drug use but rather reflects the situation in Dublin where the DTC is no longer the only drug addiction and treatment centre (for example, 652 individuals with a history drug use attended the Ana Liffey Drug Project during 1993, which was a 10% increase over the previous year) Indeed it has been suggested that there are indications of an upsurge of drug activity in Dublin (Department of Health, 1991, Irish Times editorial, 30th Sept 1994)

Estimates of the number of IVDUs in Dublin varies from 3,000 to 15,000 (Bury, 1989) (see page 11) The Catholic Social Service Conference (1988) estimated that there were 4,000 heroin users in Dublin in 1988, while another estimate placed the number of intravenous drug users in the Greater Dublin Area in 1990 at 7,000 (O'Kelly et al , 1990)

In 1989 a comprehensive Dublin Drug Misuse Reporting System was set up in the Health Research Board to collate information on drug users in 22 different treatment centres throughout the Greater Dublin Area Anonymous information on clients in treatment centres is returned to the Health Research Board on a regular basis The figures published for 1991 do not however include drug users treated in Mountjoy Prison, or those treated by general practitioners In addition there was some under-reporting in two of the participating centres (O'Hare and O'Brien, 1993)

In response to an *AIDS in the World* survey in 1992, the Irish national AIDS program estimated the number of IVDUs to be 4000 (Mann et al , 1992) According to O'Hare and O'Brien (1993), an estimated 2006 persons received treatment for drug misuse in 1991, which is 29% of the 7000 estimated by O'Kelly et al (1990) This is a very high percentage of IVDUs in treatment if it is compared with the 14% estimated by Frischer (1992)

Such information as is available on the nature and extent of drug use in Dublin refers mainly to those drug users who are in treatment This is not the same as the total population using drugs, however, since it is likely that a significant proportion of persons using drugs are not receiving any form of treatment (Klee et al , 1991b, Frischer, 1992, Des Jarlais and Friedman, 1987) Des Jarlais and Friedman (1987) state that the great majority of IV drug users are not in treatment at **any** point in time Research has shown that many Irish drug users are using drugs for an average of four years before they present for treatment (Woods, 1992) The drug using population is also difficult to quantify because given the illegality of the activity drug users are difficult to contact

The female male ratio for treated Dublin IVDUs is estimated to be 1 3 3, based on the findings from the Dublin Drug Treatment Reporting System for 1991 (O'Hare and O'Brien, 1993) However the proportion of females is probably greater than that estimated, since it is the belief of many drug workers that women tend to present for treatment later, if at all Due to the predominance of males in the IVDU community, the majority of sex partners of male IVDUs will be non-IVDU females, and so, the potential for heterosexual transmission from male IVDUs to female non-IVDUs may be considerably greater than from female IVDUs to male non-IVDUs Differences in hetero-

sexual transmission will also be affected by gender differences in sexual behaviour (male IVDUs tend to have higher numbers of sexual partners than their female counterparts) and also by asymmetry in the heterosexual transmission efficiency of HIV the transmission efficiency is estimated to be significantly greater from male to female than from female to male (Johnson & Laga 1988)

Other demographic details necessary include the rates at which people begin and cease injecting drugs intravenously, the rates at which people begin and cease sexual activity, and the extent of recruitment into the drug using and sexually active populations Richardson et al (1993) in their retrospective study of IVDUs, found that the mean age of first injection for 150 Irish respondents was 19 7 years (s d of 4 3 years) and the mean duration of injecting was 6.3 years (s d of 4 6 years) McKeown et al (1993) found the mean age of first injection to be similar for 120 Irish subjects, with a mean of 19 4 years for women but 18 years for men, a finding consistent with previous research indicating that women start taking drugs later than men (O'Hare & O'Brien, 1992) A more recent study by Smyth et al (1994) found a mean duration of injecting of 4 9 years for 152 males, and 3 6 years for 61 females, attending the Drug Treatment Centre

Transmission models require estimates of the size of the IVDU and the bridge community (which consists of those non-IVDUs who are the sexual partners of IVDUs), but these are rarely known and may be difficult to obtain precise estimates of, for a number of reasons, not least the sensitivity of the problem Klee et al (1991a), studied 169 injecting drug users in the North West of England from a variety of settings (both in and out of treatment) to determine HIV risk behaviour They found that 54% of their sample preferred sexual partners who were non-drug users, 41% felt that drug status was irrelevant and 5% preferred drug users The study found that in general, respondents were moderately successful in acquiring partners of the preferred drug status

### 3.2.2 HIV infection amongst the IVDU population

Estimating the prevalence of HIV infection among IVDUs is methodologically difficult because true random samples of the general population of drug injectors are not obtainable (see page 13) Donoghoe et al (1993), found that London drug injectors with no experience of treatment had significantly lower rates of HIV-antibody testing, and significantly higher levels of HIV prevalence and of unreported HIV positivity than those previously or

currently in treatment The study reported by Rhodes et al (1993b), had similar findings Rhodes et al found that of 104 confirmed HIV-1 antibody positive drug injectors in London, 41 3% had never received treatment or help for their drug use, and that 52% had never received a named test for HIV antibodies In addition they found that the majonty of confirmed HIV positive respondents (70 1%) were unaware of their HIV positive status Rhodes et al (1993a), in a cross-national study of HIV prevalence and HIV risk behaviour among 1,037 IVDUs also found a higher rate of prevalence in those with no experience of drug treatment Contact with services increases the opportunities for AIDS education and the promotion of harm reducing injecting procedures McKeown et al (1993), in a survey of 120 clients of the Merchants' Quay drugs service in Dublin, found that since the drug users had come into contact with the service 38% had increased the use of clean needles and 14% had increased their use of condoms

Our study of IVDUs in a treatment setting (Dunne et al , 1995), described in detail in the Appendix shows that most IVDUs (77%) had been tested for HIV antibodies Overall 26 (29%) were seropositive, 54 (60%) were seronegative and HIV status was unknown in 10 (11%) However, almost a third (31 6%) of IVDUs in our study were unaware of their antibody status, either because they had not sought testing at time of interview, or because they had not looked for the result once tested This strongly indicates that only part of the problem is being assessed

It was pointed out by Robertson et al (1986), in a letter to the *Lancet*, that young drug users are particularly at risk of AIDS because they rarely have their own equipment and have little contact with the medical services or access to health education

These studies suggest that previous investigations of HIV prevalence among drug users may be biased by drawing on samples primarily from treatment settings

## 3.3. Behavioural data

### 3.3.1 Introduction

The rate of transmission of AIDS in a given population depends on a large number of behavioural variables the most important of these are the duration of partnerships (needle sharing and sexual), the gender-specific rate of acquisition of new partners, the type of sexual practice, and the patterns of

sexual 'mixing' such as mixing within and between populations with different disease prevalence like IVDUs and non IVDUs (Anderson and May 1988) In general, high degrees of within-group mixing tend to reduce the overall magnitude of the epidemic

### 3.3.1.1 Source of parameters for the IVDU population

The parameters for the IVDU population were obtained from groups of IVDUs from two different Irish treatment centres, (n=117), (Dunne et al , 1995) Double-site sampling helps to reduce some of the inherent bias in single-site recruitment and enables us to determine a range of plausible values for parameters in the model described in Chapter 6 These parameters include age of first heterosexual activity, rate of needle sharing, whom sharing with (strangers or always the same people), injecting behaviour of sex partners, number of new sex partners per unit time, use of condoms and type of sexual activity, and HIV status We also use the results of a survey of 62 HIV positive women attending an HIV clinic between 1989 and 1991 to assess special groups within the parameter ranges and to complement our work (Comiskey et al , 1993)

Studies in drug users are fraught with difficulties and, as mentioned earlier, recruitment of users into studies may be biased by selecting drug users from treatment programmes (Kozel and Adams 1986, Fnscher et al , 1992)

### 3.3.1.2 Source of parameters for the non-IVDU population

Since research on sexual behaviour carried out in other countries cannot be applied with confidence to the Irish situation (Johnson et al , 1989a), the parameters for the general non-IVDU population were obtained from two studies dealing with sexual habits in Ireland, which were conducted in the recent past The first, by Lansdowne Market Research (1992), assessed the attitudes, opinions and beliefs of 604 adults, aged 18-64 who returned self-completed questionnaires in August 1992 These respondents were initially contacted through a survey amongst a nationally representative sample of 1,400 adults aged 15 and older This two stage process resulted in an imbalance by age group, (too high a proportion aged 18-34 and too few aged 50-64), and region, (too high a proportion living in Dublin), and so the findings are likely to reflect more liberal and less conservative attitudes and behaviours than if the sample had more exactly replicated the adult population aged 18-64 Nevertheless, the authors contend that the sample size (604) is large enough and its composition sufficiently widespread demographically and

geographically to give credibility to the survey findings as representative of a substantial part of the adult population of this country

The second survey was carried out by Irish Marketing Surveys on behalf of LRC Products (1993), which manufactures Durex This survey measured sexual behaviour and attitudes to condoms and AIDS, of a statistically representative sample of 766 persons aged 17-49 living in the Republic of Ireland The questionnaire in this instance was administered in two parts, the core questions were asked via face-to-face interviews whilst a self-completion booklet covering the most sensitive behavioural topics was used to give respondents complete privacy and confidentiality

### 3.3.2 Needle sharing partnerships

#### 3.3.2.1 Rate of needle sharing

Clearly, the level of sharing is an important determinant of HIV spread (Schoenbaum et al , 1989) A study conducted by Richardson & Papaevangelou (1994 a) for the E U Study Group, in two phases (1990-91 & 1992-93), of the high risk drug use practices in European IVDUs (half of whom were recruited out of treatment settings) found that injecting practices carrying a high risk of HIV transmission remain common in European IVDUs Only the self reported efficiency of cleaning showed improvement 42% of respondents in the second phase had injected with another IVDU's used needle (45% on phase 1), and 46% said they never gave used equipment to others 40% (24% on phase 1) of those who used another's needle had used an effective method of cleaning

A study conducted by Kelaher & Ross (1994) found that high risk behaviour in Australia was most likely in situations where needle availability was low, craving was high and others present were well known and had previously shared together The results suggest that HIV risk behaviour is strongly linked to the environmental context rather than high risk individuals The authors suggest that easy access to needles may have contributed to the relatively low probability of HIV risk associated with predominant patterns of injecting drug use in Australia

**However**, Italy provides a strong counter example The legal availability of sterile needles and syringes without prescription has not prevented the rapid spread of HIV among IVDUs in the northern part of the country (Des Jarlais &

Friedman, 1987) This is perhaps indicative that availability does not necessarily imply usage

Robert et al (1990) studied behavioural changes in intravenous drug users in Geneva and found that the incidence of new HIV infection peaked before 1984 (seroprevalence increased from 6% in 1981 to 38% in 1983) and has since declined (IVDU s starting methadone maintenance in 1987-1989 in this city had a seroprevalence rate of 22%) The authors suggest that this decline is mainly due to decreased needle sharing

Coming nearer to home, by 1984, Edinburgh had a HIV infection epidemic among IVDUs Indeed seroprevalence rose to approximately 50% within 2 years of the first seropositive sample By the end of 1988, 1578 people —55% of them IVDUs mainly concentrated in Edinburgh—were HIV positive in Scotland (Delamothe, 1989) It was also noted by Robertson et al , (1986) that the level of sharing among IVDUs in Edinburgh (where there was a policy of restricting injecting equipment from 1982 to 1985) was significantly far higher than in Glasgow This finding was interpreted by the authors as being the key factor in explaining the differential patterns of HIV infection among IVDUs in the two cities and consequently they proposed that needles and syringes be made freely available to IVDUs This policy has since been implemented in Glasgow Frischer et al (1993), believe that this policy has been instrumental in maintaining low HIV prevalence among IVDUs in Glasgow and so lends support to the hypothesis that availability of clean injecting equipment may be an important factor in preventing the rapid increase in HIV infection Not withstanding this policy however, Frischer et al (1992), used a multi-site sampling strategy and found that a third of IVDUs in Glasgow continued to inject with used equipment

Klee et al (1991b) found that age and length of drug use (which predictably increased with increasing age) were important factors in sharing in the North-West of England Sharing was least prevalent among older respondents and long-term users maintained on methadone in long-term treatment More non-agency respondents in this study were currently sharing than those in contact with treatment services However, although no differences were found between agency and non-agency respondents in the younger age groups, regarding how recently sharing had occurred, significant associations were found for those over 25 years with non-agency respondents sharing on a more recent basis The authors suggest that the positive influences of treatment upon risk behaviour may be heavily dependent upon age and that a reduction of risk observed in an 'agency' group could therefore

be a reflection of the entry into treatment of a group already pre-disposed to share less They also point out however, that a predisposition becomes reality more surely if it receives environmental support These findings are backed up by Schoenbaum, (1989) who found that longer time in methadone treatment was associated with substantial lower HIV seroprevalence rates

A number of Irish studies have addressed this question Williams et al (1990) looked specifically at Irish IVDUs receiving methadone maintenance and known to be seropositive (N = 48), and investigated whether they had altered their behaviour as a result of being infected They found that since diagnosis the cohort had made significant alterations in their at risk behaviour for HIV transmission The number of IVDUs sharing injecting equipment reduced from 47 (98%) to 30 (63%, p < 0 001, McNemar test for matched pairs data) Of those who continued to share after diagnosis, only 6 (20%) did so regularly (P < 0 001) Forty-one (87%) had shared regularly prior to diagnosis However, despite this positive change, there remained a high level of at risk behaviour for further HIV transmission Despite being seropositive 30 individuals (63%) had continued to share injecting equipment (even if at a reduced risk level)

Pomeroy et al (1991) assessed the needle sharing behaviour amongst 60 patients attending a methadone programme in Dublin They found that with the advent of HIV there is some evidence of a change in needle using habits amongst IVDU in Dublin Although 97% admitted to previous needle sharing, only 22% shared needles in the previous 6 months despite continued intravenous drug use.

O'Mahony and Barry (1992), in a study of HIV risk behaviour amongst HIV-infected prisoners in the Irish prison system, found that 38% had shared needles while free, with others whom they did not know to be HIV positive, despite knowing that they themselves were HIV positive

A study of 120 clients of the Merchants' Quay drug service (McKeown et al , 1993) found that 53% of those who inject also share needles and that there was no difference in sharing between women and men In addition 41% of those who share do not always clean their needles Of those who share and do not always clean 64% are HIV seropositive

In the study of 62 HIV positive women attending an HIV clinic between 1989 and 1991, conducted by Comiskey et al (1993), all 51 (82 3%) Irish female IVDUs admitted to having shared needles There appear to be gender differences in needle sharing behaviour patterns (Barnard, 1993)

Our two site study of 117 IVDUs (Dunne et al , 1995, see Appendix), found that 67% of those who injected in the previous three months (n=79) had shared equipment There were no significant differences found in needle sharing risk behaviour by sex The vast majority, 93 (80 2%) of the total group reported that they always cleaned needles 21 (18 1%) said they sometimes cleaned and 2 reported that they never cleaned injecting equipment However when questioned about the methods they employed in cleaning the equipment, only 60 (52 6%) subjects effectively cleaned the equipment

Several studies have reported evidence for behavioural change towards injecting risk reduction among IVDUs (Hart et al , 1989, Williams et al , 1990, Robert et al , 1990, Klee et al , 1991a, Pomeroy et al , 1991, O'Mahony & Barry, 1992, Comiskey et al , 1993, Desenclos et al , 1993, Rhodes et al , 1993a, b) Increasingly those in treatment are using sterile injecting equipment and reducing the number of people with whom they share (Richardson & Papaevangelou, 1994 a, Pomeroy et al , 1991, Robert et al , 1990, Williams et al , 1990)

### 3.3.2.2 Numbers of needle sharing partners

Little data are available on which to base estimates of rates of change of needle sharing partners by IVDUs (Kaplan, 1989, Blower and Medley, 1992) Williams et al (1990) in a study of Irish IVDUs receiving methadone maintenance and known to be seropositive (N = 48) found a significant reduction in the number of IVDUs sharing with two or more others, 42 (89%) to 19 (63%) ($P < 0.001$), after diagnosis of seropositivity

O'Mahony and Barry (1992), in a study of HIV risk behaviour amongst 38 HIV-infected prisoners in the Irish prison system, found that subjects who shared injection equipment reported an average number of 9 5 different needle sharing partners in the total time since they were diagnosed HIV positive A majority, (68 4%), of the subjects had been diagnosed seropositive for at least 5 years, (mean 4 7 years)

Comiskey et al. (1993) in a study which included Irish female IVDUs, found that the number of people shared with in one week ranged from 1 to 40 with a mean of 6 94 and standard deviation of 9 43

Finally, in our study of HIV transmission (Dunne et al , 1995, see Appendix), it was found that the average number of people shared with in a week when subjects were injecting, ranged from 0 to 48 with a mean of 2 9 and a standard deviation of 7.1. For females the mean was found to be 2 24 (Std Dev =2 65) and the corresponding figure for males was 3 14 (Std Dev = 8 11)

In addition despite being seropositive, 17 subjects (65 4%) admitted to having continued to share injecting equipment in the previous 6 months Of these, only one person said they limited sharing to one other person while 11 of the 17 (64 7%) had shared with more than one other person (data were missing for 5 subjects)

### 3.3.3 Sexual partnerships

#### 3.3.3.1 Age of first heterosexual activity/sexual intercourse

Johnson et al (1989a), found that men and women in younger cohorts had experienced first sexual intercourse earlier than people in older cohorts This supports the findings of the two surveys conducted on sexual behaviour in Ireland

Lansdowne Market Research (1992), found the average age of first sexual intercourse to be 21 for the group as a whole and for the female and male respondents The corresponding average age for Dublin respondents was 20 Table 3 1 outlines the findings of the survey with regard to age of first sexual intercourse

In their study, Comiskey et al (1993), found that female IVDUs became sexually active at a younger age than other women The mean age of first sexual activity for female IVDUs was found to be 16 04 (95% C I of 15 33 to 16 75) years and 17 55 (95% C I of 16 41 to 18 69) years for other women

Dunne et al , (1995) found the mean age of first sexual intercourse for the total group to be 15 7 years (S D 2 4, range 9-29 years, median 15) 70% of the total group had initiated sexual intercourse by age 16, and over half of the subjects in all agency/sex groups reported initiating sexual intercourse by age 15 51 7% of women (15 out of 29) and 52 3% of men (46 out of 88) had experienced intercourse by the time they were 15 years old There were no significant differences between the sexes, or between the different age groups regarding age of first sexual intercourse

**Table 3.1 Findings of survey conducted by Lansdowne Market Research regarding age of first sexual intercourse**

| | % of Females | % of Males | % aged 18-24 | % in Dublin | Overall % |
|---|---|---|---|---|---|
| Under 15 | 2 | 2 | 6 | 2 | 2 |
| 15 years | 2 | 4 | 6 | 4 | 3 |
| 16 years | 5 | 7 | 12 | 10 | 5 |
| 17 years | 6 | 7 | 10 | 8 | 6 |
| 18 years | 7 | 16 | 14 | 12 | 11 |
| 19 years | 8 | 9 | 7 | 10 | 8 |
| 20 years | 9 | 7 | 3 | 10 | 8 |
| 21 years | 8 | 5 | 3 | 7 | 7 |
| 22 years | 6 | 3 | 3 | 4 | 5 |
| 23 years | 9 | 3 | 1 | 7 | 6 |
| 24 or older | 23 | 21 | 1 | 11 | 21 |
| Not yet | 10 | 9 | 28 | 7 | 9 |
| No information | 6 | 8 | 6 | 8 | 9 |
| Mean age | 21 | 21 | 17 | 20 | 21 |

### 3.3.3.2 Rate of acquiring new sexual partners

The risk of acquiring HIV infection depends heavily on the number of sexual partnerships formed per unit of time, (Schoenbaum et al , 1989, Wiley et al , 1989, May and Anderson, 1987) Schoenbaum et al (1989) found that the odds of being infected with HIV increased by 24 percent with each additional sex partner who used intravenous drugs (from one to five or more), this association was independent of drug-use practices Data on rates of sexual partner change are limited at present, particularly for heterosexual populations, but the data that does exist suggests that the mean number of partners per year is related to the age and the sex of the individual, as might be expected Younger age groups tend to have a higher rate of sexual partner change than older age groups (Anderson, 1988, Johnson et al, 1989a, Lansdowne Market Research, 1992, LRC, 1993) The quantities that influence the dynamics of transmission are not simply the mean numbers of new sexual partners per unit time, but rather the mean number of partners per unit time plus the variance to

mean ratio, $s$ for females acquiring male partners and $\hat{s}$ for males acquiring female partners Although the mean rate at which females acquire new male sexual partners must obviously be identical with the mean rate at which males acquire new female partners, $s$ and $\hat{s}$ will not be identical if the variability in levels of sexual activity among females **differs significantly** from that among males Measurement of $s$ and $\hat{s}$ therefore requires information, which is not always available, on the full distribution of partner-change rates

Lansdowne Market Research, (1992), found the majority of respondents (51%) to have had one sexual partner only in their life to date (However 16% of 18-24 age group reported having had two partners by the time of the survey) The majority, 58%, of female respondents had one sexual partner only and the corresponding proportion for male respondents was 44% (see Table 3 2)

**Table 3.2 Findings of survey conducted by Lansdowne Market Research regarding number of sexual partners**

| No. of partners | % of Females | % of Males | % in Dublin | Overall % |
|---|---|---|---|---|
| 1 only | 58 | 44 | 46 | 51 |
| 2 only | 13 | 10 | 13 | 11 |
| 3 only | 5 | 7 | 7 | 6 |
| 4 + | 10 | 25 | 23 | 17 |
| None | 10 | 10 | 7 | 10 |

The Durex Report (1993), found the average number of sexual partners in the past 12 months of those aged 17-49 to be 1 38 The corresponding average for those who were married was 1 03 for female and 1 05 for male respondents The averages for single female and male respondents were 1 25 and 2 72 respectively 21% of single men claim to have had at least three sexual partners within the past twelve months The 21-24 age group (single or married) was the one with the highest average number of sexual partners (2 17) in the past 12 months

When questioned about whether concern about HIV had resulted in changing their sexual behaviour 21% of all respondents acknowledged that they had adapted their lifestyles 5% of the cohort reported having fewer sexual partners, and 10% reported taking more care about the type of partner because of their concern about HIV (see also Mann et al , 1992)

Comiskey et al (1993) found that 45 (66 7%) of the women surveyed had at least one or more different heterosexual partners in the preceding year, half of whom were HIV negative or of unknown serostatus They also found that female IVDUs had fewer partners in the preceding year than the non IVDU women The range in the number of partners in the year before the study for female IVDUs was 0 to 1 partner, the mode was 1 and the mean was < 1 The range in the number of different heterosexual partners of non IVDU women was 1 to 36 partners, the mode was also 1 partner and the mean approximately 4 partners, so evidently the distribution was highly skewed

McKeown et al (1993), in a survey of 120 clients of the Merchants' Quay drugs service found that the vast majority (82%) of sexually active respondents had only one partner in the 6 months prior to the survey 18% had more than one partner, with an overall average number of sexual partners of 1 7 in the 6 month period However O'Mahony and Barry (1992), in a study of HIV risk behaviour amongst HIV-infected prisoners in the Irish prison system, found that the subjects reported an average number of 7 different sexual partners in the total time since they were diagnosed HIV positive A majority, (68 4%), of the subjects had been diagnosed seropositive for at least 5 years (mean 4 7 years)

In our study of HIV transmission (see Appendix), 46 (43 8%) of the respondents claimed to have had more than one sexual partner during the preceeding 12 months The mean number of sexual partners in the total group was 2 35 (S D 2 7, range 0-14) The median number of sexual partners was 1 There were no significant differences between the sexes or the age groups regarding whether subjects had had more than one sexual partner in the previous year The mean number of sexual partners for women was 1 9 (S D 2 1, range 0-8), the corresponding figure for women was 2 5 (S D 2 8, range 0-14) The median number of sexual partners for women and men was 1 The prevalence of sex with a non-IVDU was high in the group as a whole with 67% of subjects reporting at least one partner who was a non-IVDU However, this differed widely between the sexes Men were far more likely than women to have had a non-IVDU sexual partner in the previous year 77 9% of men compared to only 34 5% of women had a sexual partner who was a non-IVDU ($\chi^2$=18 5, df =1, p < 0 0001) On the other hand women tended to have more drug using sexual partners than men 75% of women had at least one IVDU sexual partner in the previous year compared to 41% of men (p = 0 014, Fisher's exact test)

### 3.3.3.3 Condom use

There is less evidence for sexual risk-reduction among IVDUs than for injecting risk-reduction Many diverse studies of sexual behaviour report low levels of condom use among drug users and few signs of an increase in their popularity (Robert et al , 1990, Pomeroy et al , 1991, Klee et al , 1991a, O'Mahony and Barry, 1992, Murphy et al , 1993, Rhodes et al , 1993a, Richardson & Papaevangelou, 1994 b) Condom use reduces the spread of HIV infection and other sexually transmitted diseases The European Study Group (1992), in a study of the risk factors for heterosexual transmission of HIV found that none of the 24 partners of HIV infected persons in their study who had used condoms systematically since the first sexual contact was infected A study of discordant couples in the U S conducted by Fischl et al (1987) found that only one partner out of ten couples who had used condoms seroconverted, whereas 12 partners out of 14 couples who had not used condoms seroconverted

In Ireland, Lansdowne Market Research, 1992, questioned subjects on the types of birth control which they personally used in the past year 50% of men and 30% of women reported using a condom The overall percentage was 38% for Ireland, but was 46% for Dublin respondents The highest percentage of condom users were in the 25-34 year age group (55%), with 65% of men under 35 years reporting their use

The Durex Report (LRC, 1993) found that 28% of the population surveyed regarded use of condoms as their main method of contraception The condom was found to be particularly popular amongst those aged 25-29 and those who lived in urban areas 39% of those who reported using condoms did so primarily as protection from AIDS/STD

When questioned about whether concern about HIV had resulted in changing their sexual behaviour 21% of all respondents acknowledged that they had adapted their lifestyles However, the majority of these people still appear to be putting themselves at risk of contracting HIV by failing to use a condom with new sexual partners Only 5% of the cohort reported initialising use of condoms because of their concern Single men have more sexual partners on average than other groups but among them only 10% reported use of a condom because of their concern about HIV Although these single males recognise the threat of AIDS, they continue to put themselves at risk 20% of them had sex with a new partner in the year before the survey and did not use a condom

The Durex Report (LRC, 1993) forecasted a 12% growth in the condom sales market following the changes in Irish legislation in July 1992, which legalised condom sales through retail outlets other then pharmacies The Irish condom market has grown by 66% in the years 1985-1992 The year of greatest growth was 1992 when condom sales increased by 16% over those in 1991

Intravenous drug users have been a particular focus of public-health efforts to encourage the use of condoms because they are at risk of infection through sexual behaviour In a study of the seroprevalence of HIV antibody in 452 persons enrolled in a methadone-treatment programme in the Bronx, New York, Schoenbaum et al (1989), found that heterosexual activity was an independent risk factor for drug users

In a study of risk behaviour among 104 HIV positive drug injectors in London, Rhodes et al (1993b), found that respondents who were unaware of their HIV positive status were less likely to use condoms with primary sexual partners than respondents aware of their HIV status

Studies have suggested that use of condoms is higher with **casual** rather than **steady** partners (Hart et al , 1989, Klee et al, 1991a, Rhodes et al , 1993a, Watkins et al , 1993, Richardson & Papaevangelou, 1994b) In a study of HIV prevalence and HIV risk behaviour among 1,037 injecting drug users in London and Glasgow conducted by Rhodes et al (1993a), it was found that 70% of London respondents and 75% of Glasgow respondents never used condoms with primary partners, and 34% of London and 52% of Glasgow respondents never used condoms with casual partners Half (48%) of London respondents and 42% of Glasgow respondents reported sexual intercourse with non-injecting private sexual partners

Similarly, Watkins et al (1993), in a study of the factors associated with condom use in a cohort of 158 sexually active heterosexual in- or out-of-treatment IVDUs in Philadelphia, found that being HIV-positive and having a casual partner was associated with increased probability of using a condom They found that HIV positive subjects were 10 6 times more likely to use a condom than HIV negative subjects This suggests that knowing that one is HIV-positive is an important determinant of condom use and that HIV testing and counselling may therefore increase the use of condoms They also found that drug use and risky drug behaviours, were not associated with condom use, and neither were partner use of IV drugs Condom use by HIV positive subjects was not significantly influenced by the likelihood of the partner being infected However there was an interaction between serostatus and the

likelihood of the partner being HIV-infected Subjects who were HIV-negative and who perceived their partner as potentially infected were 2 5 times more likely to use a condom than subjects who thought their partner was unlikely to be infected Subjects with a casual partner were 4 4 times more likely to use a condom than subjects whose partner was a spouse or steady partner The authors found no significant differences between female and male behaviour in this regard

A study conducted by Richardson & Papaevangelou (1994 b) for the E U Study Group, in two phases (1990-91 & 1992-93), of the use of condoms by European IVDUs (half of whom were recruited out of treatment settings) found that the level of condom use in the total sample was similar in the two phases The study found that in the second phase 72% of the female and 68% of the male respondents never used condoms with their regular partners, while 56% of the female and 46% of the male respondents never used condoms with their casual partners Indeed only 30% of female and 28% of the male respondents always used condoms with their casual partners Their findings suggest that high-risk sexual behaviour continues at high prevalence among European IVDUs

In Ireland a study on changes in risk behaviour of IVDUs receiving methadone maintenance and known to be seropositive conducted by Williams et al (1990), found that since diagnosis of HIV seropositivity the number of subjects using condoms had increased significantly Results are summarized in Table 3 3

**Table 3.3 Behavioural change following diagnosis of HIV infection.**

| | | N = 48 | |
|---|---|---|---|
| | Before | After | McNemar test for matched pairs data |
| Sexually active | 98% | 88% (64% with one partner) | |
| Using condoms | 13% | 64% | p < 0 001 |
| Always use condoms | 2% | 38% | |

However, despite this positive change, there remained a high level of at risk behaviour for further HIV transmission Despite being seropositive more than one third (36%) (down from 87%) who remained sexually active, did not use condoms

Pomeroy et al (1991) found that 40% of their cohort of IVDUs attending a Methadone Programme in Dublin, used condoms on a regular basis

O'Mahony and Barry (1992), found that 51% of HIV infected prisoners in Dublin had unprotected sexual intercourse, while free, with others whom they did not know to be HIV positive Only 14% reported always using a condom This group reported an average number of 7 different sexual partners since they were diagnosed HIV positive The authors also found that there was considerable independence between risk-taking behaviour in the sexual and in the drug-taking domains, in that risk-taking in one area was not highly predictive of risk-taking in the other More HIV positive IVDU prisoners report risk behaviours in the sexual domain rather than in the drug domain O'Mahony and Barry point out that these findings highlight the potential of this group as a bridgehead for spread of HIV into the heterosexual population (see also Moss, 1987 and McKeown et al , 1993)

Many of these findings are also confirmed anecdotally by Irish medical and social-workers, who report that HIV risk behaviour is more common in the sexual domain than in the drug domain and that condom use is more likely to occur with a casual partner than with a steady partner Sexual relationships between steady partners are based on trust, and the introduction of condoms into an ongoing relationship may be perceived as a violation of that trust Indeed France et al (1988) in a study of heterosexual spread of HIV in Edinburgh found that few regular partnerships always practised safe sexual techniques, even after a partner was known to be positive for HIV Therefore large proportions of those most at risk (non-IVDU steady partners) do not use the only known safe prophylactic against HIV infection For heterosexual transmission to decrease, interventions must also focus on changing behaviours within ongoing steady relationships

A study conducted by McKeown et al (1993), for the Merchants' Quay drug/HIV service, found that 63% of respondents do not always use a condom Further analysis revealed that 21% of sexually active respondents were involved in some kind of risky sexual behaviour (i e unprotected sex between partners one of whom is either HIV positive or has unknown HIV status)

Of the 45 women attending an Irish HIV clinic surveyed by Comiskey et al (1993) who had at least one or more different partners (half of whom were HIV negative or of unknown serostatus), only a little over a quarter (12) always used condoms Many of the male sexual partners were not intravenous drug users Only 7 (20 6%) of the 34 sexually active IVDU women and 5 (45.45%) of the 11 other women always used condoms, not withstanding the fact that all

the women were regularly attended a HIV clinic and received regular counselling on HIV transmission

Another study of Contraceptive practices in HIV seropositive females in Ireland attending the G U M Department of St James's Hospital found that only 22% used condoms (Murphy et al , 1993) Those who were currently injecting drugs were less likely to use reliable contraception than the heterosexual group The heterosexual group were more likely to use condoms consistently in comparison to the current IVDU group In fact only 7 (35%) of the heterosexual group and only 1 (4%) of the current IVDUs used condoms consistently All of these women had been fully counselled on safe sexual practices The vast majority (88%) of the sexually active women stated that they had one regular partner

Similarly, our study of HIV transmission (see Appendix) found that of the total group only 28 (23 9%) subjects reported that they always use condoms 53 (45 3%) reported sometimes using them and 36 (30 8%) never use them Men were less likely than women to always use condoms (22% of men compared to 31% of women, $\chi^2$= 7 1, df =2, p = 0 029) In the total group there were no significant differences between the age groups, or the HIV status of subjects, regarding condom use

Our study also analysed the use of condoms by stratifying by the number of sexual partners in the previous year, and by sexual contact with intravenous drug users There was no significant difference between those subjects who had had more than one partner in the previous year and others regarding condom use In the total group no difference in condom use was seen between subjects who reported sexual contact with intravenous drug users and subjects who did not, nor between subjects who reported sexual contact with non-IVDUs and subjects who did not. This also held true when the group was stratified by sex A **high** proportion of men reported sexual contact with a non-IVDU woman, indicating the potential for **widespread** heterosexual transmission of HIV to non-IVDU women from infected male drug users

There was a significant difference in condom use when measured against those who had been tested for HIV and those who had not been tested 26 7% of those who had been tested always use condoms compared to only 14 8% of those who had not been tested ($\chi^2$= 6 47, df =2, p = 0 039)

It seems reasonable to infer that, if a significant proportion of drug users who are in contact with services and have been tested for HIV, are engaging in behaviours which effectively spread HIV then an even higher proportion of IVDUs who are not in contact with these services and have not been tested for

HIV are probably involved in similarly risky behaviour We note that risky behaviour is not confined to drug users however, and appears to be quite prevalent among non-drug using Irish persons who are heterosexuals (Condon et al , 1993, LRC, 1993)

Currently, estimation of the appropriate values for many of the sexual and IVDU behavioural parameters for transmission models is limited by the availability of the data These types of behaviour patterns are extremely heterogeneous and significant gender differences are found for both, (Schoenbaum, 1989) Our model (Chapter 6) therefore includes gender-specific behavioural heterogeneity In our work we have endeavoured to estimate such parameters from studies conducted among the Irish populations with which we are concerned. More quantitative information is, however, required on sexual activity patterns both in the general heterosexual population and in the IVDU population

## 3.4 Biological data

It is necessary to estimate the values of several biological parameters for transmission models, for example, the incubation period, the survival times, the heterosexual transmission probabilities per sexual partnership (i e the probability that a person will acquire the virus from their seropositive sex partner during a sexual partnership), and the probability of HIV transmission by sharing one infected needle

### 3.4.1. Incubation period

The incubation period of AIDS is defined as the time between first infection with HIV and the development of AIDS Variations exist in the timing of the diagnosis of disease because of differing interpretations of the definition of AIDS (Centers For Disease Control (CDC)) and because of different experiences of investigators

Much work has focused on the estimation of the distribution of the incubation period in homosexual and transfusion-associated cases, using a variety of models, and different averages such as the mean and median, (Medley et al , 1987, 1988a, b, Blythe & Anderson, 1988b, Anderson, 1988, Biggar, 1990) The median here measures the time by which 50% of the infected population develop AIDS These studies are presently such that there is often relatively direct information on the distribution of incubation times up to

4-7 years, but beyond that one is extrapolating on the basis of the assumed mathematical form of the distribution The most reliable estimates are obtained when considering the probability or hazard of developing AIDS in the first years after seroconversion This implies that the mean, which depends critically on the upper tail of the distribution for a distribution with a positive skew, is not a good indication of the information in the data (Medley et al , 1987, Mariotto et al , 1992) The rate at which individuals develop AIDS is a function of time-since-infection (the hazard function), the age of the patient, probably the risk group to which the infected person belongs, and possibly the patient's sex, (Anderson et al , 1986, Medley et al , 1987, 1988a, b, Goedert et al , 1987 and 1988, Longini et al , 1991, Mariotto et al , 1992, The Italian Seroconversion Study, 1992)

Lagakos and De Gruttola (1989) found no significant differences in the conditional distributions of the incubation time of females and males in nonparametric analyses of data from 1,206 persons who developed AIDS as a result of contaminated blood transfusions However, Medley et al (1987), in a study of transfusion infected patients, found that the incubation times for females were longer than those for males Notional means (and medians) for the females and males are 8 8 years (8 4 years) and 5 6 years (5 5 years), respectively, on the basis of a model that assumes exponential growth in incidence of infected transfusions and a Weibull distribution for the incubation period The Weibull distribution is a generalisation of the exponential and has the advantage of considering a non-constant hazard over time (Kalbfleisch & Prentice, 1980) The Weibull distribution is equivalent to supposing that the risk of converting to AIDS increases as the time from HIV infection increases (Cox and Oakes 1984) It should be borne in mind that as more data become available the estimate of the average incubation period is likely to increase

Unfortunately, there is a relative dearth of studies of the incubation period of HIV in women, IVDU groups or in heterosexual groups Disease progression among IVDUs may differ from that of seropositive subjects belonging to other transmission groups because of different age and sex distributions (Mariotto et al , 1992, Fernandez-Cruz et al , 1990) It has also been suggested that progression rates for IVDUs are higher than in the homosexual/bisexual population, because of an already weakened immune system, suggesting that IVDUs have a poorer prognosis However, there is little evidence to support this hypothesis Most studies indicate that HIV progression does not differ significantly between IVDUs and other risk groups (Biggar, 1990, Mariotto et al , 1992, Selwyn et al , 1992)

Currently there is no evidence to suggest that progression rates differ between female and male IVDUs (The Italian Seroconversion Group, 1992, Selwyn et al , 1992, Mientjes et al , 1993) However, age has been found to be significantly associated with progression younger IVDUs having less rapid disease progression than those who were older at the time of infection (The Italian Seroconversion Group, 1992, Mariotto et al , 1992, Selwyn et al., 1992, Mientjes et al , 1993)

As indicated in Table 3 4, current estimates of the mean and median periods, for sexually active adults tend to lie in the range of 6-15 years, irrespective of risk group (Longini et al , 1989, De Gruttola et al , 1988, Medley et al , 1987, Medley et al , 1988 a, b, Mariotto et al , 1992) However as well as being limited in their value, most of these estimates have very wide confidence intervals The incubation period is expected to increase with time because of increasing opportunities for treatment at an earlier point in the disease process (Schechter et al 1989) This increase with time has to some extent been seen by the Italian Seroconversion Group (1992), which found that the risk of developing AIDS was 21% within 7 years following seroconversion, which suggests that the lower bound of the estimate of median incubation period suggested above (6 years) may be an underestimate for more recent years

**Table 3.4 Estimates of the median incubation period of AIDS (sexually active adults)**

| Risk/Data group | Sample size | Reference | Median time (years) |
|---|---|---|---|
| Homo/Bisexual men | 155 | De Gruttola et al 1988 | 8 8 |
| The U S Army | 1796 | Longini et al 1991 | 9 6* |
| IVDUs | 343 | Alcabes P et al 1992 | 10 0 |
| Mixed (278 were IVDU) | 420 | Mariotto et al 1992 | |
| aged 16-24 years | | | 15 2 |
| aged 25-34 years | | | 8 2 |
| aged ≥ 35 years | | | 6 1 |

* Refers to the time from seroconversion to opportunistic infection diagnosis

### 3.4.2. Survival time

The inability of the person with AIDS to withstand infection means that survival times are relatively short Most studies which have estimated the survival time of persons with AIDS have concentrated on homosexual and transfusion-associated cases There are few published studies of survival time of AIDS in IVDUs (Lundgren J et al , 1994, Seage et al , 1993, d'Arminio Monforte et al , 1992, Rasch et al , 1992, Batella et al , 1989) Once an individual develops AIDS, the average survival time appears to be between one and three years (WHO 1993) This will be dealt with in more detail in Chapter 4

### 3.4.3. Transmission

In studying the transmission dynamics of HIV infection it is important to ascertain the relationship between the incubation period of the disease AIDS,

and the duration and intensity of infectiousness over the incubation period Individuals infected with HIV pass through a series of progressive irreversible stages (at least 4), from infected but antibody negative to acquired immune deficiency syndrome diagnosis (Redfield et al , 1986) Studies suggest that infectiousness varies with disease stage, reaching a maximum shortly before the onset of AIDS, but this has been difficult to measure (Pedersen et al , 1987, De Vincenzi, 1988, Goedert et al , 1987 and 1988, Johnson et al , 1989b, Laga et al , 1988 and 1989, European Study Group, 1989 and 1992, Padian et al , 1991,) These studies suggest that infectiousness is at a low level (possibly even zero) throughout most of the incubation period, but then rises sharply during a period of perhaps one to three years before the onset of AIDS Infectiousness may also be heightened for a short period (a few months to a year or more) immediately after infection, but this is not well established (Bongaarts, 1989)

Variable infectiousness as suggested by the studies named above contradicts the assumption of a constant value for the transmission parameter $\beta$ but such an assumption has been judged not too unreasonable for 'population based' studies (Anderson & May, 1991)

Other complicating factors such as susceptibility of the contact, condom use, and co-factors such as the presence of other sexually transmitted diseases, and the type of sexual contact also affect the risk of transmission The European Study Group (1992) found that older age of the female partner increased the risk of male to female sexual transmission

### 3.4.3.1 Heterosexual transmission

Sexual partnership studies have been conducted to estimate the value of the heterosexual ( female to male and male to female) transmission efficiencies (Tables 3 5 and 3 6) (Goedert et al , 1988, De Vincenzi, 1988, Laga et al , 1988, Peterman et al , 1988, Johnson & Laga, 1988, Padian et al , 1987 and 1991, European Study Group, 1989 and 1992) These studies involve monitoring monogamous couples in which one partner is HIV-infected and the other is uninfected Although these studies have limitations due to their small sample sizes and selection biases, they are the only means by which the heterosexual transmission efficiencies of the virus may be evaluated Strikingly, the majority of recent studies have found no relationship between the risk of transmission and length of relationship or number of acts of sexual intercourse (Table 3 5) These studies seem to indicate that there is marked heterogeneity in infectivity and possibly susceptibility between individuals, and

that infectivity may vary over the long incubation period from HIV infection to AIDS

**Table 3.5 European and American studies of sexual transmission of HIV from men to women**

| Reference | Major risk factors in index case | No of partners studied | % of partners with antibodies to HIV |
|---|---|---|---|
| Padian et al 1987 | Bisexual/injecting drug user | 97 | 24% |
| Goedert et al 1988 | Haemophiliacs | 124 | 14% |
| Peterman et al 1988 | Blood transfusion | 55 | 18% |
| De Vincenzi 1988 | Mixed | 104 | 28% |
| Laga et al 1988 | African connections/ heterosexuals | 62 | 53% |
| European Study Group 1989 | Mixed | 155 | 27% |
| Padian et al 1991 | Mixed | 307 | 20% |
| European Study Group 1992 | Mixed | 404 | 20% |

**Table 3.6 European and American studies of sexual transmission of HIV from women to men**

| Reference | Major risk factors in index case | No of partners studied | % of partners with antibodies to HIV |
|---|---|---|---|
| Padian et al 1987 | Injecting drug users | 20 | 0% |
| Peterman et al 1988 | Transfusion associated | 25 | 8% |
| De Vincenzi 1988 | Mixed | 27 | 4% |
| Laga et al 1988 | 50% African heterosexuals | 16 | 13% |
| Padian et al 1991 | Mixed | 72 | 1% |
| European Study Group 1992 | Mixed | 159 | 12% |

These studies have reported that transmission from infected men to women is more likely than from infected women to men Indeed Johnson and Laga (1988), suggest that there may be a two-to threefold difference in the probabilities The European Study Group (1992) found that male to female transmission is 1 9 times more effective than female to male transmission

Peterman et al (1988), has documented transmission from male to female and female to male following one or two acts of penile-vaginal contact It has however also been found that many women and men remain seronegative despite hundreds of episodes of unprotected intercourse, which suggests that factors other than numbers of exposures play an important role in determining susceptibility to infection

Estimates of heterosexual efficiencies are subject to much uncertainty, and are extremely heterogeneous ranging from 0 to 71 (Anderson & May, 1988, European Study Group, 1989, 1992, Johnson & Laga, 1988, Padian et al , 1987, 1991) The variability in the results of these studies may be due to the differences in the study methodology, how the cases were ascertained, the risk group studied, the clinical status of the index case, the definition of the contact cases (some examined only long-term partners), the small sample sizes, the heterogeneity in sexual practices, the behavioural-biological cofactors, the partnership duration and the differences in condom use The results of the studies imply that the value of the heterosexual transmission efficiency ($\beta$) is almost always below 0 5 Anderson et al (1992) considered a range of transmission risks whose means for female-male and male-female range from 0 09 to 0 2 per partnership Studies of non-IVDUs suggest that the value of $\beta$ is skewed towards the low end of the probability scale, but studies of heterosexual transmission in IVDUs suggest that the value of $\beta$ may be much higher than in non-IVDUs (this may be another factor contributing to the atypical nature of HIV transmission in Ireland)

#### 3.4.3.2. Transmission through needle sharing

It is known that the probability of transmission during needle sharing is at least as great as that due to sexual contact

In the case of intravenous drug users the likelihood of transmission appears to correlate with the number of injections involving the sharing of unsterilized needles (Friedland & Klein, 1987, Schoenbaum et al , 1989)

The transmission risk per partner given by Blower et al (1991) was 0 5 In our model a more conservative estimate of 0 25 per partner is used as a base estimate (see Williams and Anderson, 1994), but it seems likely that a wide range of values is possible as found for other parameters

## 3.5. Conclusions

There is a clear need for the collection of much more detailed data on all the parameters discussed above, although the social, ethical, and practical problems surrounding such research are formidable

Detailed quantitative information is needed on patterns of sexual behaviour in different areas of Ireland in order to properly model the epidemic

in all its detail (Kingman et al , 1988) This will require the conduct of extensive sociological and behavioural surveys

It is difficult to evaluate behaviour in any human group and perhaps most difficult of all in a population of IVDUs One such difficulty is that such data are subject to recall error The findings of studies of interpartner reliability of reporting, have been reasonably favourable however, with both partners providing reliable information on recent sexual behaviours (Upchurch et al , 1991, Padian et al , 1990). A second factor is the sensitive nature of the information sought, and the possible tendency of IVDUs to give socially desirable answers to such questions A third factor is that these behaviours, especially sexual behaviour, involve aspects that are difficult to investigate fully within limited time spans and attention spans Finally there is the difficulty that much of the available information relates to groups that are in some sense self selected, for example, consisting of individuals attending drug treatment centres

Despite these problems of accurate parameter estimation, the extent of the potential benefits arising from prediction of infection levels, even with wide bounds, makes it worthwhile proceeding with a mathematical model

# Chapter 4

# Survival with AIDS

## 4.1 Introduction

Survival studies of patients with AIDS are an important aspect of monitoring the AIDS pandemic They provide information on the response of different subgroups to the syndrome, and enable mathematical modellers and health care professionals to estimate future needs

Statistics on AIDS cases and deaths in Ireland are compiled by the Department of Health Up to the end of June 1994, the cumulative total number of recorded AIDS cases in Ireland was 408 This represents 27 3% of all known HIV seropositive individuals

A total of 209 deaths due to AIDS have occurred up to the end of June 1994 41% of these are related to IV drug use and 10% relates to those who acquired the infection through heterosexual contact

### 4.1.2 Life expectancy of AIDS patients

Once AIDS is diagnosed, the life expectancy of patients is relatively short, although it depends on factors such as age, risk group, and the nature of the opportunistic infection or cancer that triggered the diagnosis of the disease Most studies to date, of the survival times of AIDS patients have concentrated on homosexual men We analysed the pattern of survival for patients diagnosed with AIDS in Ireland, the majority of whom are intravenous drug users Our cohort of 193 patients represents 61% of all those who were diagnosed with AIDS in Ireland up to March 1993 We also assessed the relative influence of sex, age-group, risk-group, manifestation of disease at diagnosis, and treatment with anti-viral therapy on survival

## 4.2 Methods

### 4.2.1 Patients

The study cohort was made up of 193 patients of St James' Hospital, Dublin, who were diagnosed as having AIDS, between 1986 and the 15th March 1993 There were 4 other patients whose death was attributed to AIDS, but since there was no date of diagnosis available for them (except perhaps date of death), they were omitted from the cohort In addition to these omissions one other patient who was still alive in September 1994, claimed to have been diagnosed with PCP in 1982, in London This patient first visited St James's Hospital in 1992 and was not diagnosed with an AIDS defining illness by this hospital up to March, 1993 Since there was no official confirmation of the PCP diagnosis, and, since such a long survival with AIDS (12 years) is unlikely, this patient too was omitted from our analysis

Reporting of AIDS in Ireland began in 1982 and was based on the clinical case definition established by the Centres for Disease Control, which included pathological confirmation of the presence of opportunistic disease The AIDS case definition was revised in 1985 and in 1987 and further revised in 1993

### 4.2.2 Missing values

Midpoint intervals were assumed in year and month of diagnosis of AIDS and of death if data were missing This was the case for three subjects where only year of death was recorded, for sixteen subjects where only year and month of death were available, and for ten cases where only year of diagnosis was recorded

### 4.2.3 Censoring

In addition to missing values two of the patients who had died had not died of AIDS related illnesses, (both of whom were male, under 30 years of age and intravenous drug users, and one had committed suicide), and for two other patients it was unknown whether or not their death was due to an AIDS related cause, and so it was decided to censor the data for these cases Patients who were alive at the end of the study (30th September 1994) and who had visited the hospital since the 30th of September 1993 were assumed to be alive and were censored at the study end date Patients who were not known to be dead but who had not visited the hospital since before the 30th of September 1993 were censored at the mid point between the date of their last visit and the 30th of September 1994 There were 19 patients in the latter group

### 4.2.4 Covariates

The following major variables were evaluated sex, age at diagnosis (< 30, 30 to 34, 35 to 39, or ≥ 40 years), risk group (indicating probable route of acquisition intravenous drug use, homo/bisexual activity only, intravenous drug use and homo/bisexual activity or other risk factor), treatment, year of diagnosis and manifestations of AIDS at diagnosis

Manifestation of disease at diagnosis was categorised in two different ways Using the criteria which are defined in the protocol of AIDS diseases developed by the CDC (see section 4 3 1 4), and labeled by us as GRP+, we categorise the cohort into six groups (A, B, C1, C1+D, D, and E)

In order to better compare our results with other studies, we also categorised the manifestation of disease at diagnosis according to criteria used in previous studies, and labelled by us as PCP+ This criteria divides the cohort into seven groups, (Kaposi's sarcoma alone, Kaposi's sarcoma and P carinii pneumonia (PCP), Kaposi's sarcoma with other infections or conditions, PCP alone, PCP with other infections or conditions, one other infection alone — i e , only one condition was recorded as manifestation of disease at diagnosis, and two other infections — i e , two or more manifestations were recorded)

Both categorisations of manifestation of disease were based on any manifestations which were recorded within one month of AIDS diagnosis

### 4.2.5 Data analysis

Data were analysed using the statistical package SAS (SAS Institute Inc, 1988) and the LIFETEST procedure in particular Survival curves were investigated using non-parametric methods specifically obtaining life-table estimates of survival LIFETEST was also used to test (using the Wilcoxon test) the variables of interest for their association with each other and pooled over the defined strata Cox proportional hazards regression analysis (P2L procedure [BMDP]) was used to construct a proportional hazards model for predicting length of survival and to identify the independent predictors of survival among the covariates (Hopkins, 1985) The model was constructed using a stepwise procedure (maximum partial likelihood ratio method) with a p value of 10 as the entry criterion and 15 as the removal criterion at each step Differences in survival were summarised by calculating relative hazard estimates for the different levels of each variable

Survival was examined in the total group and in each of the subgroups of interest Since 365 day intervals were used to calculate the survival curves,

the numbers of patients surviving per year are approximations For convenience of presentation, the cumulative probability of survival and its standard error are expressed as percentages The median **conditional** survival - the time at which the cumulative probability of survival is 50 percent - is the expected median survival if all subjects in the cohort were followed until death and no new cases of AIDS were diagnosed It must be distinguished from the median **observed** survival, which is the median value in the distribution of the lengths of survival Due to the rapid increase in cases, the median observed length of survival in the cohort (full group) was shorter than the expected value (observed vs expected, 491 vs 576 days [Table 4 1])

All percentages quoted refer to the group as a whole unless otherwise stated

## 4.3 Results

### 4.3.1 Patient details

#### 4.3.1.1 Sex

The cohort was 80 8% male and 19 2% female (Table 4 1) This provided a male/female ratio of approximately 4 2/1 54% of women were less than 30 years of age while only 35% of men belonged to this age group ($\chi^2 = 4\ 4$, $p < 0\ 04$) The mean age for men was 33 years and that for women was 30 years

#### 4.3.1.2 Age

All patients were between 21 and 55 years of age at the time of diagnosis The mean age was 32 and the median age was 31 The largest age group comprised subjects less than 30 years of age (see comparison with other studies in the discussion), accounting for 38 9% of the cases followed by subjects 30-34 years of age, accounting for 28% of the cases, and those in the 35-39 years of age category with 21 2% The smallest grouping comprised 23 subjects who were 40 years of age and older (11 9%), 22 of whom were male, 21 of whom were Homo/bisexual, and 18 of whom died within the study period 69 3% of all those under 30 years of age were I V drug users 91 3% of subjects over 40 were homosexual or bisexual men The mean age of those in the 40+ age group was 46 years

**Table 4.1. Distribution of Patients with AIDS (St. James' Hospital, Dublin, 1986-1993), According to Study Variables and Length of Survival.**

| VARIABLE | NO OF SUBJECTS | LENGTH OF SURVIVAL MEDIAN*** days |
|---|---|---|
| Entire cohort | 193 | 576 |
| Sex | | |
| Men | 156 | 576 |
| Women | 37 | 590 |
| Risk group | | |
| Intravenous drug use | 98 | 574 |
| Homo/Bisexual activity | 72 | 548 |
| H/Bisexual & IVDU | 7 | 561 |
| Other risk factor | 16 | 643 |
| Age | | |
| < 30 | 75 | 590 |
| 30-34 | 54 | 397 |
| 35-39 | 41 | 715 |
| 40+ | 23 | 331 |
| Manifestation of disease (PCP+) | | |
| Kaposi's sarcoma alone | 14 | 395 |
| Kaposi's sarcoma and PCP | 4 | 328 |
| K S and another disease | 1 | 548 |
| P *carinii* pneumonia alone | 61 | 696 |
| PCP and another disease | 10 | 574 |
| One other disease alone | 94 | 500 |
| Two other diseases alone | 9 | 441 |

*** Median cumulative survival, derived from product-limit curves

#### 4.3.1.3 Risk group

The percentage of intravenous drug users was 50 8%, that of homo/bisexual men 37 3%, that of subjects who were both intravenous drug users and homo/bisexual men 3 6% and that of subjects whose risk group was neither of the above 8 3%, (16 subjects, 10 of whom were female)

83 7% of IVDUs were less than 35 years of age, whilst only 43% of homo/bisexual men were aged less than 35 years Indeed 29 2% of homo/bisexual men were over 40 years of age (the comparable proportion for IVDUs was only 2%) The mean age for those whose risk was homo/bisexual activity was 36 years whilst that of IVDUs was 30 years Homo/bisexual men therefore tended to be older than IVDUs When risk-groups other than IVDU alone and homo/bisexual activity alone were omitted from the analysis homo/bisexual men were significantly older than IVDUs (n = 170, $\chi^2$ =37 2, df=3, p<0 0001)

#### 4.3.1.4 Manifestation of disease at diagnosis

PCP was the manifestation with the highest frequency (37%), followed by Oesophageal Candida in 13% of cases A detailed protocol definition of AIDS diseases divides patients into 5 subgroups A, B, C1, D and E Subgroup A includes patients with constitutional disease such as wasting syndrome due to HIV Subgroup B includes patients with neurological disease such as HIV encephalopathy Subgroup C1 includes patients with symptomatic or invasive disease due to one or more secondary infectious diseases such as oesophageal candidiasis, PCP or cryptococcosis Subgroup D includes patients with secondary cancers such as Kaposi's sarcoma and subgroup E includes patients with other clinical findings or diseases, such as Cervical cancer Table 4 2 shows a frequency table of all diseases recorded within one month of diagnosis, grouped according to the above definition, and table 4 1A shows the distribution of patients with AIDS according to Disease Group and length of survival

However in order to better compare results with other studies the manifestations of disease at diagnosis were classified into groups as described in the section on methods One other disease alone was the predominant manifestation of AIDS at diagnosis (48 7%), followed by PCP alone in 31 6%, Kaposi's sarcoma alone in 7 3%, PCP and another disease in 5 2%, two or more other diseases in 4 7%, Kaposi's sarcoma with PCP in 2 1% and Kaposi's sarcoma with another disease which only accounted for 0 5% The mean age of those whose manifestation of disease at diagnosis was Kaposi's sarcoma either alone or with PCP (18 subjects) was 39 years This contrasts with those, whose manifestation was other than the above, whose mean age was 32 (see table 4 1 for details of relative sizes of groups)

#### 4.3.1.5 Year of diagnosis

Although diagnosis of AIDS in the cohort began in 1986 only 4 7% of cases were diagnosed before 1988 76 2% of the cohort were diagnosed between 1989 and 1992

**Table 4.1A. Distribution of Patients with AIDS (St. James' Hospital, Dublin, 1986-1993), According to Disease Group and Length of Survival.**

| VARIABLE | NO OF SUBJECTS | LENGTH OF SURVIVAL MEDIAN*** days |
|---|---|---|
| Entire cohort | 193 | 576 |
| Disease Group (GRP+) | | |
| A | 3 | --- |
| B | 13 | 216 |
| C1 | 146 | 672 |
| C1 + D | 6 | 416 |
| D | 24 | 216 |
| E | 1 | 229 |

**TABLE 4.2 Frequency Table of Disease Group (GRP+) at Diagnosis**

| Disease Group | Frequency | Percent | Cumulative Frequency | Cumulative Percent |
|---|---|---|---|---|
| A | 3 | 1 6 | 3 | 1 6 |
| B | 13 | 6 7 | 16 | 8 3 |
| C1 | 146 | 75 6 | 162 | 83 9 |
| C1+D | 6 | 3 1 | 168 | 87 0 |
| D | 24 | 12 4 | 192 | 99 5 |
| E | 1 | 0 5 | 193 | 100 0 |

## 4.4 Survival

The crude mortality ratio in the cohort (the total number of deaths divided by the total number of cases) was 79 3% The proportion surviving by this crude measure was therefore 20 7% 68% of those who were aged 35-39 had died compared to more than 78% of those in each of the other age groups 30 subjects (15 5%) survived for more than three years 26 of these were male giving a male female ratio of 6 5 1 as compared to 4 2 1 for the full group, and 15 (50 %) were aged less than 30 years as compared to 38 9% of the full group Only 4 (13 3%) of those who survived for more than three years were aged 30 - 34 as compared to 28% of the full group 13 subjects (6 7% of the total group) -10 of whom were male and 6 of whom were under 30 years of age- survived for more than four years Only one patient survived long enough to be censored at the study end point (7 3 years after AIDS diagnosis)

The life-table method estimates long-term survival more appropriately The survival graph for the cohort is shown in Figure 4 1 The cumulative probability of survival (mean ± SE) at five years (1825 days) was 6 5 ± 2 5 percent (Table 4 3) The median conditional probability of survival from the date of diagnosis was 576 days as noted above in Table 4 1 The graph suggests three main phases with the end of the second year and the end of the fourth year marking the turning points The phases suggest no dramatic changes over time, but failure rate was slightly more rapid in the early years than in the later years The final phase is based on survival in 13 subjects and is truncated in Figure 4 1 at 2661 days

### 4.4.1 Survival in major subgroups

The values for survival in each of the major subgroups are shown in Tables 4 1, 4 1A, 4 3 and 4 3A

**Overall Survival of 193 patients with AIDS**

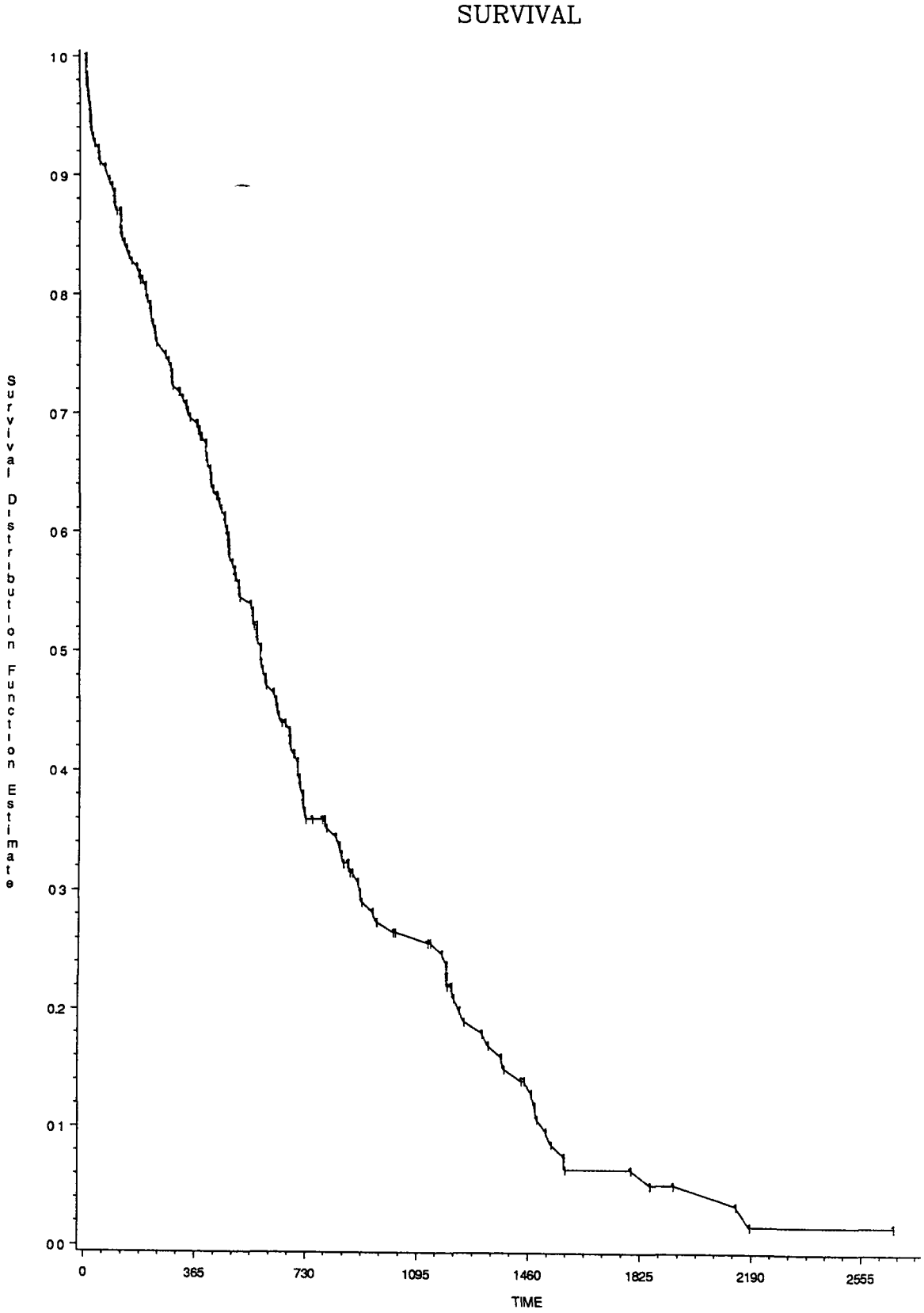



*Figure 4 1 Overall Survival of 193 patients with AIDS*

**Table 4 3. Cumulative Probability of Survival, According to Study Variables and Length of Survival.**

| VARIABLE | CUMULATIVE PROBABILITY OF SURVIVAL | | | | | |
|---|---|---|---|---|---|---|
| | 1 YR | 2 YRS | 3 YRS | 4 YRS | 5 YRS | 6YRS |
| | *percentages (mean ± SE)* | | | | | |
| Entire cohort | 69 0± 3 3 | 36 8± 3 6 | 27 4± 3 6 | 14 7± 3 2 | 6 5± 2 5 | 2 2± 1 7 |
| Sex | | | | | | |
| Men | 70 3± 3 7 | 37 1± 4 0 | 28 6± 4 0 | 13 4± 3 4 | 7 8± 2 9 | 2 6± 2 0 |
| Women | 63 4± 8 1 | 36 0± 8 6 | 21 6± 8 3 | 21 6± 8 3 | | |
| Risk group | | | | | | |
| IVDU | 67 9± 4 7 | 35 7± 5 1 | 25 5± 4 9 | 13 6± 4 2 | 5 2± 3 0 | 5 2± 3 0 |
| Homo/Bisexual | 67 6± 5 5 | 38 4± 5 9 | 32 5± 5 9 | 17 5± 5 5 | 8 7± 4 5 | |
| IVDU and H/B | 85 7±13 2 | 39 0± 19 2 | | | | |
| Other risk factor | 75 0±10 8 | 35 5±13 2 | | | | |
| Age | | | | | | |
| < 30 | 79 7± 4 7 | 37 7± 5 8 | 26 0± 5 4 | 13 0± 4 4 | 8 3 ± 3 9 | 5 0± 3 4 |
| 30-34 | 55 1± 6 8 | 28 7± 6 5 | 17 9± 6 4 | 17 9± 6 4 | | |
| 35-39 | 80 2± 6 3 | 49 3± 8 3 | 41 1± 8 7 | 19 2± 8 5 | 6 4± 5 9 | |
| 40+ | 46 7±10 5 | 31 9±10 1 | 31 9±10 1 | 10 6± 9 3 | 10 6 ± 9 3 | |
| Manifestation of disease (PCP+) | | | | | | |
| KS alone | 57 1±13 2 | 26 7±12 1 | 26 7±12 1 | 26 7±12 1 | 13 3±11 2 | |
| KS and PCP | 25 0±21 6 | | | | | |
| KS+another dis | 100 0± 0 0 | | | | | |
| PCP alone | 85 0± 4 6 | 48 4± 6 7 | 28 2± 6 5 | 4 2± 3 2 | | |
| PCP+other dis | 60 0±15 5 | 27 3±14 6 | 27 3±14 6 | 13 6±12 1 | 13 6±12 1 | |
| Another dis alone | 63 2± 5 0 | 34 4± 5 2 | 28 8± 5 3 | 23 8± 5 4 | 6 0± 3 9 | |
| 2 other diseases | 66 7±15 7 | 33 3±15 7 | 33 3±15 7 | 16 7±14 2 | 16 7±14 2 | 16 7±14 2 |

**Table 4.3A Cumulative Probability of Survival, According to Disease Group (GRP+) and Length of Survival.**

| VARIABLE | CUMULATIVE PROBABILITY OF SURVIVAL | | | | | |
|---|---|---|---|---|---|---|
| | 1 YR | 2 YRS | 3 YRS | 4 YRS | 5 YRS | 6YRS |
| | *percentages (mean ± SE)* | | | | | |
| Entire cohort | 69 0 ± 3 3 | 36 8 ± 3 6 | 27 4 ± 3 6 | 14 7 ± 3 2 | 6 5 ± 2 5 | 2 2± 1 7 |
| Disease Group (GRP+) | | | | | | |
| A | 66 7 ±27 2 | | | | | |
| B | 46 1 ±13 8 | | | | | |
| C1 | 77 7 ± 3 5 | 43 7 ± 4 3 | 31 8 ± 4 3 | 15 9 ± 3 8 | 6 8 ± 2 9 | 2 9 ± 2 2 |
| C1+D | 50 0 ±20 4 | 16 7 ±15 2 | | | | |
| D | 37 5 ± 9 9 | 18 7 ± 8 3 | 18 7 ± 8 3 | 18 7 ± 8 3 | 9 4 ± 7 8 | |
| E | 0 0 | | | | | |

#### 4.4.1.1 Age

The subgroup with those who were aged 35-39 years had a more favourable survival pattern, with a median survival of 715 days and a cumulative probability of survival of 80 25 ± 6 3 percent at one year ($p < 0\ 04$ when compared to all other patients, Wilcoxon test of equality over strata) On the other hand, subjects aged 30-34 or those aged over 40 years had the least favourable prognosis particularly in the early stages, ( median 395 days, cumulative probability of survival at one year 52 6 ± 5 7 percent, $p < 0\ 002$ when compared to all other patients, Wilcoxon test) Figure 4 2 shows survival stratified by age

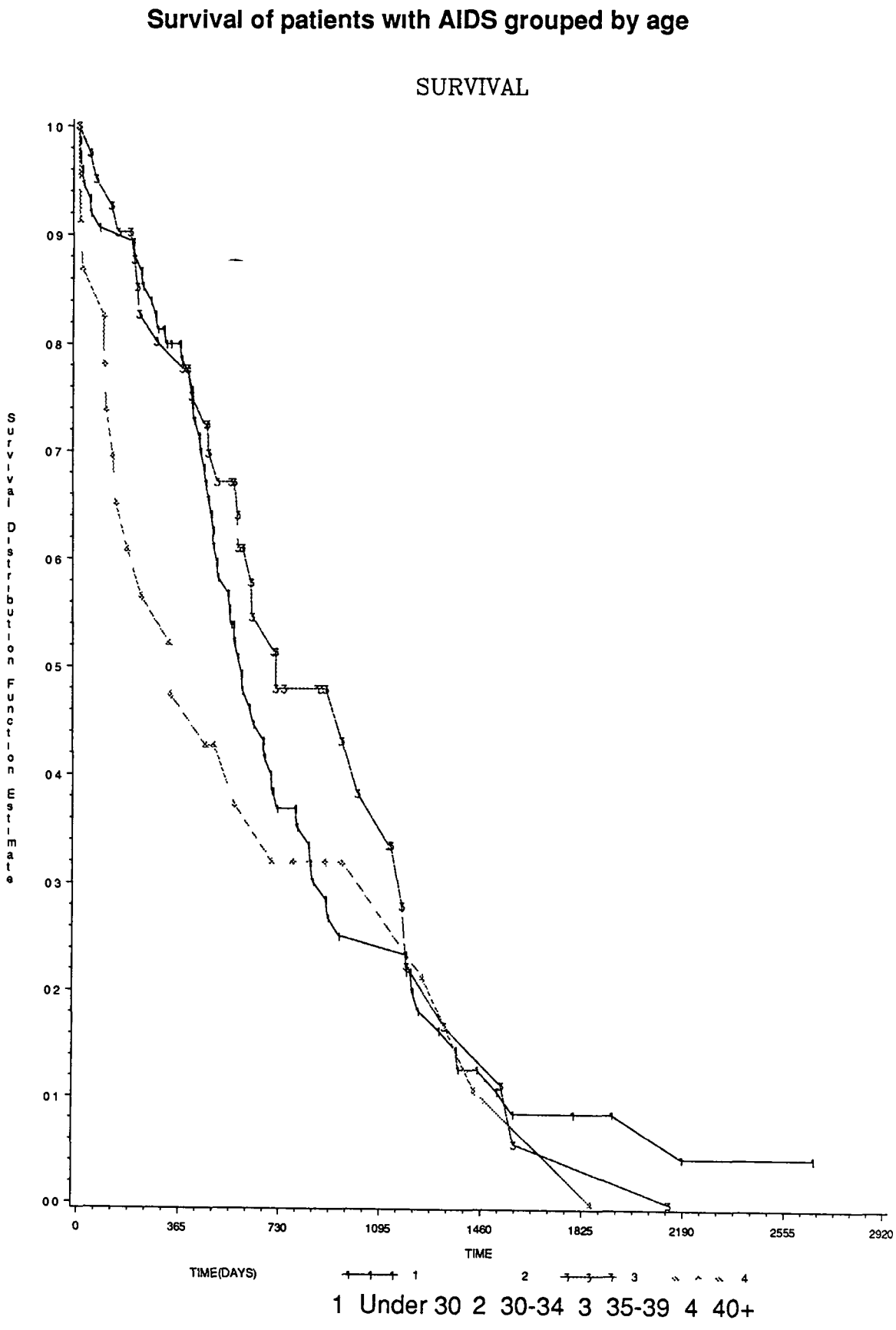



*Figure 4 2 Survival of patients with AIDS grouped by age*

#### 4.4.1.2 Sex

Sex differences are apparent primarily at larger survival times, i e no women survived after the fifth year However the difference is not significant Figure 4 3 shows survival stratified by sex

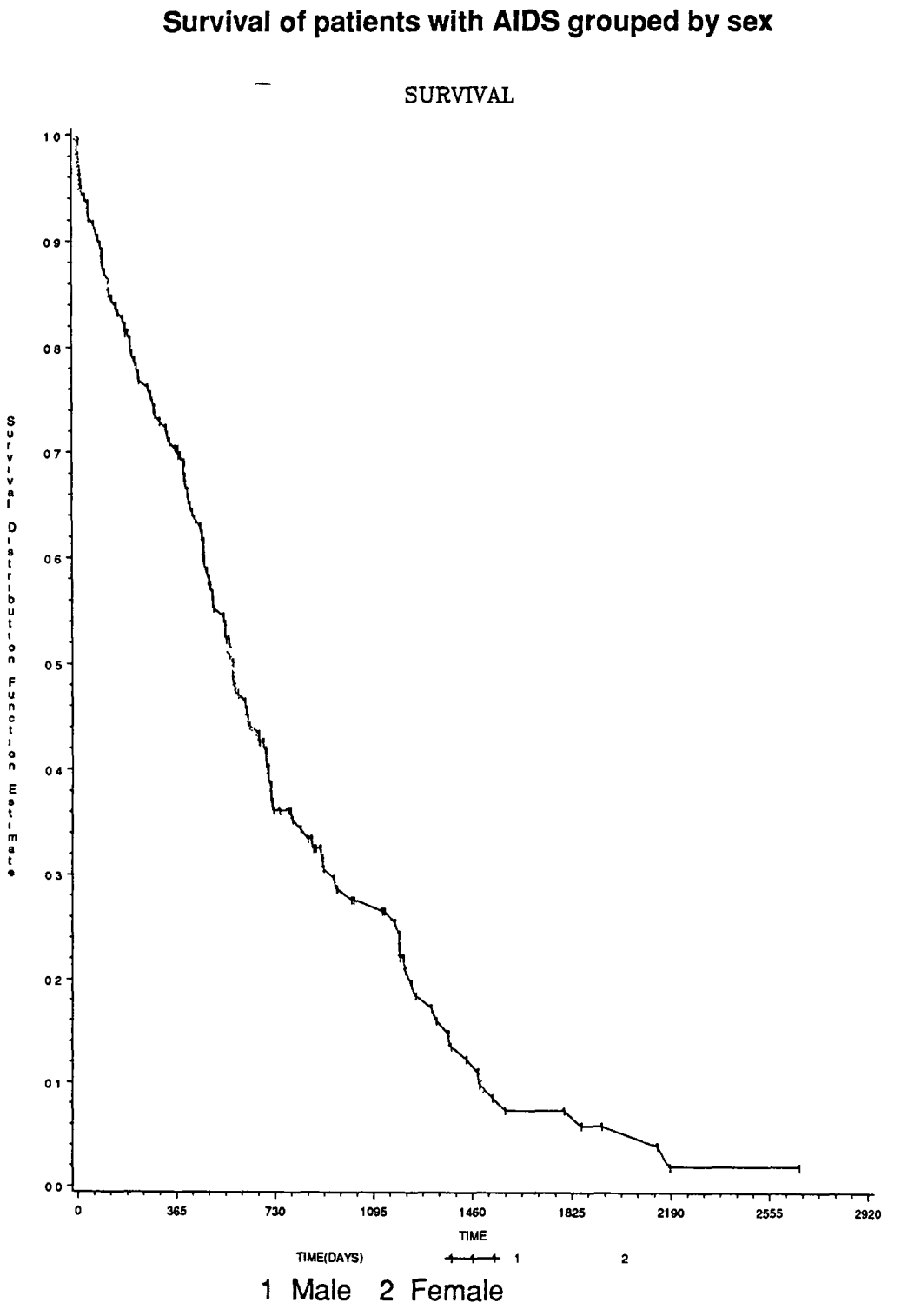



*Figure 4.3 Survival of patients with AIDS grouped by sex*

#### 4.4.1.3 Risk group

There were no significant differences in survival when patients were stratified by risk group (Figure 4 4)

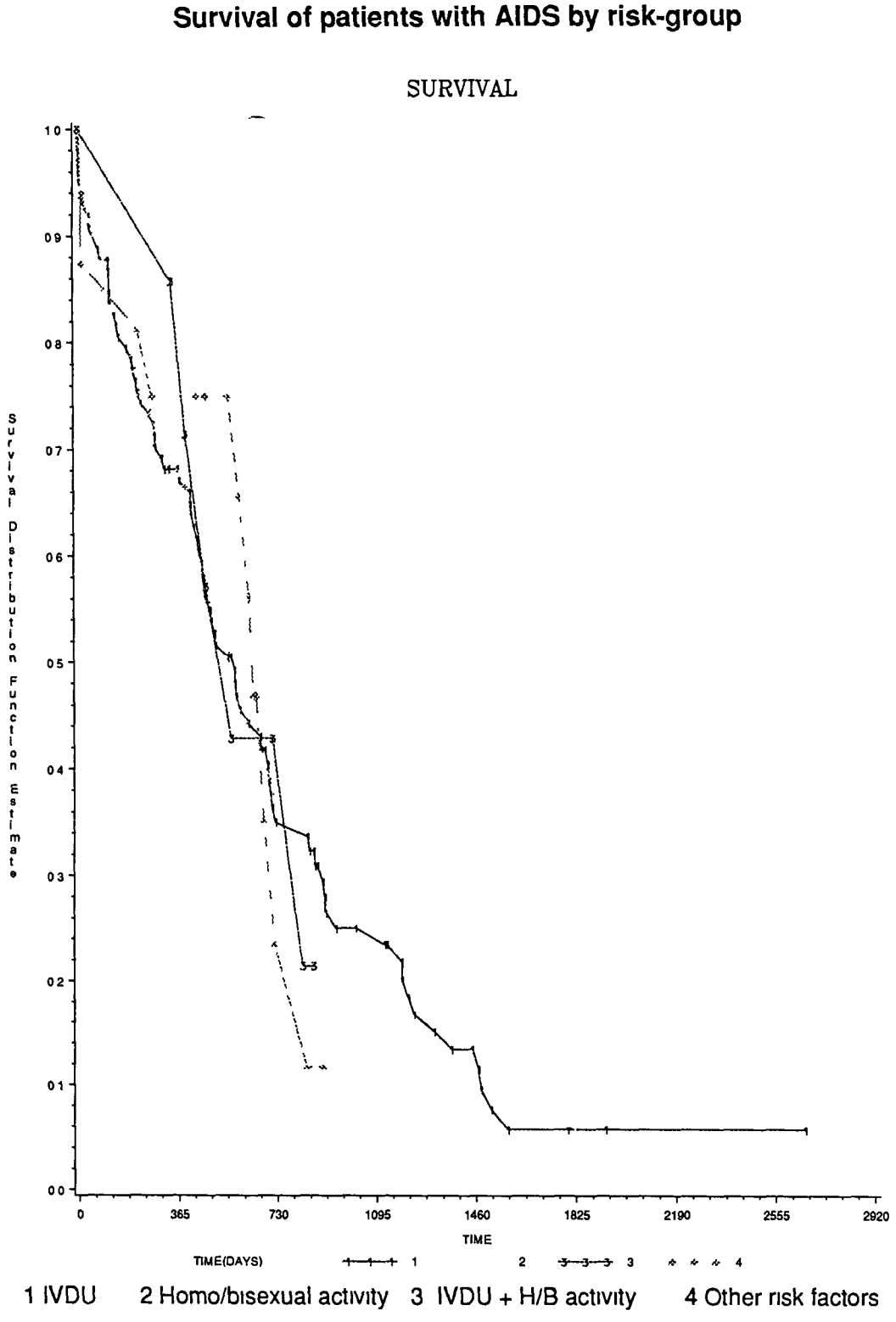


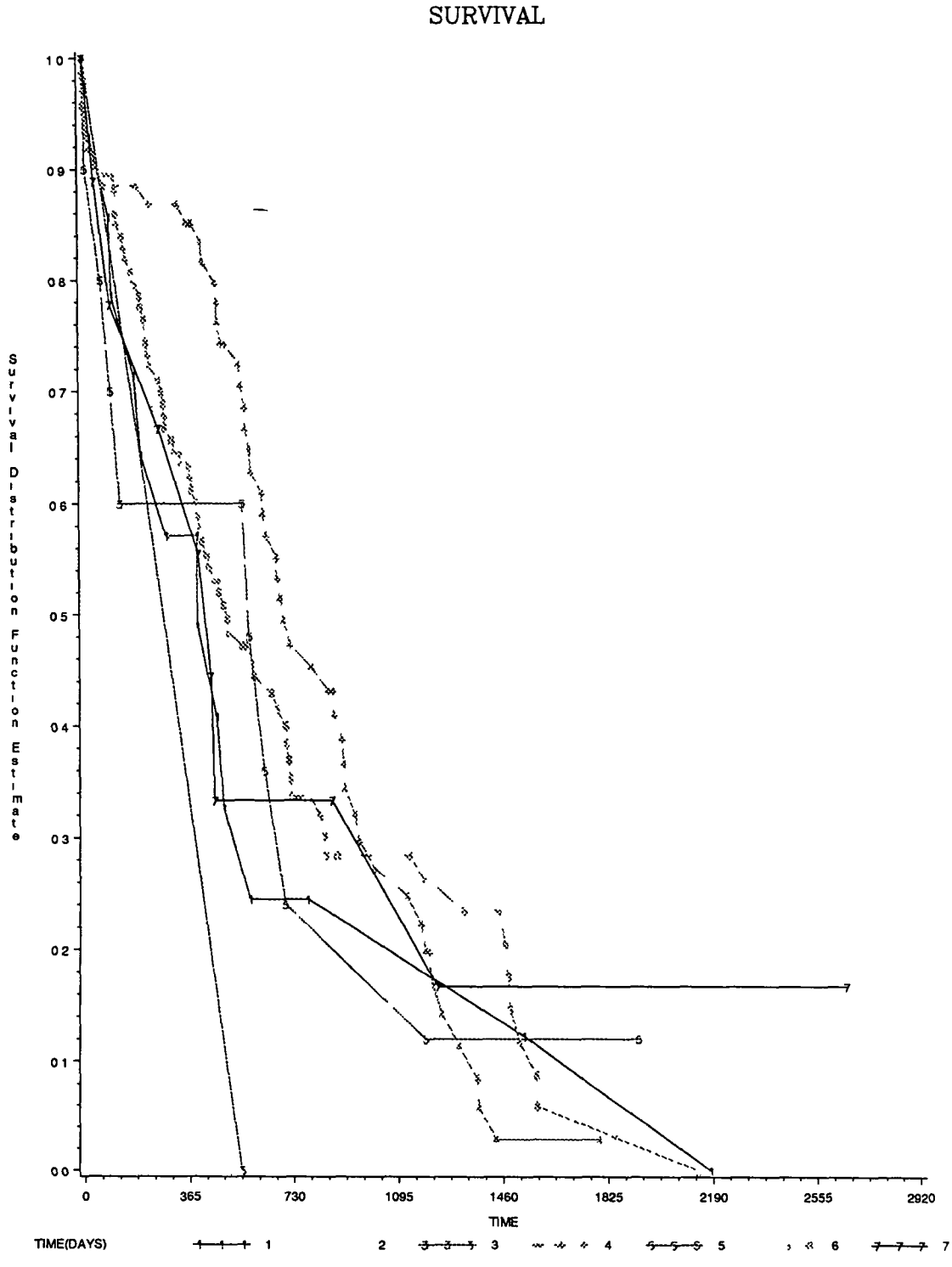

*Figure 4 4 Survival of patients with AIDS by risk-group*

#### 4.4.1.4 Manifestation of disease at diagnosis

In order to better compare results with other studies the manifestations of disease at diagnosis were classified into groups as described in the section on methods PCP alone (61 subjects) was the manifestation of disease with the **most** favourable survival pattern, with a median survival time of 696 days and a cumulative probability of survival of 85 ±4 6 percent at one year On the other hand, subjects whose disease at diagnosis was Kaposi's sarcoma either alone or with PCP had the **least** favourable prognosis (18 subjects, median 363 days, cumulative probability of survival at one year 50 ± 11 8%) However the above results were not statistically significant, and, as pointed out earlier (section 4 3 1 4), the mean age of those whose manifestation of disease at diagnosis was Kaposi's sarcoma either alone or with PCP was 39 years contrasting with that of 'other' manifestations (mean age was 32)

The difference in survival time between subjects with Kaposi's sarcoma and those with other diagnostic features were contrary to those found in other studies In this study K S is the manifestation with the second shortest survival time The Reeves and Overton study (1988) and the Rothenberg and Woelfe et al study (1987) both agree that K S is the manifestation with the longest survival time between diagnosis and death The discrepancies between this study and the aforementioned may be explained by the tendency of homosexuals with AIDS to get K S and the older age of homosexual subjects in this study (see patient details) Patients with Kaposi's sarcoma in this case were generally older than those with other manifestations of disease The discrepancy may also be partly explained by the fact that only 19 subjects (9 8%) had Kaposi's sarcoma recorded as a manifestation of disease, a smaller proportion than in other studies (see discussion). Figure 4 5 shows survival stratified by manifestation of disease (PCP+) and Figure 4 6 shows survival stratified by disease group (GRP+)

**Survival of patients with AIDS by manifestation of disease (PCP+)**




1 Kaposi's sarcoma alone 2· KS and PCP 3 KS and another disease 4 PCP alone 5· PCP and another disease 6· One other disease alone 7 At least two other diseases

*Figure 4 5 Survival of patients with AIDS by manifestation of disease (PCP+)*

**Survival of patients with AIDS by disease group (GRP+)**

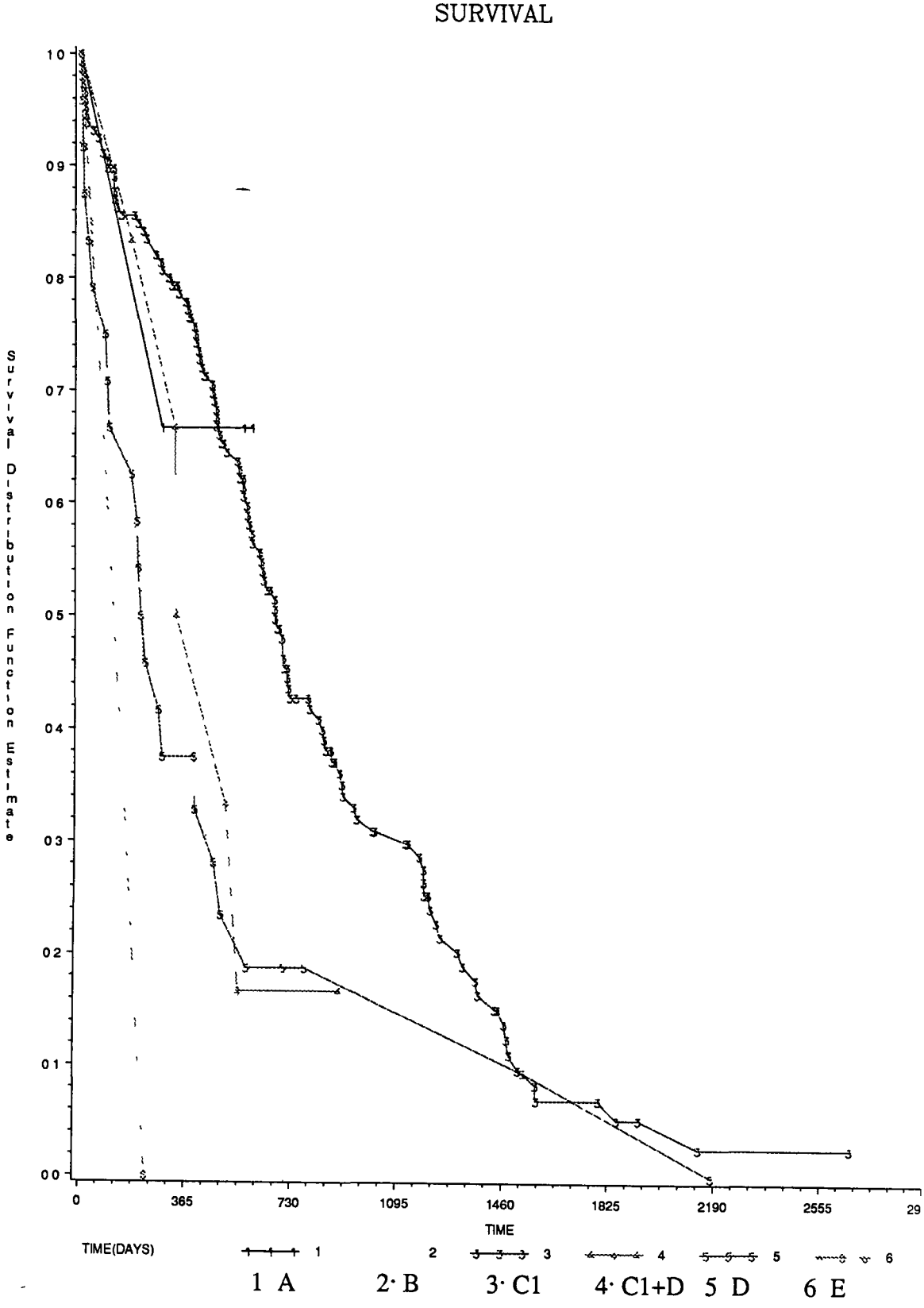
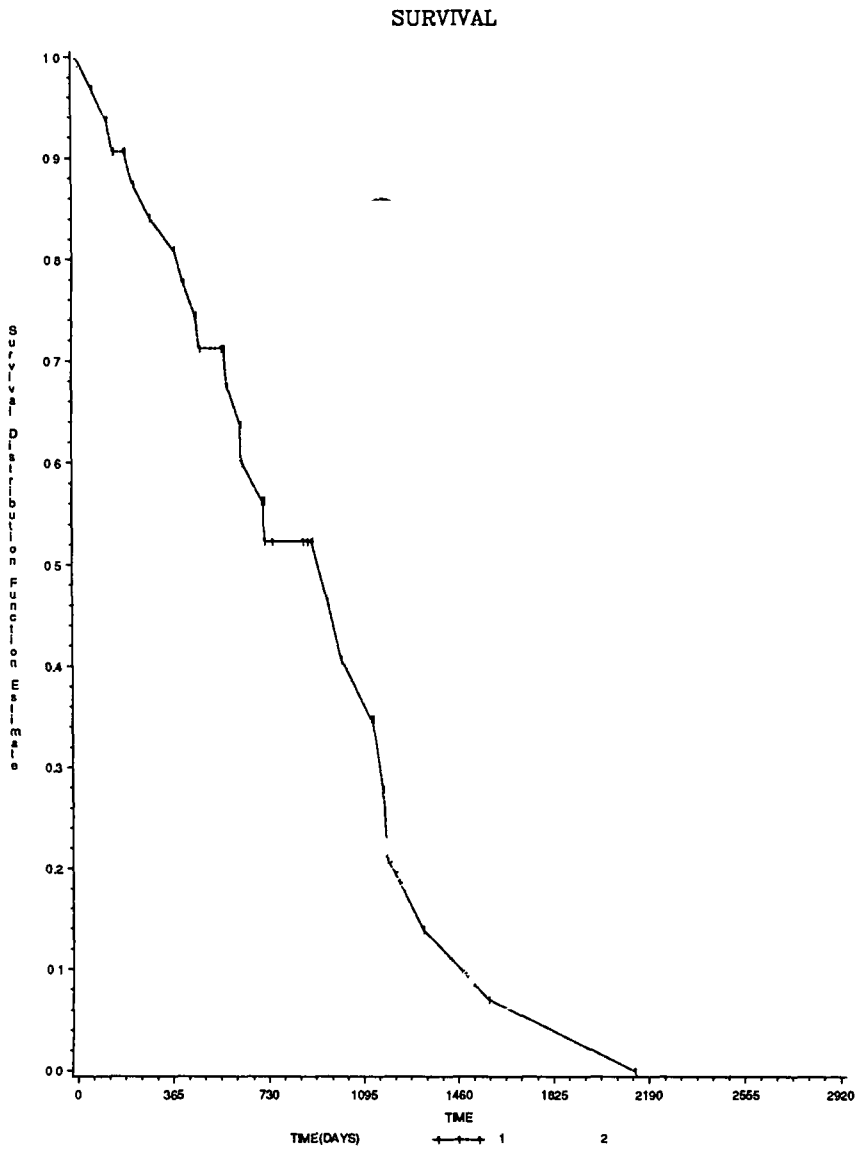



*Figure 4 6 Survival of patients with AIDS by disease group (GRP+)*

### 4.4.2 Patients with the most favourable survival

Figure 4 7 shows survival time in the subgroup with the "more favourable" survival (patients aged 35-39 years who were initially diagnosed with an opportunistic disease) compared to all others The graphs are different with respect to the likelihood of early death but coincide more closely after about 3 years, although clearly, numbers are smaller as the tails are approached The cumulative probability of survival at one year among patients aged 35-39 years who were initially diagnosed with an opportunistic disease was significantly better at 84 1 ± 6 5 percent ($p < 0$ 03, Wilcoxon test of equality over strata ), with a median conditional survival of 956 days, the corresponding value at one year among the remainder of the cohort was 66 0 ± 3 8 percent, with a median conditional survival of 547 days The survival curve for the comparison group crossed that of the 'more favourable' subgroup after the third year

**Survival in the subgroup which showed a 'more favourable' survival time compared to all others**




1 Patients aged 35-39 years initially diagnosed with an opportunistic disease (n = 32)

2· All Others (n = 161)

*Figure 4 7 Survival in the subgroup which showed a 'more favourable' survival time compared to all others*

### 4.4.3 Short - term survival

Overall, 14 persons (7 3% of the full cohort) died within one month of diagnosis of AIDS with the percentage of women dying within this short period higher than that of men (5(13 5%) of all women vs 9(5 8%) of all men) 7 of

the 14 were aged between 30 and 34 years, and only 28 6% were under 30 years Interestingly none were aged 35-39 and only three were on anti-viral therapy 4 of the 14 were patients with a manifestation of disease from group D, which gives a higher proportion than that in the full cohort Severity of disease at diagnosis was not available in the data set Numbers in this group are clearly very small

Within the first six months of diagnosis 37 persons (19 2% of the full cohort) had died, of whom 17 (45 9%) were aged between 30 and 34 years, 9 (24 3%) were 40 years of age and older, 21(56 8%) were IVDUs, nearly a quarter (24 3%) had been diagnosed with a disease from group D, and 21(56 8%) were on anti-viral therapy

## 4.5 Treatment with anti-viral therapy

Zidovudine treatment of AIDS patients was licensed in 1987 Survival for 167 subjects who were treated with zidovudine or 2', 3'-dideoxyinosine (ddI) or DDC (only one subject) at some point during their illness was compared with survival for 26 subjects who were not receiving any anti viral therapy (11 of whom it is important to note died within one month of diagnosis of AIDS, and one of whom was treated with a prophylactic drug (septrin)) In addition 2 of the subjects who were included with those on treatment were involved in a drug trial and it is therefore unknown whether they were, in fact, on treatment or on a placebo

Since we have no evidence of the selection procedures used nor of the state of health of individuals at either the time of diagnosis or the time of first treatment we cannot be sure that the two groups (i e those on treatment and others) are comparable

Survival is calculated without regard to actual duration of therapy Therapy with either zidovudine ddI or DDC was significantly associated with increased survival in the group as a whole, and, when stratified by the covariates age-group, sex, and risk-group ($p < 0.0002$, Wilcoxon test for the association of survival with covariates) There was no significant difference in survival between the sexes for those who were on therapy But of those who were not on therapy, women had a longer median survival time (300 days) than did men (40 days) However this difference was not significant The mean age for those on treatment was 32 and that for those who were not on treatment was 34

## 4.6 Proportional-Hazards-Model.....coefficients for covariates.

The influence of each of the six covariates (sex, risk-group, age-group, treatment, year of diagnosis and manifestation of disease at diagnosis in the presence of each of the others was assessed in a single proportional hazards model to predict length of survival (see Table 4 4 for significant results) In this model a relative risk of 1 and positive coefficients imply an increased risk and therefore indicates a negative relationship with survival Anti-viral drug treatment was the best independent predictor of survival followed by year of diagnosis and disease group (GRP+) Sex, manifestation of disease at diagnosis (PCP+), age-group and risk-group were not significant predictors and were excluded by the model

The proportional hazards model also suggests that improved survival was associated with being on anti-viral therapy and having a disease from the C1 group (GRP+) Being aged 35-39 years was also associated with improved survival but did not fall within a 95% confidence interval Survival was shortest for those patients aged 30-34 and those aged over 40 years, those who were not receiving anti-viral treatment, those whose manifestation of disease at diagnosis included Kaposi's sarcoma or other cancer, or those whose disease was neurological Referent groups were those determined to have the best survival curves by the categories given below (see figures 4 2-4 6)

**Table 4.4 Effect of significant covariates on relative hazards for persons with AIDS**

| Patient Characteristics | Coefficient ± SE* | Relative hazard ** | p value |
|---|---|---|---|
| Not on Therapy | -0 185 ± 0 236 | 0 31 | <0 0001 |
| Year of Diagnosis ‡ | 0 203 ± 0 055 | 1 22 | <0 0001 |
| Disease Group (GRP+) | 0 206 ± 0 107 | 1 23 | <0 061 |

** Proportionate increase or decrease in hazard compared with baseline of 1 0, with effects of all other covariates held constant

‡ The time dependent covariate Year of diagnosis was used to test the proportionality assumption, the result of which suggested that the proportional hazards model is valid

**Table 4.5 Proportional-Hazards-Model Coefficients for Covariates with Referent Group**

| Covariate | Referent | Coefficient* ± SE | Relative risk of death ** | p value |
|---|---|---|---|---|
| **Sex** | Men | | | |
| Women | | *not significant* | | |
| **Age-group** | 35-39 | | | p=**0.0764** |
| <30 | | 0 170 ± 0 229 | 1 19 | |
| 30-34 | | 0 567 ± 0 246 | 1 76 | |
| 40+ | | 0 449 ± 0 303 | 1 57 | |
| **Risk-group** | IVDU | | | |
| Homo/bisexual | | *not significant* | | |
| IVDU & H/Bisex | | | | |
| Other | | | | |
| **Treatment** | | | | |
| Not on therapy | On therapy | 1 249 ± 0 233 | 3 49 | p=0 0001 |
| **Disease grp** (GRP+) | C1 | | | p=0 0003 |
| A | | -0 369 ± 1 007 | 0 69 | |
| B | | 1 164 ± 0 314 | 3 20 | |
| C1+D | | 0 592 ± 0 461 | 1 81 | |
| D | | 0 634 ± 0 243 | 1 92 | |
| E | | 1 542 ± 1 012 | 4 67 | |
| **Manifestation** | PCP alone | | | |
| KS in any form | | *not significant* | | |
| PCP with another disease | | | | |
| One other disease alone | | | | |
| 2 or more other diseases | | | | |

*A coefficient is the logarithm of the relative risk of death at any time, as compared with the value in the referent group A value of zero implies an identical risk of death, whereas a positive (or negative) coefficient implies an increased (or decreased) risk

** exp (Coeff )

## 4.7 Significant findings

In the overall analysis the influence of each of the major variables in the presence of the others was tested Treatment with anti-viral therapy, year of diagnosis, and disease group to which the patient belonged at diagnosis, had a significant influence on the survival of the cohort ($p<0.0002$, $p<0.0006$ and $p<0.02$ respectively, Wilcoxon test for the association of survival with covariates) They also remained significant when the cohort was stratified over sex, risk, age, and manifestation of disease groups

Age-group, disease-group, treatment-group (i e either on anti-viral treatment or not on treatment), and year of diagnosis showed significant differences between strata ($p < 0.01$, $p < 0.002$, $p < 0.0002$ and $p < 0.04$ respectively, Wilcoxon test of equality over strata) Patients aged 35-39 showed longer median survival times (715 days) than all other age groups (median survival= 547 days), ($p < 0.04$, Wilcoxon test) Patients whose disease group was opportunistic disease/s alone (CDC IV group C1) had a significantly longer median survival (672 days) than did all others (i e those whose disease was Kaposi's sarcoma (K S ) or other cancers, those with neurological disease, or, those with other diseases), (median survival= 281 days), ($p < 0.0002$, Wilcoxon test)

Survival did not differ significantly by sex or risk group alone, nor did it differ significantly by manifestation of disease when grouped according to criteria used in previous studies, and labeled by us as PCP+

Five (2 6%) patients survived more than 5 years after AIDS was diagnosed, all of whom were male

## 4.8 Discussion

In our cohort of 193 subjects, the cumulative probability of survival at one-year was estimated to be $69 \pm 3.3$ percent and the five-year cumulative probability of survival was estimated to be $6.5 \pm 2.5$ percent As currently estimated the spectrum of survival is bounded by 14 persons who died within one month of diagnosis and by one person who survived past the truncation time Within these bounds there is considerable heterogeneity

The probability of survival is most strongly influenced by treatment with anti-viral therapy It is strongly influenced too by year of diagnosis and disease-group at diagnosis

Among groups defined by a single factor, subjects aged 30-34 and those aged over 40 years, those who did not receive anti-viral therapy, those whose manifestation of disease at diagnosis included Kaposi's sarcoma or other cancer, or those whose disease was neurological appeared to have the poorest prognosis

### 4.8.1 Comparison with other studies

To date a number of studies have estimated survival among AIDS patients Median survival ranged from 280 days to 760 days The survival time found by this study is therefore comparable to previous first world studies of the survival of persons with AIDS However only 13 of these 19 studies were conducted on subjects who were diagnosed since 1987, the date of the introduction of anti-viral therapy For all cases, the median survival was 576 days in this study, 581 days in Cologne (Faetkenheuer et al , 1991), and 608 and 633 days respectively for those patients diagnosed in 1987 in the U K (Peters et al , 1991) and in Washington State (Lafferty et al , 1991) The cumulative probability of survival for 12 months, after a diagnosis of AIDS was 69 0 ± 3 3 percent in this study compared with 54 ± 1 percent in Massachusetts (Seage et al , 1993) and 48 8 ± 0 7 percent in New York City (Rothenberg et al , 1987), (see table 4 6) The cumulative probability of survival for 3 years after diagnosis, was 27 4 ± 3 6 percent in this study compared to 13 1 percent in San Francisco (Lemp et al , 1992) and 22 ± 0 8 percent in New York City (Rothenberg et al , 1987)

The natural history of AIDS in this study as indicated by the survival time is therefore similar to that in other Western countries The main discrepancies between median survival times for this study and the others reside in the times for certain age groups and the times for those patients with Kaposi's sarcoma Many studies however indicate that of all the age groups those over 40 years have the worst prognosis (e g Seage et al , 1993, Lemp et al , 1992, Whitmore-Overton et al , 1993, Altes et al., 1992, d'Arminio Monforte et al , 1992, and Morlat et al , 1991) and this is in agreement with our findings

In this study the survival curves varied significantly with age at the time of diagnosis of AIDS, with the median survival time ranging from 715 days in those who were aged 35-39 years to 331 days in those who were 40 years of age or older at the time of diagnosis

The median survival time for patients who were infected by way of homosexual practices was 548 days this study and 578 days for those diagnosed between 1988 and 1990 in San Francisco (Osmond et al , 1991)

There was no significant difference, in this study, in survival times between those infected in this way and those infected because of their use of intravenous drugs Batalla et al (1989) studied the survival time of AIDS in 289 IVDUs and found the survival time of IVDU-related AIDS to be slightly longer than the estimated survival times calculated for other risk groups Seage et al (1993) found the contrary to be the case

There were marked differences in the median survival of patients whose manifestation of disease at diagnosis was Kaposi's sarcoma alone and those patients in other studies who were initially diagnosed solely with this disease This study showed a median survival time of 395 days compared with one of 645 days in the U K. (Marasca & McEvoy, 1986) and 750 days in New York City (Rothenberg et al , 1987) However there were only 14 (7 3%) such patients in this study However an Australian study showed similar survival times to this one with a median survival time of 377 days for patients with K S (Whyte et al , 1989), (see table 4 6)

Therefore, when considering the data which concern the mode of transmission, and the survival time, it is apparent that survival with AIDS in Ireland is similar to that in other developed countries even though Ireland has one of the highest percentages of drug related AIDS cases among those countries who report to AIDS Surveillance in Europe (WHO-EC Collaborating Centre on AIDS, 1993)

A comparison of recent studies forms the basis of the final table in his chapter The survival times found in this study are more in line with more recent studies (i e those conducted since 1990) than with earlier ones However the significant differences (in this study) between Kaposi's sarcoma and other diagnostic features were if anything contrary to those found in other studies In this study K S is the manifestation with the second shortest survival time The Reeves and Overton study (1988) and the Rothenberg and Woelfe et al study (1987), (see table 4 6), have overall agreement between them The two sets of results are very close They both agree that K S is the manifestation with the longest survival time between diagnosis and death and that of all the age groups, those over 40 have the worst prognosis Our study would agree with both studies mentioned only with respect to the latter finding The discrepancies between this study and the aforementioned may be explained by the time difference (in so far as this study includes diagnoses up to 1993 and survival may have improved with knowledge gained over the years, in particular with regard to treatment of PCP) and by the fact that only 13 (18%) subjects out of the 72 homo/bisexual men and only 7 3% of the total Dublin

cohort, had Kaposi's sarcoma recorded as the manifestation of disease at diagnosis Thirteen of the 14 of those whose manifestation of disease at diagnosis was recorded as Kaposi's sarcoma alone in this study were homo/bisexual men and one was an IVDU Nine subjects out of the 14 were 35 years of age and older

The epidemiology of AIDS in Ireland has been described previously (Comiskey, 1991) and has been shown to be unlike that in other developed countries in terms of the distribution of cases by sex, the age-groups that are affected and the risk activities that lead to infection with HIV Of all the cases of AIDS in this study, 66 8% of cases were found in patients who were 34 years of age and younger, 90 2% who were aged 40 or younger and 97.4% in patients who were aged 50 or younger

The age group of those patients 30 years of age and younger (the largest age group in this study), comprised 38 9% of the entire cohort compared to only 18% of the New York City cohort (and the smallest age-group) described by Rothenberg et al , (1987) On the other hand one third of the New York City cohort were aged 40 and older compared to only 11 9% of this study's cohort In all the New York City cohort comprised 43% of subjects 34 years and younger and 57% of subjects over 34, while the corresponding figures for this study were 66 9% and 33 1% respectively

The mean age (32 years) for cases of AIDS found in the present study was lower than that which has previously been reported in other studies from the United Kingdom (38 yrs) (Marasca & McEvoy, 1986), in New York City (Rothenberg et al , 1987) and for adult men (37 years) and women (35 years) in the United States (Centers for Disease Control, 1986)

This difference in the ages of patients with AIDS in Ireland compared with the U K and the United States is understandable when the method of infection of these patients is considered The high proportion of patients whose risk activity included intravenous drug use and the generally young age of intravenous drug users clearly influences the younger mean age of persons with AIDS in Ireland and in this study Supportive evidence of the relatively young age of intravenous drug users with AIDS is found in Glasgow (mean age, 21 years) (Robertson et al , 1986), and Dublin (mean age, 25 for those IVDUs in treatment), (O'Hare & O'Brien) The Dublin report states that preliminary information from the Pompidou Group (Hartnoll, 1993, E C project) shows Dublin with the lowest mean age for census clients (December 1990) at 25.7 years Of the other cities in the study the mean age for clients was almost six years older in Copenhagen and eight in Amsterdam It points out that while

census data are not in all cases representative for cities they do indicate a trend of older long term users in those cities like Amsterdam, Copenhagen and Stockholm with a longer history of problem drug use. The report further states that available data for all treated drug users (as distinct from census clients only) show current Dublin users to be younger than most of their European counterparts, with the exception of Lisbon, Glasgow and Edinburgh

The crude mortality ratio in this study was 79 3% while that in New York City (Rothenberg et al , 1987) was 66 8%

Among those in this study who received anti-viral therapy, survival did not differ by gender This is consistent with the findings of Lemp et al (1992)

Our study observed a higher rate of parenteral drug use but a smaller percentage of homosexual or bisexual men compared with the same risk factors seen in the other studies mentioned Our cohort enumerated 91 (47 2%) active drug users and 7 (3 6%) who were former drug users contrasted with only 72 (37 3%) who described themselves as homo-or bisexual Drug users (active and former) outnumbered homo-or bisexual men by 1 36 to one This finding reflects the higher prevalence of HIV infection among IVDUs in Ireland

Table 4 6 compares the current study to some of the more comprehensive previous reports on survival, published between 1987 and 1993 The differing results may be attributed in part to differing features, including a wide variation in sample size, differences in the starting date (i e , date of diagnosis) used for survival curves, variation in the type, timing, and analysis of diagnostic categories, and differing approaches to criteria for diagnosing AIDS, including adherence to the case definition of the Centres for Disease Control and the use of serologic evaluation

**Table 4.6. Median Cumulative Survival and Characteristics of Previous Studies as Compared with the Current Study**

| | New York City 1987 | U.K. 1988 | Australia 1989 |
|---|---|---|---|
| Median cumulative survival (days) | 347 | 377 | 316 |
| Sex | | | |
| Men | 357(90 5%) | 383(97%) | 347(96 2%) |
| Women | 263( 9 5%) | 106( 3%) | 116( 3 9%) |
| Risk group | | | |
| Intravenous drug use | 282(28.5%) | | 328( 0 5%) |
| Homo/Bisexual activity | 392(58 3%) | 383(89%) | 347(87 0%) |
| Other risk factor | 255( 7 5%) | | |
| Age | | | |
| < 30 | 371(18 4%) | 435(19%) | 347(11 4%) |
| 30-34 | 387(24 6%) | 468(19%) | 347 |
| 35-39 | 357(23 6%) | 398(23%) | 347 |
| 40+ | 300(33 3%) | 301(39%) | |
| Manifestations | | | |
| Kaposi's sarcoma alone | 750(17 0%) | 456(23%) | 377(19 3%) |
| K S and another disease | 325( 3 3%) | | 246( 3 2%) |
| K S and PCP | 381( 5 8%) | 322( 6%) | |
| P *carinii* pneumonia alone | 318(43 6%) | 389(46%) | 347 |
| P C P and another disease | 301(12 3%) | | |
| One other disease alone | 209(13 9%) | ⌈152-298(25%) | |
| Two other diseases alone | 235( 3 7%) | ⌊ | |
| No of cases | 5833 | 663 | 554 |
| Mean age | | 37 | 37 |
| Diagnoses included | Two major diseases | At presentation | At presentation |
| Period studied | 1981-1985 | 1982-1987 | 1982-1987 |
| Starting date | Date of diagnosis | Date of diag | Date of diag |
| Censoring date | Sept 1986 | March 1987 | July 1987 |

**Table 4.6. Median Cumulative Survival and Characteristics of Previous Studies as Compared with the Current Study**

| | Massachusetts 1993 | Current Study 1994 |
|---|---|---|
| Median cumulative survival (days) | 406 | 576 |
| Sex | | |
| Men | 411 (90%) | 576(80 8%) |
| Women | 347(10%) | 590(19 2%) |
| Risk group | | |
| Intravenous drug use | 342(18%) | 574(50 8%) |
| Homo/Bisexual activity | 444(62%) | 548(37 3%) |
| Other risk factor | 341 (16%) | 643(8 3%) |
| Age | | |
| < 30 | 416(22%) | 590(38 9%) |
| 30-34 | 447(27%) | 397(28 0%) |
| 35-39 | 443(22%) | 715(21 2%) |
| 40+ | 345(29%) | 331(11 9%) |
| Manifestations | | |
| Kaposi's sarcoma alone | 505(10%) | 395( 7 2%) |
| K S and another disease | 328( 2%) | 548( 0 5%) |
| K S and PCP | 391( 5%) | 328( 2 1%) |
| P *carinii* pneumonia alone | 458(41%) | 696(31 6%) |
| P C P and another disease | 405(14%) | 574( 5 2%) |
| One other disease alone | ⌈313(27%) | 500(48 7%) |
| Two other diseases alone | ⌊ | 441( 4 7%) |
| No of cases | 1931 | 193 |
| Mean age | 36 | 32 |
| Diagnoses included | At presentation | At presentation |
| Period studied | 1979-1989 | 1986-1993 |
| Starting date | Date of diag | Date of diag |
| Censoring date | Dec 1989 | March 1993 |

## 4.9 Recommendations

From a public policy point of view, mortality information is particularly important to both health care planners and disease modellers, who need the information to accurately project the needs of the future AIDS population As prophylaxis and treatment for opportunistic diseases improve, and as ever larger numbers of patients receive antiretroviral therapy with zidovudine and other drugs still under development, it can be expected that the number of persons living with severe HIV-related immunosuppression and /or AIDS will increase

The impact of prolonged survival of people living with AIDS on the health care system needs evaluation In particular, the observed increases in survival with AIDS, noted in most recent studies (Faetkenheuer et al , 1991, Peters et al , 1991, Merrick et al , 1992, Rasch et al , 1992, and Lafferty et al , 1991) mean that it is important to begin to view AIDS not as an acute condition but as a chronic condition Thus the development of appropriate home and chronic care services, and long-term HIV prevention programs will need to be addressed

## 4.10 Conclusions

The St James' Hospital cohort differed from the other studies documented in this report which classified risk category, in that it had higher proportions of intravenous drug users (50 8% were IVDUs and 37 3% were homo/bisexual men ) and younger subjects (mean age was 32) These differences do not seem to have affected overall survival Other demographic details which may have had a bearing on survival patterns included a male female ratio which was approximately 4 2 1, (80 8% male and 19 2% female) This study therefore included a larger proportion of female subjects than did any of the other studies (Faetkenheuer et al., 1991, Seage et al , 1993, Rothenberg et al , 1987, Reeves & Overton, 1988, Whyte et al , 1989, and Rasch et al , 1992) to which this report referred, with male female ratios ranging from 9 1 to 32 1

The cumulative probability of survival was 69% at one year and 6 5% at five years, with median conditional probability of survival of 576 days, in comparison to 581 days in Cologne (Faetkenheuer et al , 1991), 608 days in the United Kingdom (Peters et al , 1991), 633 days in Washington State for

cases diagnosed during 1987 (Lafferty et al , 1991), and, 578 days in San Francisco for those diagnosed between December 1988 and August 1990 (Osmond et al , 1991)

Short-term and long-term survival patterns were distinctive with 'late' presentation a feature (see also Murphy et al , 1991, on the Irish situation) Fourteen patients died within one month of diagnosis of AIDS and 5 (all male) survived more than 5 years after AIDS was diagnosed

Significantly longer survival times were apparent for those who were on treatment with anti-viral therapy, and patients who were aged 35-39 years at diagnosis had a significantly longer median survival (715 days) than did all others (547 days) In addition patients whose disease group was opportunistic disease/s alone (CDC IV group C1) had a significantly longer median survival (672 days) than did all others (median survival = 281 days) Survival did not differ significantly by sex or risk group

# Chapter 5

# A Perturbation Model for HIV Transmission

## 5.1. Introduction

An analytic solution to the system of equations (2 11)-(2 16) described in Chapter 2 is of course the preferred and most advantageous outcome However there are a number of difficulties in attempting this, some of which were pointed out in Chapter 2 and others which will become apparent as we describe the particular alternative approach dealt with here

Perturbation methods seek to approximate the exact solution by constructing an approximate solution as a series in ε Therefore, before turning to numerical methods and as there appeared to be a reasonably small parameter involved in equations (2 11)-(2 14) we decided to investigate the possibility of using perturbation methods to construct an approximate solution as a series in ε

There are some problems in which the function sought is not an elementary function of its arguments, as for example an equation describing a harmonic oscillation with a small amount of friction When those arguments include a small parameter, or perturbation term, ε, it is sometimes advantageous to seek a representation of the function $f(x,\varepsilon)$ in the form

$$f(x;\varepsilon)=\sum_{n=0}^{\infty} f_n(x)\varepsilon^n \qquad (5\ 20)$$

for suitable functions $f_n$ that depend only on $x_i$ and not on ε In other words the solution of some non-linear problems can be made to depend on the solutions of a sequence of linear problems (Carrier, 1990) In general it is desirable for ε to be quite small, i e $0\leq \varepsilon \ll 1$, since the infinite series will only be a good approximation to the real solution when $\varepsilon \ll 1$, and the closer ε is to 1 the more terms in the series one must use in order to get a reasonable

approximation It is better therefore that ε is such, that for small ε, the quantity $f_0 + \varepsilon f_1 + \varepsilon^2 f_2$ differs very little from $f_0 + \varepsilon f_1$

In studying scientific phenomena or technological questions, the important requirement is that a very few terms of a series of the above form (5 20), provide an approximate description of the function which has all of the accuracy which the investigation requires Procedures which provide useful series having the form of equation (5 20) are called perturbation methods because it is assumed that the difference between the given operator and the simpler operator is only a small perturbation of the latter A singular perturbation problem is a problem that depends on a parameter (or parameters) in such a way that solutions behave nonuniformly as the parameter tends toward some limiting value of interest The nature of the nonuniformity can vary from problem to problem In practice, one seeks a uniformly valid, easily interpretable approximation to the non-uniformly behaving solution (Smith, 1985)

## 5.2 Perturbation methods for HIV models

In Chapter 2 we looked at various deterministic models of the transmission dynamics of HIV and its progression to AIDS We defined a very simple model for the spread of AIDS based on the three states *susceptible*, *infected with HIV but not yet diagnosed as having (full) AIDS* and *diagnosed with AIDS* We also defined an infection rate which is the product $\beta s$ of the rate $s$ of partner change and the probability $\beta$ of transmission of infection The set of differential equations (2 11) - (2 16) described in Chapter 2, is reproduced here and is given by

$$\frac{dX_m(t)}{dt} = \lambda_m - \beta_f s_m X_m(t) Y_f(t)/N_f(t) - \mu_m X_m(t) \qquad (2\ 12)$$

$$\frac{dX_f(t)}{dt} = \lambda_f - \beta_m s_f X_f(t) Y_m(t)/N_m(t) - \mu_f X_f(t) \qquad (2\ 11)$$

$$\frac{dY_m(t)}{dt} = \beta_f s_m X_m(t) Y_f(t)/N_f(t) - (\alpha + \mu_m) Y_m(t) \qquad (2\ 14)$$

$$\frac{dY_f(t)}{dt} = \beta_m s_f X_f(t) Y_m(t)/N_m(t) - (\alpha + \mu_f) Y_f(t) \qquad (2\ 13)$$

$$\frac{dA_m(t)}{dt} = \alpha Y_m(t) - (\mu_m + \nu) A_m(t) \qquad (2.16)$$

$$\frac{dA_f(t)}{dt} = \alpha Y_f(t) - (\mu_f + \nu)A_f(t) \qquad (2\ 15)$$

where $X_m, X_f, Y_m, Y_f, A_m, A_f, \lambda_m, \lambda_f, \beta_m, \beta_f, s_m, s_f, N_m, N_f, \mu_m, \mu_f, \alpha$, and $\nu$ are as defined in chapter 2

Suppose we let $\varepsilon = \beta s$ This would appear to be reasonable since $\beta_f$ (the probability of sexual transmission from a female to a male) is in the region of 0 0054 and $s_m$, the rate of partner change for males is in the region of 1 93 The product $\beta_f s_m$ is therefore 0 0104 The corresponding figures for $\beta_m$ and $s_f$ are 0 0783 and 1 13, and the product $\beta_m s_f$ is 0 0885 If $\varepsilon$ is taken to be 0 0104 then $8\varepsilon$ approximates 0 0885 Both $\varepsilon$ and $8\varepsilon$ are smaller than 1 (If we take $\varepsilon$ to be 0 0104, then $\varepsilon^2$ will be 0 00011 and $\varepsilon^3$ will be 0 000001), and the contributions to successive terms in the series of equation (5 20) tend rapidly to zero The solution of (2 12), $X_m = X_m(t,\varepsilon)$ of the problem depends analytically on the parameter $\varepsilon$, hence $X_m$ can now be represented in the form

$$X_m(t,\varepsilon) = \sum_n^{\infty} X_m^{(n)}(t)\varepsilon^n \qquad (5\ 21a)$$

for suitable functions $X_m^{(n)}$ that depend only on $t$ and not on $\varepsilon$

The next step is to try an expression like (5 21a) as a solution for the non-linear system rather than just a single equation, so that we have

$$X_m(t,\varepsilon) = X_m^{(0)}(t) + \varepsilon X_m^{(1)}(t) + \varepsilon^2 X_m^{(2)}(t) + \varepsilon^3 X_m^{(3)}(t) + .. \qquad (5\ 21b)$$

and similar expressions for $X_f, Y_m, Y_f, A_m, and, A_f$.

Using this perturbation method the functions $X_m^{(n)}$ are determined by substituting (5 21) into the non-linear system (2 11) - (2 16) and equating coefficients of like powers of $\varepsilon$ in the resulting equations so as to obtain an infinite sequence of problems (or linear differential equations) that can be solved recursively for the unknown functions

$$X_m^{(0)}, X_f^{(0)}, Y_m^{(0)}, Y_f^{(0)}, A_m^{(0)}, A_f^{(0)}, X_m^{(1)}, X_f^{(1)}, Y_m^{(1)}, Y_f^{(1)}, A_m^{(1)}, A_f^{(1)}, \quad etc$$

The series so obtained should converge if $\varepsilon$ is small enough and if the functions $X_m^{(0)}, X_f^{(0)}, Y_m^{(0)}, Y_f^{(0)}, A_m^{(0)} and, A_f^{(0)}$ are all bounded The solutions of our system of equations are bounded since the total population is bounded over a maximum of a 30 year period In many applications all that is needed for an

adequate approximation is the term in the first power of ε, and this can usually be found quite easily

Allowing ε to equal 0, in equations (2 11) - (2 16), clearly produces a linear system with constant coefficients which we can solve exactly to obtain the analytical expressions for $X_m^{(0)}, X_f^{(0)}, Y_m^{(0)}, Y_f^{(0)}, A_m^{(0)} and, A_f^{(0)}$ which are given below

$$X_m(t;0) = \frac{-\lambda_m + \lambda_m e^{\mu_m t} + c_2 \mu_m}{\mu_m e^{\mu_m t}} \tag{5 22}$$

$$X_f(t;0) = \frac{-\lambda_f + \lambda_f e^{\mu_f t} + c_1 \mu_f}{\mu_f e^{\mu_f t}} \tag{5 23}$$

$$Y_m(t;0) = \frac{c_4}{e^{(\alpha+\mu_m)t}} \tag{5 24}$$

$$Y_f(t;0) = \frac{c_3}{e^{(\alpha+\mu_f)t}} \tag{5 25}$$

$$A_m(t;0) = \frac{c_4\alpha}{(-\alpha+\nu)e^{(\alpha+\mu_m)t}} + \frac{c_4\alpha + c_6\alpha - c_6\nu}{(\alpha-\nu)e^{(\mu_m+\nu)t}} \tag{5 26}$$

$$A_f(t;0) = \frac{c_3\alpha}{(-\alpha+\nu)e^{(\alpha+\mu_f)t}} + \frac{c_3\alpha + c_5\alpha - c_5\nu}{(\alpha-\nu)e^{(\nu+\mu_f)t}} \tag{5 27}$$

Substituting (5 21) into the non-linear equation (2 12) as described above and multiplying across by $N_f(t)$ gives

$$\begin{aligned}\left(X_m^{(0)}(t)+\varepsilon X_m^{(1)}(t)+\ \right)&\left\{N_f^{(0)}(t)+\varepsilon N_f^{(1)}(t)+\ \right\} = \lambda_m\left\{N_f^{(0)}(t)+\varepsilon N_f^{(1)}(t)+..\right\}- \\ &\varepsilon\left\{X_m^{(0)}(t)+\varepsilon X_m^{(1)}(t)+.\ \right\}\left\{Y_f^{(0)}(t)+\varepsilon Y_f^{(1)}(t)+..\right\}- \\ &\mu_m\left(X_m^{(0)}(t)+\varepsilon X_m^{(1)}(t)+..\right)\left\{N_f^{(0)}(t)+\varepsilon N_f^{(1)}(t)+...\right\}\end{aligned} \tag{5 28}$$

and similar substitutions can be made for the other equations in the system (2 11) - (2 16)

Equating coefficients of like powers of ε in this last equation and simplifying, we find

$$X_m^{(n)}(t)=\frac{1}{\varepsilon^n N_f^{(0)}}\left(-\sum_{k=0}^{n-1}\left[\varepsilon^k\sum_{j=0}^{k}\left[X_m^{(k-j)}(t)N_f^{(j)}\right]\right]-\varepsilon^n\sum_{j=1}^{n}\left[X_m^{(n-j)}(t)N_f^{(j)}\right]+\right.$$
$$\lambda_m\sum_{k=0}^{n}\left[\varepsilon^k N_f^{(k)}\right]-\mu_m\sum_{k=0}^{n}\left[\varepsilon^k\sum_{j=0}^{k}\left[X_m^{(k-j)}N_f^{(j)}\right]\right]-$$
$$\left.\varepsilon\sum_{k=0}^{n-1}\left[\varepsilon^k\sum_{j=0}^{k}\left[X_m^{(k-j)}Y_f^{(j)}\right]\right]\right) \qquad (5\ 29)$$

We similarly equate coefficients of equal powers of ε in each of the other revised equations in the system (2 11) to (2 16) to obtain expressions for the equivalent functions of $t$ only i e

$$X_f^{(n)}(t),Y_m^{(n)}(t),Y_f^{(n)}(t),A_m^{(n)}(t)and,A_f^{(n)}(t)$$

The first order expansion, $X_m^{(1)}(t)$, of equation (5 29) is then

$$\frac{dX_m^{(1)}}{dt}=-\left(\left(\mu_m X_m^{(1)}A_f^{(0)}+\mu_m X_m^{(1)}X_f^{(0)}+X_m^{(0)}Y_f^{(0)}+\mu_m X_m^{(1)}Y_f^{(0)}\right)\Big/\right.$$
$$\left.\left(X_f^{(0)}+Y_f^{(0)}+A_f^{(0)}\right)\right) \qquad (5\ 30)$$

Solving for the first order solution $X_m^{(1)}(t)$ gives us an integral equation

$$X_m^{(1)}(t)=e^{-\mu_m t}\int_0^t -c_4\mu_f\left(\lambda_m\alpha e^{-u(\alpha+\mu_f-\mu_m)}-\lambda_m\alpha e^{-u(\alpha+\mu_f)}+\lambda_m\nu e^{-u(\alpha+\mu_f)}-\right.$$
$$c_1\mu_m\nu e^{-u(\alpha+\mu_f)}+c_1\alpha\mu_m e^{-u(\alpha+\mu_f)}-\lambda_m\nu e^{-u(\alpha+\mu_f-\mu_m)}\Big)\Big/$$
$$\left(\mu_m\left(-c_6\mu_f\nu e^{-u(\mu_f+\nu)}+\lambda_f\alpha+c_2\alpha\,\mu_f e^{-u\mu_f}+\right.\right.$$
$$\lambda_f\nu e^{-u\mu_f}-c_2\mu_f\nu e^{-u\mu_f}-\lambda_f\nu+c_6\alpha\mu_f e^{-u(\mu_f+\nu)}-$$
$$\left.\left.c_4\mu_f\nu e^{-u(\alpha+\mu_f)}+c_4\alpha\mu_f e^{-u(\mu_f+\nu)}-\lambda_f\alpha e^{-u\mu_f}\right)\right)du$$

We similarly expand in each of the other equations to obtain integral equations for $X_f^{(1)}(t),Y_m^{(1)}(t),Y_f^{(1)}(t),A_m^{(1)}(t)and,A_f^{(1)}(t)$

$$X_f^{(1)}(t) = e^{-\mu_f t}\int_0^t -8c_3\mu_m\Big(\lambda_f\alpha e^{-u(\alpha-\mu_f+\mu_m)} - \lambda_f\alpha e^{-u(\alpha+\mu_m)} + \lambda_f\nu e^{-u(\alpha+\mu_m)} - c_2\mu_f\nu e^{-u(\alpha+\mu_m)} + c_2\alpha\mu_f e^{-u(\alpha+\mu_m)} - \lambda_f\nu e^{-u(\alpha-\mu_f+\mu_m)}\Big) \Big/ \Big(\mu_f\Big(-c_5\mu_m\nu e^{-u(\mu_m+\nu)} + \lambda_m\alpha + c_1\alpha\,\mu_m e^{-u\mu_m} + \lambda_m\nu e^{-u\mu_m} - c_1\mu_m\nu e^{-u\mu_m} - \lambda_m\nu + c_5\alpha\mu_m e^{-u(\mu_m+\nu)} - c_3\mu_m\nu e^{-u(\alpha+\mu_m)} + c_3\alpha\mu_m e^{-u(\mu_m+\nu)} - \lambda_m\alpha e^{-u\mu_m}\Big)\Big)du$$

$$Y_m^{(1)}(t) = e^{-(\alpha+\mu_m)t}\int_0^t c_4\mu_f\Big(-c_1\mu_m\nu e^{-u\mu_f} + c_1\alpha\mu_m e^{-u\mu_f} - \lambda_m\alpha e^{-u\mu_f} + \lambda_m\nu e^{-u\mu_f} + \lambda_m\alpha e^{-u(\mu_f-\mu_m)} - \lambda_m\nu e^{-u(\mu_f-\mu_m)}\Big) \Big/ \Big(\mu_m\Big(-c_6\mu_f\nu e^{-u(\nu+\mu_f)} + \lambda_f\alpha + c_2\alpha\mu_f e^{-u\mu_f} + \lambda_f\nu e^{-u\mu_f} - c_2\nu\mu_f e^{-u\mu_f} - \lambda_f\nu + c_6\alpha\mu_f e^{-u(\nu+\mu_f)} - c_4\nu\mu_f e^{-u(\alpha+\mu_f)} + c_4\alpha\mu_f e^{-u(\nu+\mu_f)} - \lambda_f\alpha e^{-u\mu_f}\Big)\Big)du$$

$$Y_f^{(1)}(t) = e^{-(\alpha+\mu_f)t}\int_0^t 8c_3\mu_m\Big(-c_2\mu_f\nu e^{-u\mu_m} + c_2\alpha\mu_f e^{-u\mu_m} - \lambda_f\alpha e^{-u\mu_m} + \lambda_f\nu e^{-u\mu_m} + \lambda_f\alpha e^{-u(\mu_m-\mu_f)} - \lambda_f\nu e^{-u(\mu_m-\mu_f)}\Big) \Big/ \Big(\mu_f\Big(-c_5\mu_m\nu e^{-u(\nu+\mu_m)} + \lambda_m\alpha + c_1\alpha\mu_m e^{-u\mu_m} + \lambda_m\nu e^{-u\mu_m} - c_1\nu\mu_m e^{-u\mu_m} - \lambda_m\nu + c_5\alpha\mu_m e^{-u(\nu+\mu_m)} - c_3\nu\mu_m e^{-u(\alpha+\mu_m)} + c_3\alpha\mu_m e^{-u(\nu+\mu_m)} - \lambda_m\alpha e^{-u\mu_m}\Big)\Big)du$$

$$A_m^{(1)}(t) = e^{-(\nu+\mu_m)t}\int_0^t \alpha Y_m^{(1)}(u)e^{u(\nu+\mu_m)}du$$

$$A_f^{(1)}(t) = e^{-(\nu+\mu_f)t}\int_0^t \alpha Y_f^{(1)}(u)e^{u(\nu+\mu_f)}du$$

However, except for the latter two, these integrals are not easily solved analytically and so we proceeded to obtain numerical estimates of the coefficients $X_m^{(1)}(t), X_f^{(1)},(t)Y_m^{(1)}(t), Y_f^{(1)}(t), A_m^{(1)}(t)$, and, $A_f^{(1)}(t)$ of ε by substituting the exact expressions for the zero order solutions $X_m^{(0)}, X_f^{(0)}, Y_m^{(0)}, Y_f^{(0)}, A_m^{(0)}$ and,

$A_f^{(0)}$ in equation (5 30) We thus make use of asymptotically assisted numerics by using the information obtained analytically to reduce the amount of computation required in the numerical method

The parameter set discussed in Chapter 3 and described for our specific problem in Chapter 6, with the exception of the initial conditions, is used to obtain the first order numerical solutions A starting year of 1990 is used, as the heterosexual epidemic had started in Dublin by this time Initially, 2 males and 59 females are assumed to be infected, and 0 males and 5 females are assumed to be AIDS cases These figures are obtained from the results of a full numerical solution to a system of equations describing the transmission of HIV from IVDUs to non-IVDUs (for details see Chapter 6)

When the zero order analytical solutions plus the first order numerical solutions are plotted against time, the results approximate the full numerical solutions to the system (which are obtained using the *Mathematica* computer system, see Appendix II), very well, (i e error between 0 8% and 10%),

The second and third order combined perturbation and numerical solutions may then be obtained recursively in order to improve the accuracy The second order expansion, $X_m^{(2)}(t)$, of equation (5 29) is then

$$X_m^{(2)}(t) = \Big( -\Big( \mu_m X_m^{(2)} \big(A_f^{(0)}\big)^2 \Big) - 2\mu_m X_m^{(2)} X_f^{(0)} A_f^{(0)} - \mu_m X_m^{(2)} \big(X_f^{(0)}\big)^2 + A_f^1 X_m^0 Y_f^0 - A_f^0 X_m^1 Y_f^0 - 2\mu_m X_m^{(2)} Y_f^{(0)} A_f^{(0)} - X_m^1 X_f^0 Y_f^0 - 2\mu_m X_m^{(2)} X_f^{(0)} Y_f^{(0)} + X_m^0 X_f^1 Y_f^0 - X_m^1 \big(Y_f^0\big)^2 - \mu_m X_m^{(2)} \big(Y_f^{(0)}\big)^2 - A_f^0 X_m^0 Y_f^1 - X_m^0 X_f^0 Y_f^1 \Big) \Big/ \big( X_f^{(0)} + Y_f^{(0)} + A_f^{(0)} \big)^2 \qquad (5\ 31)$$

with corresponding expressions for

$$X_f^{(2)}(t), Y_m^{(2)}(t), Y_f^{(2)}(t), A_m^{(2)}(t), and, A_f^{(2)}(t)$$

We again adopted the same procedure of substituting the zero order solutions

$$X_m^{(0)}, X_f^{(0)}, Y_m^{(0)}, Y_f^{(0)}, A_m^{(0)} and, A_f^{(0)}$$

and the numerical estimates of the first order solutions

$$X_m^{(1)}, X_f^{(1)}, Y_m^{(1)}, Y_f^{(1)}, A_m^{(1)} and, A_f^{(1)}$$

into equation (5 31) to obtain numerical estimates of the coefficients

$$X_m^{(2)}(t)X_f^{(2)}(t),Y_m^{(2)}(t),Y_f^{(2)}(t),A_m^{(2)}(t),and,A_f^{(2)}(t) \text{ of } \varepsilon^2$$

These increased the accuracy of the perturbation estimate when compared to the full numerical solutions (i e error between 0 2% and 4%, see Figures 5 1 - 5 4) The female estimates are more accurate than those describing the transmission for males

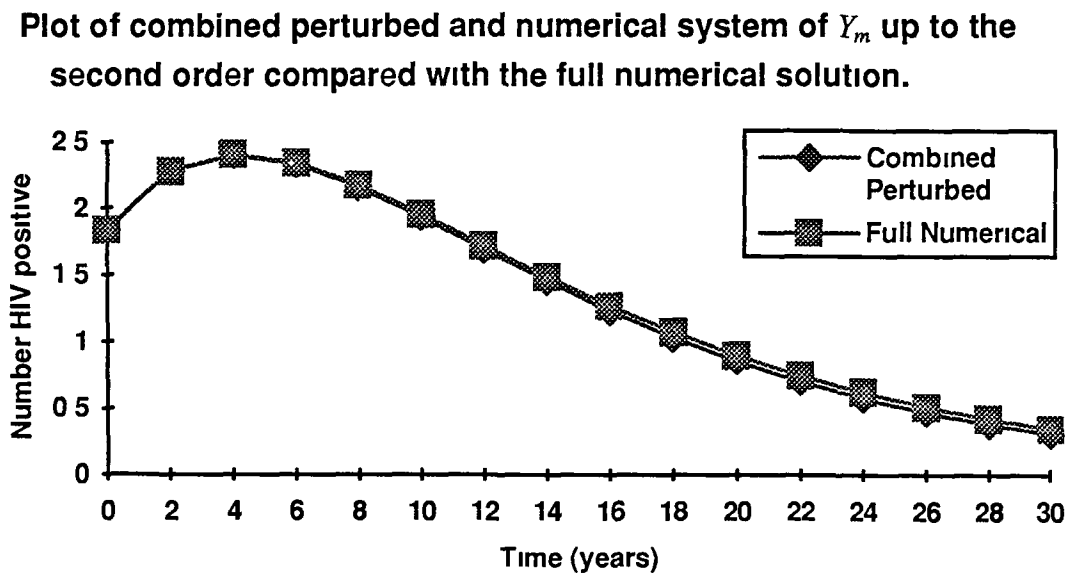



*Figure 5 1 Plot of combined perturbed and numerical system of $Y_m$ up to the second order compared with the full numerical solution*

**Plot of combined perturbed and numerical system of $Y_f$ up to the second order compared with the full numerical solution.**

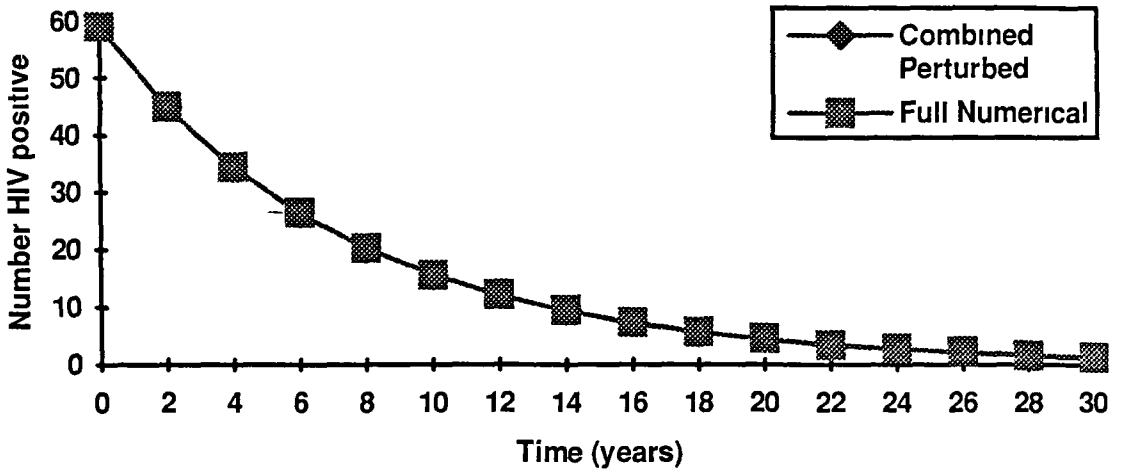



*Figure 5 2 Plot of combined perturbed and numerical system of $Y_f$ up to the second order compared with the full numerical solution*

**Plot of combined perturbed and numerical system of $A_m$ up to the second order compared with the full numerical solution.**

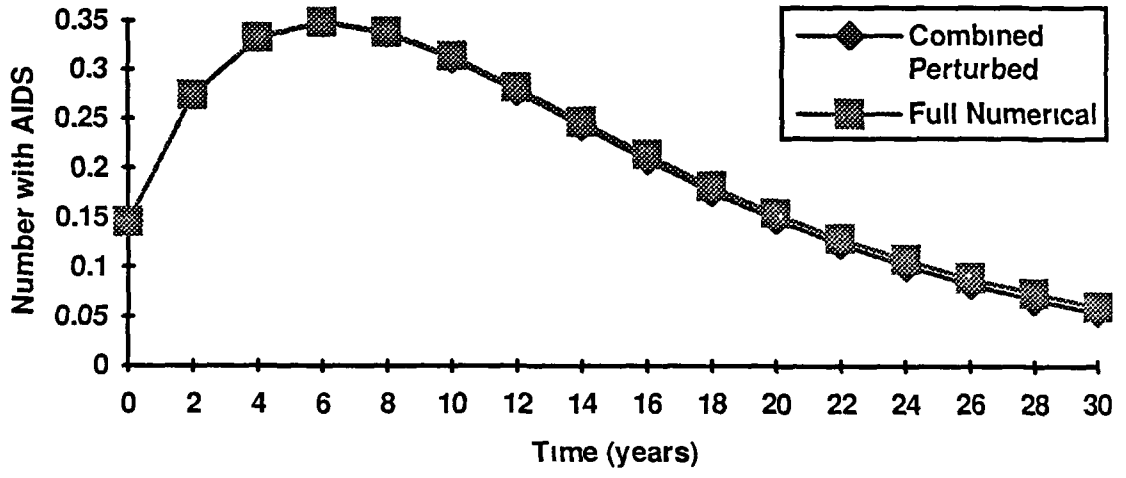



*Figure 5 3 Plot of combined perturbed and numerical system of $A_m$ up to the second order compared with the full numerical solution*

**Plot of combined perturbed and numerical system of $A_f$ up to the second order compared with the full numerical solution.**

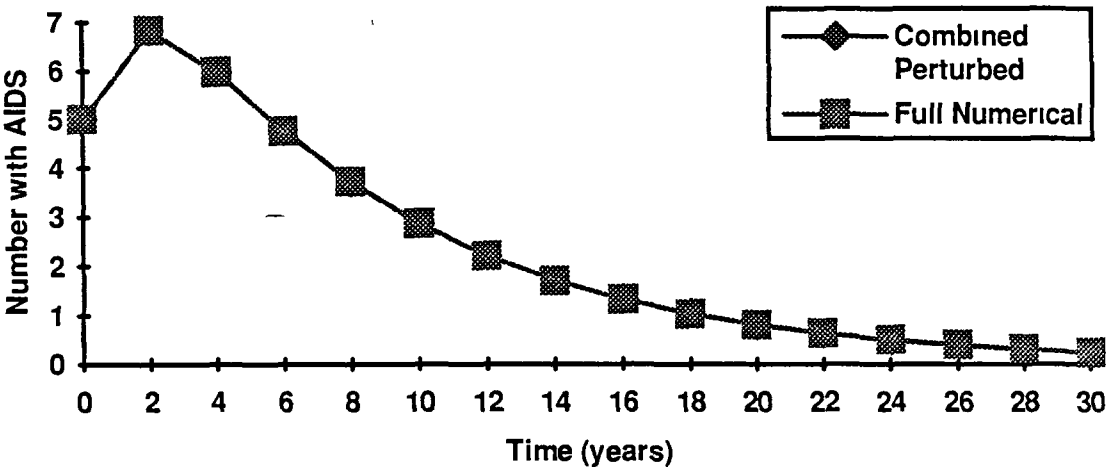



*Figure 5 4 Plot of combined perturbed and numerical system of $A_f$ up to the second order compared with the full numerical solution*

## 5.3 Sensitivity analysis varying ε

We now look at the situation where the value of ε is larger than the 0 0104 which is initially attributed to it Putting ε equal to 0 05 results in the approximate solutions diverging quite rapidly from the full numerical solutions to the system, for periods of over 5 years for $Y_m, Y_f, A_m, and, A_f$

However when ε was set to 0 03 the two solutions approximated each other reasonably well

## 5.4 Another approximate analytic approach

In this approach we take $N_m$ and $N_f$ to be straight lines An examination of census data shows that the increase in the sexually active population in Dublin over a 20 year period is linear Thus $N_m$ and $N_f$, the populations of sexually active males and females, are linear functions of time and may be expressed as lines such that

$$N_m = \phi_m + m_m t \qquad \text{and}$$

$$N_f = \phi_f + m_f t$$

where $\phi_f$ and $\phi_f$ are the initial number of sexually active females and males in the population and $m_m t$ and $m_f t$ are the respective rates of growth of sexually active males and females

Taking $N_m$ and $N_f$ as linear functions means that we are now dividing by a linear function of t as opposed to a constant in (5 29)

Using the perturbation method described above, and expressing $N_m$ and $N_f$ in terms of lines gives us the following equation in place of (5 30) above

$$X_m^{(1)}(t) = \left(-\left(\phi_f \mu_m X_m^{(1)}\right) - m_f \mu_m t X_m^{(1)} - X_m^{(0)} Y_f^{(0)}\right) \Big/ \left(\phi_f + m_f t\right) \qquad (5\ 32)$$

We similarly expand in each of the other equations to obtain equations for $X_f^{(1)}(t), Y_m^{(1)}(t), Y_f^{(1)}(t), A_m^{(1)}(t) and, A_f^{(1)}(t)$ Taking $N_m$ and $N_f$ as linear functions enables us to expand and obtain numerical solutions more easily for higher orders

## 5.5 Conclusions

With perturbation methods one always hopes that a very few terms of the expansion will be needed to describe the solution of a given problem with all necessary accuracy In the situation described here this was certainly the case when the series was expanded to the 2rd order

There is overall agreement between the full numerical method of solving the system and the perturbation method once $\varepsilon$ is smaller than 0 03 However if the model were to include IVDUs then $\varepsilon$ would be in the region of 1 19, because of the higher probability of transmission through needle sharing and because of the greater number of needle sharing partners In this case $\varepsilon$ is larger than 1 and so perturbation methods are out of the question

To conclude perturbation methods may be a useful way to model the transmission of HIV but only for a heterosexual population which does not mix sexually with IVDUs or homo/bisexuals, having on average less than 5 and 3 (for males and females respectively) sexual partners per year, and a fairly high rate of condom usage

# Chapter 6

# Data Based Mathematical Models to Assess the Epidemiological Consequences of Heterosexual and IVDU HIV Transmission.

## 6.1 Introduction

This chapter presents a simple two-population epidemic model for the spread of HIV, makes allowances for the special problem of heterosexual transmission in which female-to-male transmission may be less efficient than male-to-female transmission, and models the interaction of two populations, one of which becomes infected much more rapidly than the other The model is used to provide qualitative insights into HIV epidemiology in Dublin and to clarify the relationship between heterosexual and IVDU transmission

We have developed a model for the transmission and spread of HIV that incorporates many of the factors described in chapter 2 Our model allows two modes by which susceptibles may become infected through heterosexual contact or by the sharing of needles by IVDUs Perinatal transmission and transmission via blood products are not represented in the model, nor is homosexual transmission

In general, sets of non-linear differential equations such as those used in our model do not admit of explicit analytical solutions But for practical purposes we can use computerised forms of numerical integration to make the required time-projections into the medium-term future, (i e up to the year 2010)

### 6.1.1 Simplifying assumptions adopted:

It is assumed that the population mixes homogeneously within groups, that all infected individuals are equally infectious and that there is a constant level of infectiousness The model does not allow for variation in the rate of progression from HIV seropositive to AIDS (i e all infected individuals move out of the infectious class at the same rate) The assumption that, on average,

there is a roughly constant level of infectiousness over the entire duration of the average incubation period of AIDS is not too unreasonable for population based studies (Anderson & May, 1991) We assume too that approximately all infected individuals eventually develop AIDS This latter assumption is suggested by an increasing amount of evidence (Anderson & May, 1991) We further assume that those in the AIDS class do not contribute to the spread of the disease, that death from AIDS only occurs after an individual has passed into the AIDS (removed) class, and that deaths from causes other than AIDS can be neglected in the age-groups, and on the time-scales, of interest for the epidemic

In order to obtain a working model we have chosen to ignore several factors that we know are important, especially age structure, and geographic location (see Chapter 1) Initially we also ignore changes in behaviour, but introduce them to the model at a specific point in time No explicit allowance is made for heterogeneity of sexual/drug activity within each population subgroup considered, with the exception of the parameter for sexual partnership with IVDUs and non-IVDUs No specific allowance is made for prostitution, in particular among the IV drug using population

No allowance is made for the possible lengthening over time of the survival times of AIDS patients due to improvements in medical care This can be justified to a large extent since the survival parameter is taken from a study of patients who were only diagnosed with AIDS after 1986

Hence, we wish to stress that the qualitative insights which the sensitivity analysis produces are of much greater significance than any of the specific numerical values that are predicted for the future number of AIDS cases

### 6.1.2 The basic model

Consider a constant population of heterosexuals divided into 4 subgroups on the basis of gender and use or non-use of IV drugs The proportion of new recruits allocated to each subgroup is held constant over time and deaths can only occur from AIDS related diseases Each subgroup is divided into three types of classes that reflect the disease status of the persons in the group These classes are susceptibles, those who are at risk of acquiring the disease, infectives, those who are able to transmit the disease to a susceptible person, and AIDS or removed, those who do not take part in the transmission of the disease

Transmission of the disease may occur whenever a susceptible person engages in sexual or needle sharing activity with an infective individual, who

may be a member of any of the sub-groups It is therefore necessary to include a mechanism which allows for contact between individuals from different subgroups We have modelled the inter-group sexual mixing by means of a contact matrix $S$ with elements $s_{ij}$ which give the probability that an individual from subgroup $i$ comes into contact with an individual from subgroup $j$ (see Table 6 4 The IVDU group has a distinct set of parameters relating to sexual contact but is further distinguished by being subject to HIV through the sharing of needles used for drug injections The inter-group needle sharing activity is modelled by means of a contact matrix $N$ with elements $\eta_{ij}$ which give the probability that an individual from subgroup $i$ comes into needle sharing contact with an individual from subgroup $j$ (see Table 6 6)

The numbers of susceptibles, infectives and AIDS cases at time $t$ are denoted by $X_i(t), Y_i(t)$, and $A_i(t)$ The subscript $i$ ($i = 1, 2, 3$, and 4) denotes the four different subgroups within the population male and female drug users and male and female non-drug users respectively The model consists of a set of coupled ordinary differential equations, based on the model of Comiskey (1992), (see equations (2 17) - (2 19) in chapter 2) Our model however includes the effect of migration (due mainly to emigration), and is further distinguished in that it does not subtract migration due to cessation of sexual/needle sharing activities from the third equation This is because we want the total number of AIDS cases each year, including those who have ceased to use drugs or to be sexually active The model has the following structure

$$\frac{dX_i(t)}{dt} = \lambda_i - \sum_{j=1}^{4} \frac{\beta_{ij} s_{ij} X_i(t) Y_j(t)}{P_j(t)} - \sum_{j=1,2} \frac{\beta_{ij} \eta_{ij} X_i(t) Y_j(t)}{P_j(t)} - (\mu_i + \gamma) X_i(t) \qquad (6\ 1)$$

$$\frac{dY_i(t)}{dt} = \sum_{j=1}^{4} \frac{\beta_{ij} s_{ij} X_i(t) Y_j(t)}{P_j(t)} + \sum_{j=1,2} \frac{\beta_{ij} \eta_{ij} X_i(t) Y_j(t)}{P_j(t)} - (\alpha + \mu_i + \gamma) Y_i(t) \qquad (6\ 2)$$

$$\frac{dA_i(t)}{dt} = \alpha Y_i(t) - (\gamma_i + \nu) A_i(t) \qquad (6\ 3)$$

where $X_i(t) + Y_i(t) + A_i(t) = P_i(t)$, $\lambda_i$ are the recruitment parameters to the female and male IVDU and non-IVDU population, the mean incubation period is $1/\alpha$, and the rate of deaths due to AIDS is $1/\upsilon$ Both $1/\alpha$ and $1/\upsilon$ are assumed to be the same for all individuals The average annual rate of estimated net migration (due mainly to emigration) from the population, $1/\gamma$, is assumed to be

the same for all subgroups The rates of migration from population $i$ due to cessation of sexual activities, $1/\mu_3$ and $1/\mu_4$, are assumed to be the same for female and male non-IVDUs, and the rates due to cessation of drug using activities $1/\mu_1$ and $1/\mu_2$, are also assumed to be the same for IVDU females and males The model does not take account of those IVDUs who cease using intravenous drugs but who do not cease to be sexually active, since the proportion of susceptibles that they contribute to the non-IVDU population is negligible (in the region of 0 0029) The sexual transmission coefficients $\beta_{ij}$ for spread of infection from female to male and from male to female are also assumed to be different May and Anderson, (1987), suggest that $\beta_f < \beta_m < \beta$,, where $\beta$ is the corresponding coefficient for homosexual males Similarly, the rates for sexual partner change $s_{ij}$ of females and males are probably not the same, and are likely to be substantially smaller than the male homosexual rate $\hat{\beta}_{ij}$, the probability of transmission during a single needle sharing act from an infectious in group $j$ to a susceptible in group $i$ is assumed to be the same for females and males

## 6.2 Initial choice of parameter values

Initial values are allocated to each of the parameters as detailed below in Tables 6 1 - 6 5 Plausible ranges for parameter values are fully explored in Chapter 3 The parameter value relating to the incubation period, in the projection, is that recommended by the UN/WHO modelling workshop (United Nations and World Health Organisation, 1989) and was used in the model developed by Bulatao (1991) for the World Bank

A starting year of 1982 gave the best match to the official Department of Health data The epidemic is assumed to have been seeded by a single infective male IVDU with all other individuals uninfected

### 6.2.1 Initial population

The transmission of the AIDS virus from IVDUs to non-IVDU heterosexuals, is modelled within the Dublin population of those aged 15 to 45 years, since the vast majority of IVDU are within this age range Census data for 1981 give the population for Dublin in the age range 15-45 years as 460,243 We use this figure as the base figure for the number of sexually active individuals in Dublin, in the population under consideration, (including IVDUs who share needles) This is based on the findings of Lansdowne

Market Research (1992), who found that the average age of first sexual intercourse for all those aged 18-24 was 17 years (see Table 3 1) Also, in our HIV Transmission Survey (1994), we found the average age of sexual intercourse for IVDUs to be 15 years (see Appendix) However, this figure includes persons who are exclusively homosexual, and those who are celibate, or in closed partnerships over the course of the epidemic The overall population figure here is reduced by an arbitrary 7% to 428,026, to account in part for these factors in line with the model described by Williams and Anderson, (1994), where an arbitrary 2% was subtracted to account for the above factors excluding male homosexuals, whom they incorporated into their model. The balance of 5% is based on a conservative estimate of homosexual prevalence in a typical Western European capital city (see Johnson A M et al , 1992, Bajos N et al , 1991, Rogers S M & Turner C F , 1991, and Sundet J M et al , 1988)

The estimate of the number of IVDUs (4,000), is based on the estimate of the Irish national AIDS program (Mann et al , 1992) According to O'Hare and O'Brien (1993), an estimated 2006 persons received treatment for drug misuse in 1991 Our figure of 4000 suggests that one in two (50%) IVDUs are in treatment, which is a very high proportion of IVDUs in treatment if it is compared with the 14% estimated by Frischer (1992), (see Chapter 3 section 3 2 1)

We assume initially that 95% of IVDUs share injecting equipment based on the findings of numerous studies such as that of Pomeroy et al , (1991), where 97% of the study group had shared needles prior to the advent of HIV (see Chapter 3, section 3 3 2 1) In addition a study by McKeown et al , (1993) found that there was no difference in sharing between females and males The female male ratio (1 3) of IVDUs, is estimated on the basis of the findings from the Dublin Drug Treatment Reporting System for 1991 (O'Hare and O'Brien, 1993), (see chapter 3 section 3 2 1)

The figure for female non-IVDUs, 218,663, is the residue after deducting the estimates for female IVDUs The figure for male non-IVDUs is similarly obtained Table 6 1 provides details and Chapter 3 considers parameter estimation in more detail

The parameter value $1/\gamma$ given for migration from the population (due mainly to emigration), is taken from the Census data for 1991

### 6.2.2 Rates of joining and leaving the non-IVDU population

Numbers of females and males becoming sexually active each year were estimated to be the same as the number of females and males of 15 years of age in the Dublin population (1981 census), minus the numbers entering the IVDU population The rate of leaving the non-IVDU heterosexual population 1/30 is set to correspond to the 15-45 years age range (see Table 6 1)

### 6.2.3 Rates of joining and leaving IVDU population

The rates of recruitment are estimated on the basis of the findings of the 1990 and 1991 Health Research Board (HRB) reports on treated drug misuse in the Dublin area (O'Hare and O'Brien, 1992, 1993) The reports detail information on first treatment contact and estimate treated incidence relating to those clients who received treatment for the first ever time during 1990 and 1991 We conservatively assume that the number joining the IVDU population is comparable to twice (see section 6 2 1) the number seeking treatment for the first time in any year, although obviously the subjects joining the population of IVDUs are unlikely to be the same subjects as those seeking treatment for the first time, i e a simple multiple of a constant rate throughput

The HRB found that 574 drug users entered treatment for the first time in 1990, of whom 59% had been IVDU at some time In 1991 the corresponding figures were 450 drug users of whom 42% had injected at some time We combine the figures to get an average number of IVDUs seeking treatment for the first time over the two year period

New recruits are then split between groups in the same proportions as in the original population throughout the simulations The resulting estimated figures for female and male recruits each year are 132 and 396 respectively

The rate of leaving the IVDU population is based on our survey of HIV transmission (see Appendix Table A 2) and is similar for females and males The mean number of years injecting for IVDUs was found to be 6 5 years This is similar to that (6 3 years) found by Richardson et al , (1993), (see section 3 2 1) The reciprocal of the mean is used as an estimate of the migration rate out of the female and male IVDU populations (see Table 6 1)

**Table 6.1 Demographic parameters employed in the numerical simulations**

| Group | Dublin Pop Split | Recruitment ($\lambda_i$) | Migration from population ($\mu_i$) |
|---|---|---|---|
| 1 Male IVDU | 3000 | 396 | 0 15 |
| 2 Female IVDU | 1000 | 132 | 0 15 |
| 3 Male non-IVDU | 205363 | 9577 | 0 033 |
| 4 Female non-IVDU | 218663 | 9568 | 0 033 |
| Initial population | 428026 | | |
| Migration (due mainly to emigration) | | | 0 007 ($1/\gamma$) |

### 6.2.4 Incubation period of Acquired Immune Deficiency Syndrome

Variation in the incubation period of AIDS which is measured as the time from infection to diagnosis of AIDS is discussed in Chapter 2 Here an overall median of 10 years is used as recommended by the UN/WHO modelling workshop (United Nations and World Health Organisation, 1989, and Bulatao, 1991) The corresponding incubation rate is therefore 0 1 per year (see Table 6 2)

### 6.2.5 AIDS-related mortality

AIDS-related mortality (which measures the time from diagnosis of AIDS to death) has been set to give a median life expectancy of 1 58 years in line with the Survival Analysis described in Chapter 3 Individuals who have developed AIDS are assumed to be no longer IVDU or sexually active, so the AIDS mortality used in the model does not directly affect the effective size of the infectious population

### 6.2.6 Sexual and needle sharing transmission probabilities

#### Sexual transmission risk

The estimation of transmission risks is subject to much uncertainty A wide range of estimates have been quoted (see Chapter 3) The mean probability of sexual transmission per partnership suggested by Anderson et al , (1992) ranged from 0 09 to 0 2 The mid-point of this range is 0 145

However the Durex survey (LRC, 1993) found that 28% of their respondents (see Chapter 3) used condoms as their main method of contraception They further found that 46% of Dublin respondents used condoms as a birth control method in the previous year The midpoint figure of 0 145 is therefore reduced by 46% and the resultant figure of 0 0783 is used as the probability of sexual transmission from male non-IVDUs to female non-IVDUs Studies involving IVDUs report the average use of condoms to be 30% (see Chapter 3) The midpoint figure of 0 145 therefore, is reduced by 30% to get the probability of sexual transmission from males to females for partnerships involving IVDUs (see Table 6 2)

The figure for the probability of sexual transmission from females to males is based on the 1% found by Padian et al , (1991) Padian's figure is also reduced by 46% and 30% to allow for condom use by non-IVDUs and IVDUs respectively

**Needle-sharing transmission risk**

The parameter for the probability of transmission through needle sharing *per partner* is set at 0 2, a more conservative figure than the 0 25 given by Williams and Anderson (1994), but in line with that used by Comiskey, (1991), in her model for the transmission of HIV in Ireland A 5% reduction in this parameter allows for those IVDUs who do not share needles Table 6 2 provides details

**Table 6.2 Epidemiological parameters used in the numerical simulations**

| | |
|---|---|
| Mortality due to AIDS per year (v) | 1/1 58 |
| *HIV incubation rates per year* ($\alpha$) | 1/10 |
| ***Transmission probability for type of contact per new partnership*** | |
| **Heterosexual** | |
| median IVDU-female to male ($\beta_{12}, \beta_{14}, \beta_{32}$) | 0 007 |
| median non-IVDU-female to non-IVDU-male($\beta_{34}$) | 0 0054 |
| median IVDU-male to female ($\beta_{21}, \beta_{23}, \beta_{41}$) | 0 1015 |
| median non-IVDU-male to non-IVDU-female($\beta_{43}$) | 0 0783 |
| **Needle sharing** | |
| $\hat{\beta}$ | 0 19 |

### 6.2.7 Rate of sexual partner change

Rates of changes of sexual partners of non IVDUs were calculated on the basis of the findings of the Durex Report (1993), (see section 3 3 3 2) The report found that the average number of sexual partners in the previous 12 months for those who were **married**, was 1 03 for female and 1 05 for male respondents The averages for **single** female and male respondents were 1 25 and 2 72 respectively The figures in Table 6 3 were calculated by applying these figures to the 1991 census data on the number of married and single females and males in the population

Rates for the IVDU population were found from the HIV Transmission Survey described in the Appendix (Dunne et al , 1995) The mean number of sexual partners for female and male IVDUs was 1 9 and 2 5 respectively (see Table 6 3)

**Table 6.3 Initial parameters relating to rates of change of sexual partners**

| Group | Rates (average number of new partners per year) |
|---|---|
| *Rate of sexual partner change (s)* | |
| Male IVDU | 2 48 |
| Female IVDU | 1 88 |
| Male non-IVDU | 1 93 |
| Female non-IVDU | 1 13 |

#### 6.2.7.1 Between-group mixing

The size of the bridge group, i e , that group of non-IVDUs who are in sexual partnerships with IVDUs, has only been crudely estimated This crude estimate is based on the results of the HIV transmission survey described in the appendix, which suggests that the size of the bridge group is approximately 67 per cent of the size of the IVDU community The sex ratio in the bridge community is female-biased because the sex ratio in the IVDU community is male-biased and hence male IVDUs are more likely than female IVDUs to have non-IVDU sex partners This likelihood is confirmed by our HIV transmission survey, (see Appendix, Dunne et al , 1995)

According to the results of the survey, the prevalence of sex with a non-IVDU was high in the group as a whole with 67% of subjects (n = 77; 2 missing

values), reporting at least one partner who was a non-IVDU However, this differed widely between the sexes Men were far more likely than women to have had a non-IVDU sexual partner in the previous year 77 9% of men (n = 67) compared to only 34 5% of women (n = 10) had a sexual partner who was a non-IVDU ($\chi^2$=18 5, df =1, p < 0 0001)

On the other hand women tended to have more drug using sexual partners than men 75% of women had at least one IVDU sexual partner in the previous year compared to 41% of men (p = 0 014, Fisher's exact test)

In our transmission model we denote the rate of sexual partner change that an individual in group $i$ has per unit time with a member of group $j$, by $s_{ij}$ For example $s_{12}$ is the average number of female IVDU partners a male IVDU has in unit time Dunne et al , (1995, see Appendix), found that female IVDU respondents had a mean of 0 59 non-IVDU sexual partners in the previous year Similarly the rate of sexual partner change for female IVDUs with male IVDUs is 1 29 The corresponding rates for male IVDUs were 1 76 for non-IVDU female sexual partnerships and 0 [illegible] for partnerships with IVDU females (see Table 6 4)

However estimating the parameter for the rate of sexual partner change of non-IVDU females and males with IVDU males and females proved to be more difficult We had no information on the extent to which non-IVDUs mixed sexually with IVDUs To estimate this parameter for non-IVDU females we calculate

$$s_{41} = f\frac{gh}{gh+ko}$$ where

f = mean number sexual partners of a non-IVDU female,

g = mean number of non-IVDU female partners which an IVDU male has,

h = proportion of the male population which is IVDU,

k = mean number of sexual partners of a non-IVDU male,

o = proportion of the male population which is non-IVDU

The corresponding parameter for non-IVDU males is similarly estimated The results are as follows

**Table 6.4 Matrix of mean number of sexual partners per year $s_{ij}$**

| | Male IVDU | Female IVDU | Male non-IVDU | Female non-IVDU |
|---|---|---|---|---|
| Male IVDU | 0 00 | 0 72 | 0 0 | 1 76 |
| Female IVDU | 1 29 | 0 00 | 0 59 | 0 00 |
| Male non-IVDU | 0 00 | 0 0046 | 0 00 | 1 9254 |
| Female non-IVDU | 0 0148 | 0 00 | 1 1152 | 0 00 |

### 6.2.8 Needle sharing partnership rates

As with the rates of change of sexual partners little data are available on which to base estimates of rates of change of needle sharing partners by IVDUs Comiskey et al , (1993) used a value of 6 94 as the yearly needle sharing parameter Needle sharing partnership rates used in this model are based on the HIV Transmission Survey described in the Appendix The mean number of needle sharing partners **per week** was found to be 2 24 (Std Dev =2 65) for females, and 3 14 (Std Dev = 8 11) for males The distribution was therefore very skewed and highly variable

The mean number of needle sharing partners of females and males (per week) is multiplied by a conservative factor of 2 to obtain the parameter for the average number of needle sharing partners **per year** (see Table 6 5)

**Table 6.5 Initial parameters relating to rates of change of needle sharing partners**

| Group | Rates (new partners per year) |
|---|---|
| *Needle sharing partnerships (n)* | |
| Male IVDU | 6 28 |
| Female IVDU | 4 48 |

## 6.3 The result of taking the chosen parameter values

Taking due note of the serious limitations in assigning fixed or exact parameter values based on variant populations, as described in section 6 2, we now consider what insights emerge from the numerical study of the model behaviour

### 6.3.1 AIDS cases

Ten years after the introduction of one infectious person (1992), and no change in sexual or needle sharing behaviour, 209 cases of AIDS are predicted, as shown in Figure 6 1 Table 6 6 provides details of the number of AIDS cases in each risk group

**Table 6.6 Predicted numbers with AIDS**

| | | | Heterosexual | |
|---|---|---|---|---|
| **Year** | **Male IVDU** | **Female IVDU** | **Male non-IVDU** | **Female non-IVDU** |
| 1982 | 0 | 0 | 0 | 0 |
| 1984 | 0 | 0 | 0 | 0 |
| 1986 | 2 | 0 | 0 | 0 |
| 1988 | 10 | 3 | 0 | 1 |
| 1990 | 49 | 14 | 0 | 7 |
| 1992 | 141 | 41 | 1 | 26 |
| 1994 | 219 | 67 | 2 | 64 |
| 1996 | 241 | 77 | 4 | 106 |
| 1998 | 236 | 76 | 7 | 144 |
| 2000 | 225 | 73 | 9 | 174 |
| 2002 | 217 | 70 | 11 | 197 |
| 2004 | 211 | 68 | 14 | 214 |
| 2006 | 207 | 67 | 15 | 227 |

The number of IVDUs with AIDS increases rapidly until 1996 and then begins to slowly decrease because of the fall in the size of the susceptible IVDU population This is due to the fact that 70% are already infected with HIV by 1996 The IVDU population is therefore quickly saturated with the infection However the number of non-IVDUs, particularly females, with AIDS continues to increase, although from the early 1990s the doubling time is reduced and the percentage increase in the number of AIDS cases falls each year (see Figure 6 1)

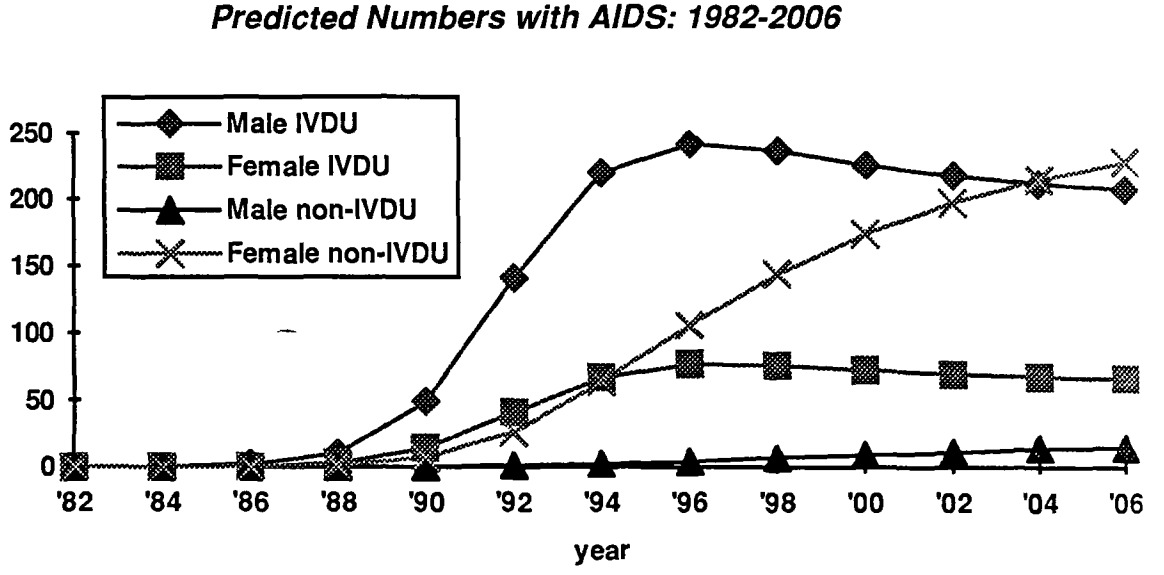



*Fig. 6 1* *Predicted Numbers with AIDS in the IVDU and non-IVDU subgroups (y= AIDS prevalence)*

### 6.3.2 HIV infection

Six years after the introduction of one infectious person (1988), and no change in sexual or needle sharing behaviour, already (approximately) 5 percent (42) of female and 6 percent (151) of male IVDUs are **infected** by the virus, as shown in Figure 6 2 After 10 years 50 per cent (423) of IVDU women and 56 percent (1408) of IVDU men are infected, whereas for the same period only 0 14 per cent (315) of the non-IVDU women and only 0 0045 percent (10) of the non-IVDU men are infected (see Table 6 7)

**Table 6.7 Predicted numbers infected with HIV**

| Year | Male IVDU | Female IVDU | Heterosexual Male non-IVDU | Heterosexual Female non-IVDU |
|---|---|---|---|---|
| 1982 | 1 | 0 | 0 | 0 |
| 1984 | 5 | 1 | 0 | 0 |
| 1986 | 27 | 7 | 0 | 3 |
| 1988 | 151 | 42 | 0 | 18 |
| 1990 | 646 | 183 | 3 | 94 |
| 1992 | 1408 | 423 | 10 | 315 |
| 1994 | 1637 | 519 | 23 | 620 |
| 1996 | 1560 | 505 | 39 | 888 |
| 1998 | 1461 | 474 | 55 | 1092 |
| 2000 | 1392 | 451 | 71 | 1244 |
| 2002 | 1350 | 436 | 85 | 1359 |
| 2004 | 1325 | 427 | 97 | 1446 |
| 2006 | 1310 | 422 | 108 | 1513 |

The number of IVDUs who are infected increases rapidly until 1994 and then begins to slowly decrease because of the decline in the size of the susceptible IVDU population The number of non-IVDUs who are infected increases at a slower pace, but continues to increase into the long-term future However from 1994 onwards the increase in the number of non-IVDUs who are infected becomes less and less rapid The female non-IVDU population is much more seriously affected than the corresponding male population (see Figure 6 2)

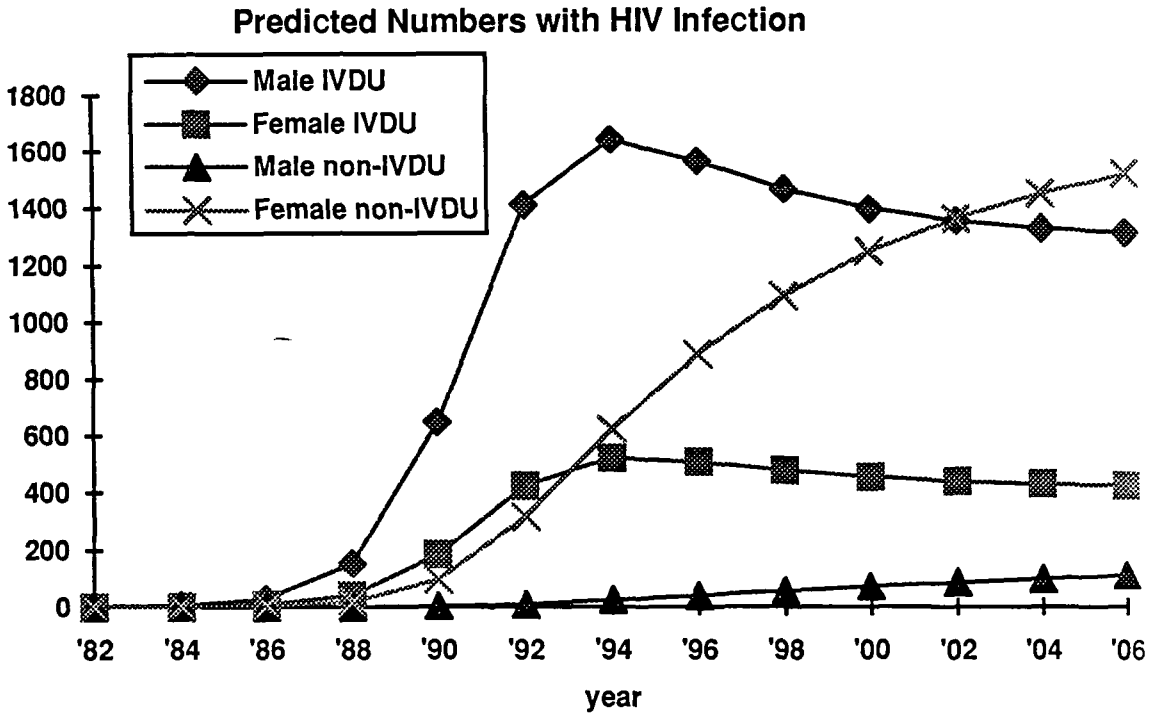



*Fig 6 2 Numbers infected with HIV in the IVDU and non-IVDU subgroups. (y = HIV prevalence)*

### 6.3.3 Comparison with actual data

To ensure that the parameter values for our model are reasonable, we compare the predictions they produce with surveillance data on the number of AIDS cases attributed to IVDU use or heterosexual activity The true number of cases of AIDS acquired through heterosexual contact is only crudely estimated by surveillance data, because of difficulties in documenting such transmission All AIDS patients who use IV drugs are considered to have acquired the disease parenterally (through the skin or intravenously), even though some of them may have had HIV-infected sexual partners Because of this the percentage of AIDS patients ascribed to heterosexual contact is most probably an underestimate

Two hundred and forty six cumulative adult AIDS cases (that are attributable to either IVDU or heterosexual transmission) were reported to the Department of Health by the end of December 1994 of whom 124 had died (see Tables 6 8 and 6 9) These actual numbers of reported cases minus those who had died, can be compared with the number of AIDS cases that are predicted by the model (see Table 6 6) When comparing the two sets of figures, it

should be remembered that the reported AIDS cases may reflect only a fraction of the true HIV morbidity and mortality in IVDUs, due to reporting delays and under-reporting errors The AIDS case definition was originally devised based upon AIDS cases in homosexual men It became apparent that IVDUs appear to present with a larger spectrum of HIV-related infections than other risk groups, and that therefore AIDS cases were being under-reported This was a major factor in the expansion of the AIDS case definition in 1987 It is evident, therefore, that the reported AIDS cases may be expected to be far fewer than the predicted cases due to under-reporting, especially in the years before 1988

The predicted figures can be compared with the official Department of Health data on both AIDS cases and HIV infection Tables 6 8, 6 9, and 6 10 provide details

**Table 6.8 Actual Department of Health AIDS cases**

| | | | Heterosexual | |
|---|---|---|---|---|
| **Year** | **IVDU** | **Cumulative** | **non-IVDU** | **Cumulative** |
| 1982 | 0 | 0 | 0 | 0 |
| 1984 | 2 | 2 | 0 | 0 |
| 1986 | 3 | 5 | 0 | 0 |
| 1988 | 21 | 26 | 2 | 2 |
| 1990 | 50 | 76 | 10 | 12 |
| 1992 | 58 | 134 | 18 | 30 |
| 1994 | 64 | 198 | 18 | 48 |

**Table 6.9 Actual Department of Health AIDS deaths**

| | | | Heterosexual | |
|---|---|---|---|---|
| **Year** | **IVDU** | **Cumulative** | **non-IVDU** | **Cumulative** |
| 1982 | 0 | 0 | 0 | 0 |
| 1984 | 2 | 2 | 0 | 0 |
| 1986 | 2 | 4 | 0 | 0 |
| 1988 | 7 | 11 | 1 | 1 |
| 1990 | 14 | 25 | 4 | 5 |
| 1992 | 30 | 55 | 10 | 15 |
| 1994 | 48 | 103 | 6 | 21 |

The figures in Tables 6 8-6 9 are national figures and not just figures for Dublin They possibly include non-IVDUs who may have been infected via homosexual or bisexual contact

**Table 6.10 Actual Department of Health cumulative HIV seropositive individuals**

| Year | Male IVDU | Female IVDU | Heterosexual Male & Female non-IVDU |
|---|---|---|---|
| 1986 | 258 | 78 | 0 |
| 1988 | 351 | 112 | 2 |
| 1990 | 430 | 140 | 91 |
| 1992 | 517 | 169 | 166 |
| 1994 | 573 | 185 | 209 |

The figures in Table 6 10 are the total number of individuals who tested seropositive to the virus (see Chapter 1) They therefore include results for the whole country and for those who may have developed AIDS or died since testing seropositive In addition these figures may include heterosexuals who may have been infected via homosexual or bisexual contact

Although the initial set of parameter values produce AIDS prevalence curves that are close to the observed data for 1982-1990, they differ widely in the number of cases projected for the year 1994 (compare Table 6 6 with Tables 6 8 and 6 9) The actual figures shown in Tables 6 8 and 6 9, are much less than the figures predicted by the model (see Table 6 6) The difference is too large to be explained by under-reporting It may be that the model may be too stringent in some areas, or alternatively, this difference may be due to intervention policies by Drug Treatment agencies The following section examines the scenario in which some intervention takes place

## 6.4 Behaviour change due to intervention policies

The number of IVDUs which the model predicts to be infected with the AIDS virus, by the end of 1989, is 422 The number of AIDS cases predicted

for that year is 29 These figures are similar to the actual number of seropositive individuals and cases recorded by the Department of Health for 1989 If, as the predicted figures and the actual figures suggest, the number of IVDUs who are infected is in the region of 420-520 in 1989, then the IVDU community must be aware, at this time, of the impact of AIDS.

The first needle exchange centre began operating in Baggot St in February 1989, and others have been established since then Needle exchange has been shown to reduce the level of sharing among IVDUs (see Chapter 3, section 3 3 2) If we therefore halve the probability of transmission through needle sharing from 1989 onwards, so that $\hat{\beta}$ = 0 095, the results are as follows (see Tables 6 11-6 12)

**Table 6.11 Predicted numbers with AIDS given intervention $\hat{\beta}$ = 0.095 from 1989 onwards**

| | | | Heterosexual | |
|---|---|---|---|---|
| Year | Male IVDU | Female IVDU | Male non-IVDU | Female non-IVDU |
| 1982 | 0 | 0 | 0 | 0 |
| 1984 | 0 | 0 | 0 | 0 |
| 1986 | 2 | 0 | 0 | 0 |
| 1988 | 10 | 3 | 0 | 1 |
| 1990 | 27 | 8 | 0 | 5 |
| 1992 | 48 | 15 | 0 | 12 |
| 1994 | 76 | 24 | 1 | 23 |
| 1996 | 107 | 34 | 2 | 39 |
| 1998 | 135 | 43 | 3 | 60 |
| 2000 | 154 | 49 | 4 | 82 |
| 2002 | 164 | 53 | 5 | 104 |
| 2004 | 168 | 54 | 7 | 124 |
| 2006 | 168 | 54 | 9 | 141 |
| 2008 | 166 | 54 | 10 | 155 |
| 2010 | 163 | 53 | 11 | 166 |

When the probability of transmission through needle sharing is reduced in this way, the peak in the number of AIDS cases occurs later than in the original

model (see Figure 6 3) In the model with intervention the number of AIDS cases peaks 23 years after the introduction of the infection, whereas the original model peaks after 14 years This is because of the slower increase in the number of those infected in the former model The adjusted model predicts that by the year 2010, 48 percent of IVDU women and 50 percent of IVDU men will be infected with the virus, and that 0 48 percent of non-IVDU women (n= 1108) and 0 035 percent of non-IVDU men (n = 80) will be infected

Figure 6 3 illustrates the predictions with respect to the model with intervention

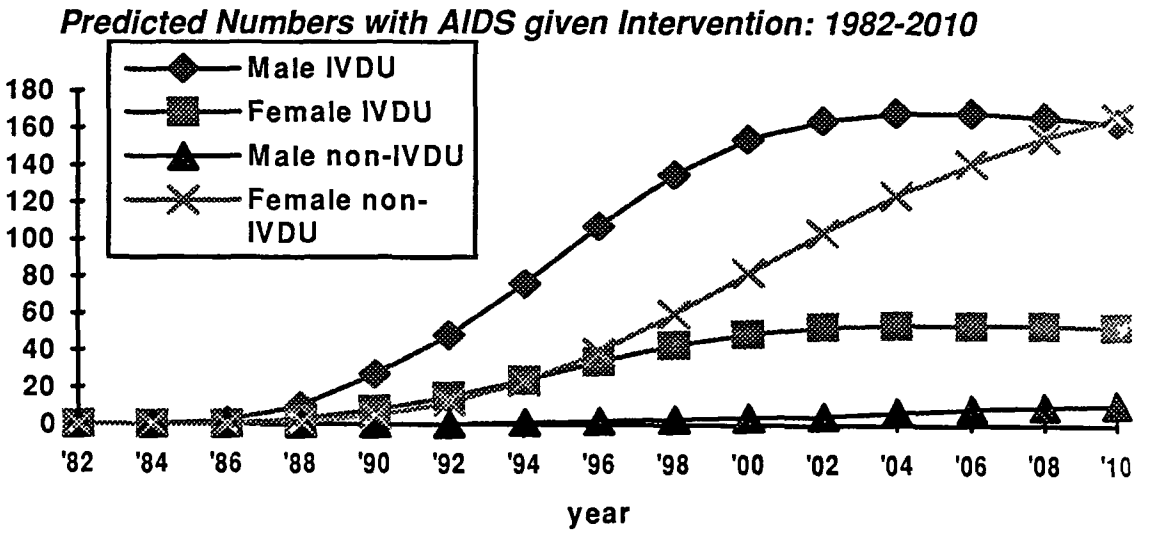



*Fig 6 3 Predicted Numbers with AIDS in the IVDU and non-IVDU subgroups given intervention (y= AIDS prevalence)*

The following table predicts the numbers of HIV infections up to the year 2010

**Table 6.12 Predicted numbers infected with HIV given intervention**

| Year | Male IVDU | Female IVDU | Heterosexual Male non-IVDU | Heterosexual Female non-IVDU |
|---|---|---|---|---|
| 1982 | 1 | 0 | 0 | 0 |
| 1984 | 5 | 1 | 0 | 0 |
| 1986 | 27 | 7 | 0 | 3 |
| 1988 | 151 | 42 | 0 | 18 |
| 1990 | 262 | 79 | 2 | 59 |
| 1992 | 429 | 133 | 4 | 123 |
| 1994 | 636 | 200 | 9 | 218 |
| 1996 | 836 | 265 | 15 | 345 |
| 1998 | 982 | 314 | 23 | 491 |
| 2000 | 1059 | 341 | 33 | 639 |
| 2002 | 1084 | 351 | 43 | 774 |
| 2004 | 1080 | 350 | 53 | 889 |
| 2006 | 1065 | 346 | 63 | 981 |
| 2008 | 1049 | 341 | 72 | 1053 |
| 2010 | 1035 | 336 | 80 | 1108 |

In the model with intervention the number of those infected with HIV also peaks later than in the original model (see Figure 6 4) The spread from the IVDU population to the non-IVDU population is first apparent four years after the introduction of the infection Non-IVDU females are infected four years before their male counterparts The number of non-IVDU females who are infected is consistently far greater than the number of non-IVDU males infected This *asymmetry* in the sex ratio of non-IVDU AIDS cases is due to the asymmetry in the heterosexual transmission efficiencies, the gender-specific differences in sexual behaviour and the asymmetnc sex ratio in the IVDU community, (the majority of IVDUs are males, consequently the majority of their sex partners are non-IVDU females)

A similar pattern is apparent in both the original and the intervention models regarding the lower percentage increase in the numbers of those infected and those with AIDS, from the early 1990s to the end of the projection period The adjusted model predicts 289 cases of AIDS, in the IVDU and

heterosexual population of Dublin, in the year 2000 It further predicts 364 cases in 2005 and 393 cases in 2010 Figure 6 4 illustrates the predictions

***Predicted Numbers with HIV-Infection given Intervention: 1982-2010***

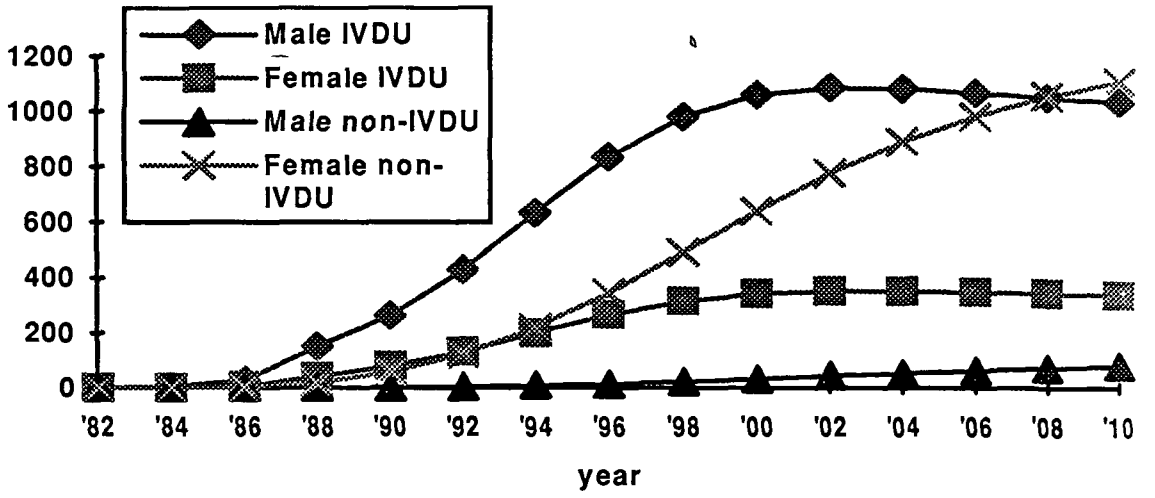



*Fig. 6.4 Predicted Numbers with HIV-infection in the IVDU and non-IVDU subgroups given intervention (y= HIV prevalence)*

### 6.4.1 Comparison of adjusted model with actual data

A good match to heterosexual and IVDU, AIDS prevalence data, was achieved ( compare Table 6 11 with 6 8 and 6 9) The figures which the adjusted model produce for the number of AIDS cases are similar to the actual number of AIDS cases published by the Department of Health In 1994 the model predicts 100 IVDU cases and 24 heterosexual cases of AIDS These figures compare favourably with those of the Department of Health which are 95 and 27 respectively when allowances are made for those who died from AIDS The differences could possibly be explained by reporting delays and under-reporting However, it should be noted that the heterosexual figure published by the Department of Health includes heterosexual cases from outside Dublin and possibly heterosexuals infected via relationships with Homo/bisexuals

## 6.5 Sensitivity of the model

Transmission models may be used to make quantitative predictions, for example, to estimate the future number of AIDS cases The precision of these predictions is often limited by the uncertainty in estimating both the sizes of the risk groups and the values of biological-behavioural transmission parameters (Blower et al , 1991, Anderson & May, 1988) Where epidemiological data are scarce and the transmission process is complex, mathematical models can be used to perform simulation studies with different parameter values A variety of outcomes are possible, depending on particular choices of critical parameters Therefore, transmission models can be analysed to assess the variability in the prediction estimates and to determine which parameters or assumptions are the most important in contributing to the imprecision in predictions In order to have confidence in the results of model projections, it is necessary to explore the effects of variation in parameters on the spread of the disease

The model (see equations 6 1-6 3) is used to predict the future number of AIDS cases in certain risk groups The sensitivity analysis involves the repeated evaluation of the previously described deterministic model, with key variable values changed in each of several runs The probable number of cumulative AIDS cases produced by the sensitivity analysis reflects the likely range of possible outcomes, rather than the absolute upper and lower bounds of the system The initial exploratory approach is to determine **which** parameters are **most** influential

In this case, the prediction variability is due to the uncertainty in estimating the values of the model's 35 different variables/parameters (23 biological-behavioural transmission parameters and the initial sizes of 4 subgroups as well as the recruitment and migration rates )

### 6.5.1 Range of parameter values chosen for the sensitivity analysis

To analyse the sensitivity of the model to the plausible ranges of parameters, we evaluated it at extremes of the range given, in particular for those parameters which had the highest degree of uncertainty We assume that the initial values chosen (see Tables 6 1 to 6 5), are at the lower end of the range (with the exception of the between-group sexual mixing parameter), and in the following section we evaluate the model at the maximum of the range Table 6 13 gives details of these parameter values

**Table 6.13 Parameters used in the sensitivity analysis (maximum of range)**

| | |
|---|---|
| ***HIV incubation rates per year*** | |
| $\alpha$ | 1/8 |
| ***Transmission probability for type of contact per new partnership*** | |
| **Heterosexual** | |
| median IVDU-female to male ($\beta_{12}, \beta_{14}, \beta_{32}$) | 0 084 |
| median non-IVDU-female to non-IVDU-male($\beta_{34}$) | 0 0624 |
| median IVDU-male to female ($\beta_{21}, \beta_{23}, \beta_{41}$) | 0 14 |
| median non-IVDU-male to non-IVDU-female($\beta_{43}$) | 0 104 |
| **Needle sharing** | |
| $\hat{\beta}$ | 0 2375 |
| ***Needle sharing partnerships per year*** | |
| Male IVDU | 9 42 |
| Female IVDU | 6 72 |

### 6.5.2 The results of the sensitivity analysis

This section examines the results of exploratory variations above and below our 'best' estimate values, as described above The adjusted parameter set is used as a basis for examining how sensitive the prediction curves produced by the model are, to modest changes in parameter values (Tables 6 14-6 18, 6 20-6 21, 6 23-6 24) Only the figures for AIDS cases are presented, since cases of AIDS are the only visible measurement of the epidemic which has some accuracy

#### 6.5.2.1 Varying the size of the initial population and the related recruitment rate

The first question which is addressed by the sensitivity analysis is the effect of varying the size of the initial IVDU population and the related recruitment rates

The number of IVDUs may be much greater than 4000 O'Kelly et al , (1990), estimated 7,000 IVDUs in Dublin, but for the sensitivity analysis we

choose a slightly more conservative figure of 6000, as the maximum in the range (which suggests that the percentage in treatment is 33%, see section 6 2 1),

The maximum number of IVDUs recruited each year is taken as three times the number entering treatment for the first time each year (see section 6 2 3) This is consistent with the factor of three times the number of IVDUs in treatment, which is allowed for in the initial population above)

The number of IVDUs recruited each year is therefore changed to 792 The female male ratio of 3 1 is maintained The resulting estimated figures for female and male IVDUs and IVDU recruits each year are 1500 and 4500, and 198 and 594 respectively The between-group mixing parameters are recalculated to allow for the larger size of the IVDU population The results are shown in Table 6 14

**Table 6.14 Predicted numbers with AIDS given intervention and larger IVDU population**

| Year | Male IVDU | Female IVDU | Male non-IVDU | Female non-IVDU |
|---|---|---|---|---|
| 1982 | 0 | 0 | 0 | 0 |
| 1984 | 0 | 0 | 0 | 0 |
| 1986 | 2 | 0 | 0 | 0 |
| 1988 | 10 | 3 | 0 | 1 |
| 1990 | 28 | 8 | 0 | 5 |
| 1992 | 52 | 16 | 0 | 13 |
| 1994 | 86 | 27 | 1 | 25 |
| 1996 | 130 | 41 | 2 | 45 |
| 1998 | 176 | 56 | 3 | 71 |
| 2000 | 214 | 68 | 5 | 103 |
| 2002 | 237 | 76 | 7 | 137 |
| 2004 | 249 | 80 | 9 | 169 |
| 2006 | 252 | 81 | 11 | 197 |
| 2008 | 250 | 81 | 14 | 220 |
| 2010 | 247 | 80 | 16 | 239 |

This scenario is similar to that described by Table 6 11 in that it also, generates considerably more AIDS cases in non-IVDU females than in non-IVDU males, which is to be expected given the gender ratio in the IVDU population and the differential in the probability of infection between females and males

However we can see that the numbers predicted by this simulation are greater than those predictions which are based on the smaller IVDU population, particularly from 1994 onwards (see Table 6 11) The overall number of AIDS cases produced here for the year 2010, is actually almost 49% greater than that presented in Table 6 11 The results (Table 6 14) confirm that the number AIDS cases is heavily dependent upon the size of the IVDU population

In this scenario, the total number of AIDS cases in 1994 is 139, a figure which is only 14% greater than the actual number of cases published by the Department of Health, for these risk groups (n=122) The difference of 17 cases could possibly be explained by reporting delays or under-reporting However it should be remembered that the official figures do not just relate to Dublin, although the IVDU population is confined to Dublin

#### 6.5.2.2 Varying the incubation period parameter

The sensitivity of the model to the length of the incubation period is analysed by taking a value of 0 125 for this parameter, which relates to an incubation period of 8 years This value is chosen to assess sensitivity based on results obtained in a recent study by Kelly, (1994) Table 6 15 is generated by the same set of values for the initial subgroup sizes and the biological-behavioural transmission parameters that were used to generate Table 6 11, with the exception of the parameter for the incubation period

**Table 6.15 Predicted numbers with AIDS given intervention and a shorter incubation period**

| Year | Male IVDU | Female IVDU | Male non-IVDU | Female non-IVDU |
|---|---|---|---|---|
| 1982 | 0 | 0 | 0 | 0 |
| 1984 | 0 | 0 | 0 | 0 |
| 1986 | 2 | 0 | 0 | 0 |
| 1988 | 11 | 3 | 0 | 1 |
| 1990 | 29 | 8 | 0 | 5 |
| 1992 | 49 | 15 | 0 | 12 |
| 1994 | 77 | 24 | 1 | 23 |
| 1996 | 109 | 34 | 2 | 38 |
| 1998 | 140 | 44 | 2 | 58 |
| 2000 | 163 | 52 | 4 | 79 |
| 2002 | 177 | 57 | 5 | 101 |
| 2004 | 183 | 59 | 7 | 121 |
| 2006 | 184 | 60 | 8 | 138 |
| 2008 | 183 | 59 | 9 | 152 |
| 2010 | 180 | 58 | 10 | 162 |

In this particular scenario, at the end of the projection period, less than 0 4% of non-IVDU women and 0 025% of non-IVDU men are infected

This set of parameter values produces AIDS projections that are close to the observed data for 1994 They are also very similar to those produced by the set of parameters described in section 6 4, in the number of cases projected for the period 1982 to 2010 (Table 6 11)

#### 6.5.2.3 Varying the transmission probabilities

**Needle sharing transmission**

To analyse the sensitivity of the model to the parameter for the probability of transmission through needle sharing, the upper bound of this probability is set at 0 2375 until 1989 and then halved This figure is 5% less than the 0 25, suggested by Williams and Anderson (1994), to allow for those IVDUs who do not share Table 6 16 provides details of the results

**Table 6.16 Predicted numbers with AIDS given intervention and needle sharing transmission probability = 0.2375**

| Year | Male IVDU | Female IVDU | Male non-IVDU | Female non-IVDU |
|---|---|---|---|---|
| 1982 | 0 | 0 | 0 | 0 |
| 1984 | 0 | 0 | 0 | 0 |
| 1986 | 4 | 1 | 0 | 0 |
| 1988 | 39 | 10 | 0 | 4 |
| 1990 | 105 | 31 | 0 | 19 |
| 1992 | 158 | 48 | 1 | 45 |
| 1994 | 189 | 59 | 3 | 76 |

It is obvious when comparing this table with Table 6 11, that the model is very sensitive to the parameter for the needle sharing transmission risk These figures do not compare favourably with the actual official statistics in that they over-predict the number of AIDS cases each year The above results suggest that either, a value of 0 2375 is too high for this particular parameter ($\hat{\beta}_{ij}$), or, that the value for the number of needle sharing partners ($n_{ij}$) is too high (see equations 6 1 to 6 3) However, considering the low number of needle sharing partners used it seems more likely that the transmission probability is too high

**Sexual transmission**

The sensitivity of the model to this parameter is measured by using the mean probability of sexual transmission per partnership (relating to an undifferentiated incubation period) found by the European Study Group, (1992) These figures, 0 12 and 0 2, for female-to-male and male-to-female transmission respectively, are reduced by 46% and 30% to allow for condom use, in the same way as in the original model (see Table 6 13) Table 6 17 gives details of the results

**Table 6.17 Predicted numbers with AIDS given intervention and changes in sexual transmission probabilities**

| Year | Male IVDU | Female IVDU | Male non-IVDU | Female non-IVDU |
|---|---|---|---|---|
| 1982 | 0 | 0 | 0 | 0 |
| 1984 | 0 | 0 | 0 | 0 |
| 1986 | 2 | 1 | 0 | 0 |
| 1988 | 13 | 3 | 0 | 2 |
| 1990 | 36 | 11 | 3 | 9 |
| 1992 | 66 | 20 | 8 | 23 |
| 1994 | 103 | 32 | 17 | 47 |

The above results are similar to the official figures for the years up to 1990, but are higher than the official statistics for the number of AIDS cases reported each year from 1990 to 1994 Again this indicates that either the greater values for this parameter ($\beta_y$) are too high, or, that the parameter for the number of sexual partners ($s_y$) is too high (see equations 6 1 to 6 3) However, considering the conservative number of sexual partners used by the model it seems that the former situation is more likely It should be noted that the model is less sensitive to the sexual transmission probability parameter than it is to the needle sharing transmission parameter (the needle sharing transmission parameter was only increased by a factor of 1 25, whereas the sexual transmission parameter was increased by a factor of 1 4 for male to female transmission and by a factor of 12 for female to male transmission

### 6.5.2.4 Varying the number of needle sharing and sexual partners

**Needle sharing partners**

To analyse the sensitivity of the model to the parameter which describes the number of needle sharing partners **per year**, a figure is used which is a conservative factor of 3 times the figure found by Dunne et al , (1995), for the mean number of needle sharing partners **per week** The number of partners is only increased until 1989 and then resumes the original, lower, value (as given in Table 6 5) The results are shown in Table 6 18

**Table 6.18 Predicted numbers with AIDS given intervention and needle sharing partnership rates = 6.7 and 9.4 (f and m)**

| Year | Male IVDU | Female IVDU | Male non-IVDU | Female non-IVDU |
|---|---|---|---|---|
| 1982 | 0 | 0 | 0 | 0 |
| 1984 | 1 | 0 | 0 | 0 |
| 1986 | 11 | 3 | 0 | 1 |
| 1988 | 107 | 30 | 0 | 11 |
| 1990 | 191 | 58 | 1 | 44 |
| 1992 | 202 | 64 | 3 | 80 |
| 1994 | 194 | 63 | 5 | 110 |

The model is very sensitive to changes in this parameter value Increasing the number of needle sharing partners by a factor of 1 5 for just the first 6 years, results in a doubling of the predictions shown in Table 6 11 for 1994 The figures shown above (Table 6 18) do not compare favourably with the official statistics for the number of AIDS cases for the years 1982 to 1994

**Sexual partners**

The sensitivity of the model to this parameter is examined by increasing the mean number of new partners per year (see Table 6 3) by 50% The same method as that used to produce Table 6 4 is used to estimate the between group mixing figures (see Table 6 19) Table 6 20 provides details of the results of such a scenario if the increase in the number of partners continues until 1994 Table 6 21 provides details of the results if the number of partners is only increased until 1989 and then resumes the original, lower, value (as given in Table 6 4)

**Table 6.19 Matrix of upper bound of the mean number of sexual partners per year $s_{ij}$**

| | Male IVDU | Female IVDU | Male non-IVDU | Female non-IVDU |
|---|---|---|---|---|
| Male IVDU | 0 00 | 1 08 | 0 0 | 2 64 |
| Female IVDU | 1 935 | 0 00 | 0 885 | 0 00 |
| Male non-IVDU | 0 00 | 0 007 | 0 00 | 2 888 |
| Female non-IVDU | 0 022 | 0 00 | 1 673 | 0 00 |

**Table 6.20 Predicted numbers with AIDS given intervention and a greater number of sexual partners for the total period**

| Year | Male IVDU | Female IVDU | Male non-IVDU | Female non-IVDU |
|---|---|---|---|---|
| 1982 | 0 | 0 | 0 | 0 |
| 1984 | 0 | 0 | 0 | 0 |
| 1986 | 2 | 0 | 0 | 0 |
| 1988 | 11 | 3 | 0 | 2 |
| 1990 | 30 | 9 | 0 | 8 |
| 1992 | 53 | 18 | 1 | 20 |
| 1994 | 84 | 28 | 2 | 39 |

This set of parameter values produces AIDS projections that are close to the observed data and the predicted figures (see Table 6 11) for the IVDU population for 1994 However they overestimate the number of AIDS cases in the non-IVDU heterosexual population

**Table 6.21 Predicted numbers with AIDS given intervention and a greater number of sexual partners until 1989**

| Year | Male IVDU | Female IVDU | Male non-IVDU | Female non-IVDU |
|---|---|---|---|---|
| 1984 | 0 | 0 | 0 | 0 |
| 1986 | 2 | 0 | 0 | 0 |
| 1988 | 11 | 3 | 0 | 2 |
| 1990 | 29 | 9 | 0 | 7 |
| 1992 | 52 | 16 | 0 | 14 |
| 1994 | 81 | 25 | 1 | 26 |
| 1996 | 112 | 35 | 2 | 43 |
| 1998 | 139 | 44 | 3 | 64 |
| 2000 | 157 | 50 | 4 | 86 |
| 2002 | 165 | 53 | 6 | 108 |
| 2004 | 168 | 54 | 7 | 128 |
| 2006 | 167 | 54 | 9 | 144 |
| 2008 | 165 | 54 | 10 | 157 |
| 2010 | 163 | 53 | 12 | 167 |

This set of parameter values produces AIDS projections that are close to the observed data for 1994 They are also very similar to those produced by the set of parameters described in section 6 4, in the number of cases projected for the period 1982 to 2010 (see Table 6 11)

### 6.5.2.5 Varying the between-group sexual mixing parameter

Dunne et al , (1995, see Appendix), found that female IVDU respondents had a mean of 0 59 non-IVDU sexual partners in the previous year and male IVDU respondents had a mean of 1 76 non-IVDU female sexual partnerships (see Table 6 4) To examine the sensitivity of the model to the between-group sexual mixing parameter the above means are halved for both females and males while retaining the mean rate of sexual partner change given in Table 6 3 (1 88 for female IVDUs and 2 48 for male IVDUs) The same method as that used to produce Table 6 4 is used to estimate the revised between group mixing figures for non-IVDU females and males (see Table 6 22) Table 6 23 shows the results of this change for the total period (1982-2010)

**Table 6.22 Matrix of varied mean number of sexual partners per year $s_{ij}$**

| | Male IVDU | Female IVDU | Male non-IVDU | Female non-IVDU |
|---|---|---|---|---|
| Male IVDU | 0 00 | 1 60 | 0 0 | 0 88 |
| Female IVDU | 1 585 | 0 00 | 0 295 | 0 00 |
| Male non-IVDU | 0 00 | 0 0023 | 0 00 | 1 9277 |
| Female non-IVDU | 0 0075 | 0 00 | 1 1225 | 0 00 |

**Table 6.23 Predicted numbers with AIDS given intervention and varied between-group sexual mixing**

| Year | Male IVDU | Female IVDU | Male non-IVDU | Female non-IVDU |
|---|---|---|---|---|
| 1982 | 0 | 0 | 0 | 0 |
| 1984 | 0 | 0 | 0 | 0 |
| 1986 | 2 | 0 | 0 | 0 |
| 1988 | 11 | 3 | 0 | 1 |
| 1990 | 29 | 9 | 0 | 3 |
| 1992 | 52 | 16 | 0 | 7 |
| 1994 | 81 | 26 | 0 | 13 |
| 1996 | 114 | 37 | 1 | 21 |
| 1998 | 141 | 46 | 1 | 32 |
| 2000 | 159 | 52 | 2 | 44 |
| 2002 | 168 | 55 | 3 | 56 |
| 2004 | 170 | 56 | 4 | 66 |
| 2006 | 169 | 56 | 5 | 74 |
| 2008 | 167 | 55 | 5 | 81 |
| 2010 | 164 | 54 | 6 | 86 |

This set of parameter values produces AIDS projections that are close to the observed data for 1994 The spread of the disease in the non-IVDU population is markedly affected by variation in the amount of contact among individuals from different sub populations According the these results, by the year 2010 only 95 non-IVDU heterosexuals have AIDS, a figure which is approximately half that found using the higher between-group sexual mixing parameter (see Table 6 11)

However such variation in this parameter does not affect the spread in the IVDU population up to the year 2010 The results of this particular scenario demonstrate the significance of the dynamic interaction of heterosexual and IVDU transmission

#### 6.5.2.6 Varying the initial number of infecteds

The epidemic may have been seeded by more than one infective and so the sensitivity of the model to the initial number of infecteds is analysed by

looking at the situation where this parameter is increased to 2 infecteds Table 6 24 gives the results of such a scenario

**Table 6.24 Predicted numbers with AIDS given intervention and initial number of infecteds = 2**

| Year | Male IVDU | Female IVDU | Male non-IVDU | Female non-IVDU |
|---|---|---|---|---|
| 1982 | 0 | 0 | 0 | 0 |
| 1984 | 1 | 0 | 0 | 0 |
| 1986 | 4 | 1 | 0 | 0 |
| 1988 | 19 | 5 | 0 | 2 |
| 1990 | 48 | 14 | 0 | 9 |
| 1992 | 79 | 24 | 1 | 21 |
| 1994 | 111 | 35 | 1 | 38 |

This set of parameter values produces AIDS projections that are an overestimate of the observed data and the predicted figures (see Table 6 11), particularly after 1990

### 6.5.3 Discussion of results of sensitivity analysis

It is apparent from the sensitivity analysis that the variability between realisations of the same epidemic model is in general high, and this has implications for prediction The 10 sets of parameter values described above (see Tables 6 1-6 2, 6 4-6 5, 6 13, 6 19 and 6 22) produce AIDS incidence curves that vary in their closeness to the observed data for 1982-1994 Often, even when particular sets of parameter values produce figures that are close to the observed data for 1982-1994, they differ widely in the number of cases projected for the year 2010 (e g compare Table 6 11 with Table 6 14 and Table 6 23) This is not altogether surprising since the longer the forecasting horizon, the more the errors are compounded

The model contains 35 variables, however only 14 (2 subgroup sizes, the initial number of infecteds and 11 biological-behavioural transmission parameters) were sampled For these 14 key parameters 2 alternative values were selected, for each of which the ratio of **female : male** non-IVDU cases is always at least 20 1 for the first 20 years However the relative efficiency of

transmission is 14 5 1 (male-to-female to female-to-male transmission) This may be explained by the differential in the number of sexual partners of females and males

#### 6.5.3.1 The qualitative relationship between the input and the output variables

The qualitative relationship is the same for nearly all the key variables, apart from the average incubation period, which is inversely proportional to the predicted number of AIDS cases This is because even though individuals remain infectious for a longer period and consequently can infect more individuals, the rate of progression to disease decreases Usually, a longer incubation period i e 10 years as opposed to 8 years results in a more drawn-out epidemic (a slower decline in cases following the peak in incidence) For all other key variables an increase in the input value leads to an increase in the future number of AIDS cases

#### 6.5.3.2 The few key parameters which are important in contributing to the prediction imprecision

The more sensitive the outcome of the model is to a particular parameter value or assumption, the more important it is to measure precisely the parameter value or to confirm the validity of the assumption However the sensitivity analysis revealed that not every variable is significant in contributing to the AIDS case prediction variability or error

The size of the IVDU population and the average incubation period parameter, have the most significant effect on the number of AIDS cases in the IVDU population in the year 2010 When the size of the IVDU population is increased by 50% there is a resultant increase of 51% in the total number of IVDU infections and AIDS cases in 2010 When the incubation period parameter is increased by 25% the total number of AIDS cases in the year 2010, in the IVDU population, increases by 10% However the figure for IVDUs who are **infected** in 2010 is decreased by 31%

The size of the IVDU population also affects the spread of AIDS in the non-IVDU population An increase of 50% in the IVDU population results in an increase of 44% in the number of non-IVDU AIDS cases in 2010

The increase of 25% in the incubation period parameter results in a decrease of 3% in the number of non-IVDU AIDS cases in 2010 and a decrease of 22% in the number of HIV infections in this group

When the parameter for probability of infection by needle sharing is increased by 25% it has little effect on the IVDU population, but results in a 27% increase in the number of AIDS cases in the non-IVDU population (HIV infections increased by 24%).

Similarly the increase in the parameter for the two heterosexual transmission efficiencies has little effect on the number of AIDS cases in the IVDU population. When this parameter is increased by 1100% for female-to-male transmission and by 40% for male-to-female transmission it produces a 242% increase in the number of AIDS cases in the non-IVDU population in the year 2010.

Increasing the parameter for the number of needle sharing partners by 50% results in a decrease of 3% in the number of IVDU HIV infections and AIDS cases. The result in the non-IVDU population is an increase of 16% in the number of AIDS cases, and an increase of 12% in the number of HIV infections.

The effect of increasing the parameter for the number of sexual partners by 50% for the first six years has little or no effect on either population. However if the increase is for the full projection period the non-IVDU population is affected to a far greater extent than is the IVDU population. In this case the number of AIDS cases in the non-IVDU population is increased by 61% in the year 2010, whereas the IVDU population figure is only increased by 2%.

When the between-group mixing parameter is decreased by 50% it has little or no effect on the number of IVDUs with AIDS in 2010, but it results in a decrease of 48% in the number of non-IVDUs with AIDS. Under conditions of highly assortative mixing the timing of the rise in heterosexual incidence depends on the level of seeding from the IVDU epidemic; as soon as the heterosexual epidemic begins to take off, especially in the female sub-population, the effect of changes in other groups is swamped by that of numbers of female heterosexual infecteds. These results show clearly the sensitivity of model outcomes to variation in the patterns of contact among individuals and the need for better data on such interactions to aid in understanding and predicting the spread of HIV (see Table 6.23).

The increase in the initial number of infecteds from 1 to 2 makes little difference to the number of IVDUs or non-IVDUs who are infected or who have AIDS in 2010.

The simulations suggest that the uncertainties in estimating the values of the biological-behavioural transmission parameters and the size of the IVDU population are critical in affecting the prediction imprecision of the future

number of non-IVDU heterosexual AIDS cases Five parameters in particular seem to be the most important in contributing to the prediction imprecision These are the size of the IVDU population, the two heterosexual transmission efficiencies, the rate of sexual partner change and the between-group mixing parameter The uncertainties in estimating the values of the remaining demographic, biological, and IVDU behavioural transmission parameters (see Tables 6 1-6 2 and 6 5) are of lesser importance in contributing to the prediction imprecision for the AIDS cases These remaining parameters are the average incubation period (or variation in the rate of progression from HIV seropositive to AIDS), the initial number of infecteds, the rate of sharing needles, and the HIV transmission efficacy of a needle sharing partnership with an infected person These results show that sexual and IVDU behavioural parameters, as well as biological parameters are important in prediction imprecision for non-IVDU AIDS cases

## 6.6 2010 and beyond

### 6.6.1 General discussion of model with intervention (see section 6.4)

Extending the time limit of the model beyond 2010, reveals that the epidemic will become endemic after 80 years of its genesis However because of the nature of deterministic models it is likely to be unreasonable to expect the model to be accurate for more than 40 years into the future (as mentioned earlier, numerical errors accumulate over long periods of time, see 6 5 3) Indeed even within a 40 year period the parameters should be continuously reassessed as they are evidently changing over time

This model predicts that 20 years after the introduction of the virus into the Irish population, the number of women and men who will have become infected but not yet developed AIDS will be 1127 and 1125 respectively (see Table 6 12)

The model can also be used to predict the date at which more non-IVDUs will have been infected than IV drug users For women this date is 1994, but for men even if the model is run for 100 years the number of non-IVDUs who are infected remains in the hundreds, whereas the number of IVDUs infected has already passed 1000 by the year 2000 (see note on asymmetry in the sex ratio of non-IVDU AIDS cases in section 6 4)

In this model the increase in the number of new IVDU infections flattens out around 1998, whereas this does not happen in the non-IVDU population for another 30 years, long after the end of the projection period

For IVDUs saturation effects in prevalence cause a peak in the number of AIDS cases after about 22 years (2004) (Fig 6 3), whereas prevalence curves for heterosexuals continue to rise for the duration of the simulations (up to year 2010) (Figs 6 3 and 6 4) Section 6 6 4 discusses the sensitivity of the transmission parameters through increased condom usage

By 2010, the end of the projection period, 2559 persons are HIV-infected These forecasts present a sufficiently servere prospect, however, the impact could be more severe in that several assumptions concerning sexual behaviour and disease parameters in the model are based on incomplete knowledge and may therefore be too optimistic Finally, although the model has been shown to simulate the growth and the impact of the epidemic quite accurately up to the present, there is no guarantee that key assumptions will remain valid in the future It should also be emphasised that in reality, in the early stages of an epidemic with small numbers of infected individuals, stochastic effects come into play which can have a marked impact on when the epidemic curve is seen to rise

### 6.6.2 Intervention

One role of mathematical modelling is the theoretical evaluation of preventive measures, particularly in the context of their intensity and the timing of their introduction In this case models can become a tool for public health decision makers With theoretical experiments the behaviour of the system is understood by altering the assumptions and /or parameter values and measuring the effect on the outcome variable Models may therefore be used to make qualitative predictions by generating particular scenarios

### 6.6.3 Timing of reduction in needle sharing

As an example of such a qualitative prediction, we look at the situation where the parameter relating to the probability of infection through needle sharing is not halved until 1990 (Table 6 11 was generated by halving this parameter in 1989) The results are given in Table 6 25

Table 6.25 **Predicted numbers with AIDS given intervention $\hat{\beta}$ = 0.095 from 1990 onwards**

| Year | Male IVDU | Female IVDU | Heterosexual Male non-IVDU | Heterosexual Female non-IVDU |
|---|---|---|---|---|
| 1982 | 0 | 0 | 0 | 0 |
| 1984 | 0 | 0 | 0 | 0 |
| 1986 | 2 | 0 | 0 | 0 |
| 1988 | 10 | 3 | 0 | 1 |
| 1990 | 40 | 11 | 0 | 6 |
| 1992 | 72 | 22 | 1 | 17 |
| 1994 | 105 | 33 | 1 | 34 |
| 1996 | 134 | 42 | 3 | 54 |
| 1998 | 154 | 49 | 4 | 77 |
| 2000 | 165 | 53 | 5 | 100 |
| 2002 | 169 | 55 | 7 | 121 |
| 2004 | 168 | 55 | 8 | 139 |
| 2006 | 166 | 54 | 10 | 153 |
| 2008 | 164 | 53 | 11 | 164 |
| 2010 | 162 | 53 | 12 | 173 |

When the probability of transmission through needle sharing is reduced one year later, the peak in the number of AIDS cases occurs later than in the model where intervention occurs earlier (see Table 6 11 and Figure 6 3) In this model the number of AIDS cases peaks 20 years after the introduction of the infection, whereas the previously mentioned model peaks after 23 years This is because of the faster increase in the number of those infected in the former model However this change in the timing of intervention does not seem to have any greater effect than to speed up the growth in the number of infecteds by one year

### 6.6.4 Greater use of condoms and needle exchange

Irish legislation contributed to limiting contraceptive availability Until 1993, condoms could only be sold by registered pharmacists or Family Planning Clinics and only to individuals of 17 years or over. As mentioned earlier the first needle exchange clinic opened in 1989, the second centre

opened in November 1991, and others have been established since then These clinics also distributed condoms and promoted condom use We shall therefore take 1992 as an estimated time point at which condom use increases and sharing of injecting equipment decreases in our next simulation To assess the impact of the timing of such changes we examine the situation if the changes do not occur until 1998 The risk through sexual intercourse, as described in section 6 2 6, is decreased by 60% for both IVDUs and non-IVDUs, and the risk through needle sharing is further decreased to one third of its original value (see Table 6 2) Tables 6 26 and 6 27 provide details of the results

**Table 6.26 Predicted numbers with AIDS given greater use of condoms and needle exchange from 1992 onwards**

| | | | Heterosexual | |
|---|---|---|---|---|
| **Year** | **Male IVDU** | **Female IVDU** | **Male non-IVDU** | **Female non-IVDU** |
| 1982 | 0 | 0 | 0 | 0 |
| 1984 | 0 | 0 | 0 | 0 |
| 1986 | 2 | 0 | 0 | 0 |
| 1988 | 10 | 3 | 0 | 1 |
| 1990 | 27 | 8 | 0 | 5 |
| 1992 | 45 | 14 | 0 | 11 |
| 1994 | 57 | 17 | 1 | 16 |
| 1996 | 66 | 20 | 1 | 21 |
| 1998 | 74 | 23 | 1 | 26 |
| 2000 | 80 | 25 | 1 | 30 |
| 2002 | 86 | 26 | 2 | 35 |
| 2004 | 90 | 28 | 2 | 39 |
| 2006 | 94 | 29 | 2 | 44 |
| 2008 | 97 | 30 | 3 | 47 |
| 2010 | 99 | 31 | 3 | 51 |

The result of the behaviour changes described above being implemented in 1992, a time point 10 years after the introduction of the virus, is dramatic. The total number of persons with AIDS in the populations under discussion, in

the year 2010, is 184, which is less than half the number of AIDS cases should there be no such changes in behaviour (see Table 6 11)

**Table 6.27 Predicted numbers with AIDS given greater use of condoms and needle exchange from 1998 onwards**

| Year | Male IVDU | Female IVDU | Heterosexual Male non-IVDU | Heterosexual Female non-IVDU |
|---|---|---|---|---|
| 1982 | 0 | 0 | 0 | 0 |
| 1984 | 0 | 0 | 0 | 0 |
| 1986 | 2 | 0 | 0 | 0 |
| 1988 | 10 | 3 | 0 | 1 |
| 1990 | 27 | 8 | 0 | 5 |
| 1992 | 48 | 15 | 0 | 12 |
| 1994 | 76 | 24 | 1 | 23 |
| 1996 | 107 | 34 | 2 | 39 |
| 1998 | 131 | 41 | 3 | 57 |
| 2000 | 133 | 42 | 3 | 66 |
| 2002 | 128 | 40 | 4 | 71 |
| 2004 | 122 | 38 | 4 | 73 |
| 2006 | 117 | 37 | 4 | 74 |
| 2008 | 113 | 36 | 5 | 74 |
| 2010 | 110 | 35 | 5 | 74 |

When behaviour changes are not implemented until 1998, a time point 16 years after the introduction of the virus, it results in a 43% decrease in the number of AIDS cases in 2010 The simulations reveal that the timing of changes in behaviour for a given forecasting horizon, has a very substantial impact on the predicted impact of the disease, particularly amongst the female non-IVDU population If control is introduced at an early stage (t = 10 years), the simulations suggest that over a time-scale of 28 years 212 less people will be infected with HIV than if control is introduced at a later stage (t = 16 years)

The epidemiological effects of behavioural change will be dependent upon both the magnitude, the type, and the timing of the behaviour change, and should ideally be investigated through a time-dependent analysis

### 6.6.5 Experimentation results of no needle sharing among IVDUs

As an example of a theoretical intervention experiment in the IVDU group, simulations were performed to study the effect of blocking HIV transmission through the sharing of contaminated needles

To illustrate how the model may be used to study the effect of blocking the transmission through needle sharing, all transmission probabilities relating to this type of partner contact are set to zero, that is $\hat{\beta} = 0$ in the model, from 1996 onwards All other parameters are the same as those used to provide the results outlined in Table 6 11 The effect on the number of AIDS cases is shown in Table 6 The effective contact rates within and between the risk groups are now due to only one mode of transmission, sexual intercourse Transmission via needle sharing is completely blocked The simulation results of this hypothetical intervention experiment are shown in Figure 6 5

**Table 6.28 Predicted numbers with AIDS given no needle sharing from 1996 onwards**

| | | | Heterosexual | |
|---|---|---|---|---|
| **Year** | **Male IVDU** | **Female IVDU** | **Male non-IVDU** | **Female non-IVDU** |
| 1982 | 0 | 0 | 0 | 0 |
| 1984 | 0 | 0 | 0 | 0 |
| 1986 | 2 | 0 | 0 | 0 |
| 1988 | 10 | 3 | 0 | 1 |
| 1990 | 27 | 8 | 0 | 5 |
| 1992 | 48 | 15 | 0 | 12 |
| 1994 | 76 | 24 | 1 | 23 |
| 1996 | 96 | 31 | 2 | 39 |
| 1998 | 75 | 27 | 2 | 51 |
| 2000 | 50 | 20 | 3 | 54 |
| 2002 | 32 | 15 | 4 | 51 |
| 2004 | 19 | 10 | 4 | 45 |
| 2006 | 12 | 7 | 4 | 39 |
| 2008 | 7 | 5 | 3 | 32 |
| 2010 | 4 | 3 | 3 | 26 |

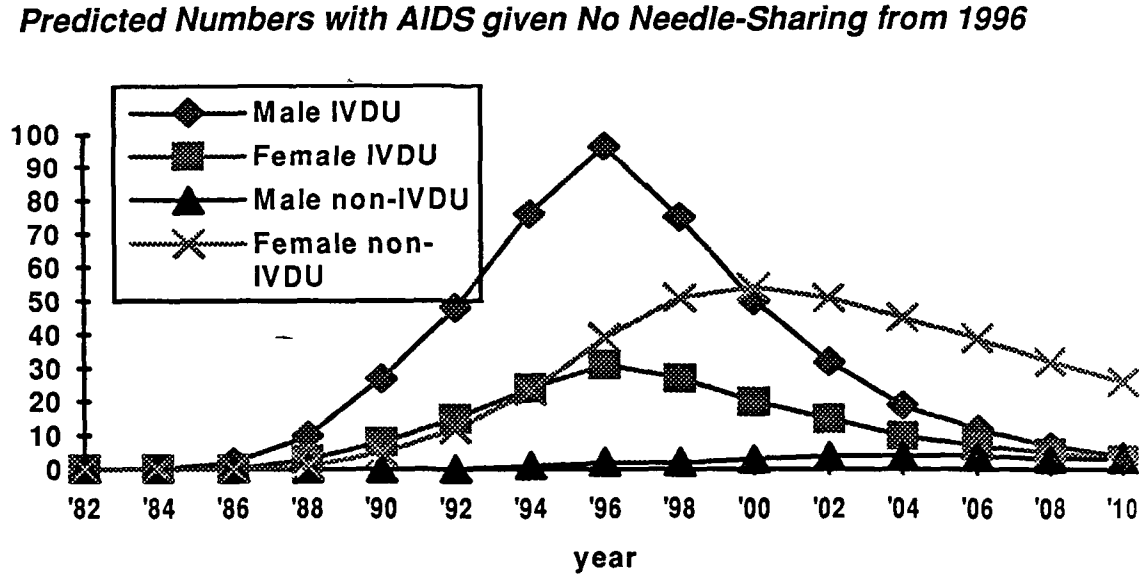



*Fig 6.5 Predicted Numbers with AIDS in the IVDU and non-IVDU subgroups given no needle sharing from 1996 on (y= AIDS prevalence)*

There is clearly a very dramatic decrease in the number of AIDS cases in the year 2010 In fact by the year 2020 there are no IVDU AIDS cases and only 4 IVDUs are infected with the virus The decrease in the non-IVDU population is slower, but no less dramatic By the year 2020 there are only 10 cases of AIDS in the non-IVDU population and 52 persons are infected with HIV

It is interesting to compare these results with model studies by Kaplan (1989), which demonstrate that policies such as the distribution of cleansing solutions and /or injection equipment among drug addicts could slow or stop the intravenous transmission of HIV (see also Hart et al , 1989)

An overall decrease in sharing injection equipment has been reported in countries that have instituted any kind of increased access to syringes Since the late 1970s the Netherlands has a national policy of harm reduction for drug users, and the first needle-exchange program was established in Amsterdam in 1984 Buning et al (1986), found that the use of needle exchanges in Amsterdam was associated with less sharing among injectors, that the frequency of injecting did not increase, and that there was no evidence of an increase in the total number of IVDUs as a consequence Hart et al (1989), evaluated a needle exchange in central London and found that the rate of sharing fell, both compared to rates prior to entry to the scheme and during the period of study Hart also found that the frequency of injecting did not increase,

that there was a reduction in the proportion of clients with multiple partners, and that needle exchanges probably played a large part in preventing acquisition of HIV in that there were stable HIV prevalence rates over time

Guydish et al (1993), in a study of all drug-treatment admissions in San Francisco County over a 4-year period, found that no negative consequences of needle exchange were detected Specifically, the presence of the exchange program was not associated with (1) increases in injection drug use, (2) increases in needle-sharing behaviour, or (3) changing drug-use behaviour from non-injection to injection They also found that neighbourhoods without needle-exchange sites showed a greater increase in proportion of admissions for injection drug use, and in frequency of injection, over time

A similar program has been implemented in Dublin since 1989 mainly because of the appeal of needle exchange as an HIV prevention strategy An evaluation of the needle-exchange program in Dublin (Dunne et al , 1993), suggests that the program contributes to decreased needle sharing among IVDUs participating in such programs Dunne et al , (1993) found that 50% of clients reported the sharing of injecting equipment in the period before the needle exchange scheme, while only 5 6% reported sharing in the period before their last visit, and only 1 3% of those who visited in the final quarter of the period under study reported sharing

Mann et al (1992) point out that the efficiency of syringe exchange in decreasing HIV behaviour depends on how much of the IVDU community can be covered If the program is not large enough to increase the proportion of sterile syringes in the IVDU community as a whole, it may have no broad impact on risk behaviour or transmission of injection-related disease, although individual participants may benefit Coverage here includes the number of IVDUs who use the service, and is also related to hours of operation and convenient access to sites

The question for the epidemiologist is whether changes in sexual and drug using behaviour are adequate to reduce the rate of virus transmission, particularly since behaviour change only commenced when a large proportion of IVDUs were already infected The risk of infection increases as the prevalence of infection in the population rises Therefore behavioural risk reduction will only reduce the incidence of infection if it is of a magnitude sufficient to outweigh the increased risk inherent in the rising prevalence, or if it occurs at an earlier stage of the epidemic when infection rates are low Here the problem may be primarily political, namely, obtaining and maintaining support for prevention prior to the emergence of a visible problem, and

maintaining it over the long term in the absence of an epidemic to generate public support

## 6.7 A final modification to the model

Comiskey assumed that those who are infected and have developed AIDS [of whom there are $A(t)$] will not transmit infection to any partners although they will still form new partnerships But it could be more realistic to assume that these individuals play no further part in the epidemic, that is, that they cease to form new partnerships (Isham, 1993) In this case the appropriate infection rate is $\beta s X(t)Y(t)/[X(t)+Y(t)]$ (see equations 6 1 and 6 2)

In Table 6 25 we see the effect of this modification for the case already illustrated in Table 6 11 (with parameters as given in Tables 6 1 to 6 5, with the exception of the parameter for the probability of infection through needle sharing)

**Table 6.29 Predicted numbers with AIDS given model modification and intervention (i.e. $\hat{\beta}$ = 0.095 from 1989 onwards)**

| | | | Heterosexual | |
|---|---|---|---|---|
| Year | Male IVDU | Female IVDU | Male non-IVDU | Female non-IVDU |
| 1982 | 0 | 0 | 0 | 0 |
| 1984 | 0 | 0 | 0 | 0 |
| 1986 | 2 | 0 | 0 | 0 |
| 1988 | 10 | 3 | 0 | 1 |
| 1990 | 27 | 8 | 0 | 5 |
| 1992 | 49 | 15 | 0 | 12 |
| 1994 | 78 | 24 | 1 | 24 |
| 1996 | 111 | 35 | 2 | 42 |
| 1998 | 142 | 45 | 3 | 64 |
| 2000 | 163 | 52 | 4 | 90 |
| 2002 | 174 | 56 | 6 | 116 |
| 2004 | 177 | 57 | 8 | 140 |
| 2006 | 176 | 57 | 10 | 161 |
| 2008 | 174 | 57 | 11 | 177 |
| 2010 | 172 | 56 | 13 | 190 |

It is clear that the effect of using the infection rate in the modified model gains on that for the model described by Table 6 11, and the corresponding epidemic spreads more quickly However, at least with these parameter values, the effect of the modification to the model is relatively small (The increase in the number of cases is 6% and 15% for IVDUs and non-IVDUs respectively by 2010)

## 6.8 Epidemiological implications and conclusions

### 6.8.1 Limitations of modelling AIDS by this approach

Much uncertainty surrounds the estimation of the epidemiological parameters used in this model, and this uncertainty is probably greater for the behavioural parameters than it is for the biological parameters

Values for certain key epidemiological parameters, such as variability in transmission probabilities have been assigned on the basis of published data relevant to developed countries (Bulatao, 1988, Padian et al , 1991, Anderson et al , 1992), with similar or at least comparable features to the Irish epidemic Quantitative data on transmission probabilities for heterosexual contact or for needle sharing activity are **very** limited at present We have again simply used the best published information available to us and from our own work It must be recognized however, that even modest improvement in the available information may be difficult if not impossible to achieve The obvious difficulties are those inherent in the study of the likelihood of transmission via intimate behaviour and the changes that are occurring in the incubation period of AIDS due to improvements in the management and treatment of patients before the development of AIDS A further complication is raised by changes in the case definition of AIDS (Brettle et al , 1993, Centers for Disease Control, 1987, 1993) Thus our understanding of the disease is changing with time as well as the parameters which describe its spread

Parameter values depicting patterns of sexual behaviour are even less reliable, though the surveys conducted by Dunne et al (1995), O'Hare and O'Brien (1992, 1993), Lansdowne Market Research (1992) and Irish Marketing Surveys (1993), (see Chapter 3) do help to provide plausible ranges for Irish estimates in terms of the rates of acquisition of needle sharing and sexual partners within the IVDU and heterosexual groups, and the sizes of the IVDU risk group Care must be exercised in the interpretation of the data, given that any survey of sexual behaviour records **self-reported activity** rather than

observed behaviours The compliance achieved in the Lansdowne Market Research Survey (1992) was acceptable given the sensitivity of the topic (43%), but the missing fraction of the designated sample may have behaviours that are atypical of the general population and possibly of great significance to the spread of HIV

An important determinant of the overall pattern of spread for a sexually transmitted infection within the general population is the degree of sexual contact within and between risk groups, but it is this area about which we know least because of the practical difficulties of ascertaining networks of sexual contact within human communities

In Ireland, we have no information to date on the patterns of mixing within specified risk groups (i e for IVDUs whether the mixing between different sexual activity classes (high / low activity) is assortative (like with like) or disassortative (like with unlike) In addition we have only very limited information on the degree of between risk group mixing ( i e for IVDUs what fraction of their sexual partners are IVDUs and what fraction non-IVDUs) Furthermore the model does not include the effects of variability over time or the effects of the non random nature of partner selection The non random selection and formation of interconnected pools of sexually active individuals would result in slower growth than that described in this chapter

Various assumptions on the probabilities involved and plausible parameter values make it clear that small changes in the values of key parameters induce significant changes in projected trends, particularly in the longer term up to the year 2010 (Tables 6 11, 6 14 6 16-6 18, 6 20, 6 23-6 24)

The model presented here shows that under what currently appear to be reasonable hypotheses about transmission, epidemics of widely varying severity are consistent with available epidemiological data

### 6.8.2 Broad conclusions for transmission models

The following conclusions emerge however, even with the limitations indicated above

- *Non-IVDU women are particularly susceptible to HIV infection.*

This is an important finding and is due to women being biologically, epidemiologically and socially more vulnerable to the infection This is respectively because semen contains a far higher concentration of HIV than vaginal fluid, non-IVDU women are more likely to have a sexual partnership

with an IVDU man than visa versa, and women are less inclined to protect themselves if in a long term relationship with an infected man

- *It seems likely that heterosexual activity will account for more new cases of AIDS than IV drug use later on in the next century, particularly among females*

In the early stages of the epidemic, IVDU transmission is more important than heterosexual transmission, however, the relative importance of heterosexual transmission increases, as the epidemic spreads from the IVDU to the bridge community As of December 1994 in Ireland, the ratio of IVDU heterosexual cases of AIDS is about 1 0 28 (Department of Health) Using figures generated by the preferred parametric choice for our model, the predicted ratio is about 1 0 24 for Dublin in 1994, but rises to 1 0 8 in 2010 (The ratio of the prevalence of heterosexually acquired AIDS among women to the total prevalence of AIDS among men is about 1 0 95 when calculated from model projections in the year 2010) Nonetheless it is likely that differences in relevant parameters that are too small to be detected in the next several years could have a serious impact on the epidemic in the more distant future The fact that the proportion of cases resulting from heterosexual contact is small and will probably remain so for the next several years does not appear to preclude the subsequent development of a major epidemic among heterosexuals

- *The model serves to highlight both the urgency of implementation and the non-linear benefits that accrue from early introduction of behaviour changes, and the degree to which behaviour needs to be changed*

However, it should be noted that small changes in behaviour can have very significant effects on projected trends, even if such changes are implemented ten or sixteen years after the introduction of the virus

- *Transmission models are of limited use at present for predicting medium-to-long-term trends in the incidence of AIDS*

Great uncertainty still surrounds future events (on the basis of current information), particularly within the heterosexual population, despite an ability to mirror accurately past trends in AIDS incidence Sometimes different parameter combinations which fit observed trends provide very different projections for the short or longer term

Prediction more than a very short while ahead is therefore probably inadvisable due to the difficulty of validating model assumptions and of obtaining more precise parameter values The main role of such models is therefore to highlight the uncertainties in future trends given **current epidemiological information** A further major role is to illustrate **how** various assumptions affect projections

- *Sensitivity analysis of the model revealed that the prediction imprecision is mainly due to the estimation uncertainty of the values of a* ***few key variables***

Long-term precise predictions of AIDS cases will not be possible until these key variables have been determined accurately The results suggest that it is most important to measure the size of the IVDU population, the heterosexual transmission efficiencies, the rate of sexual partner change and the between-group mixing parameters accurately Interpretation of existing data on heterosexual transmission depends strongly on the size of the IVDU population and the magnitude of the between-group mixing parameter Reducing the uncertainty in these key parameters will have a considerable effect on increasing the accuracy of prediction estimates This knowledge should help to focus data collection efforts

The sensitivity analysis results have significant epidemiological implications The analysis revealed that many key variables are important in contributing to the prediction imprecision, but that only a few are significantly so Therefore, the results suggest that it is most important to quantify accurately these key variables, and hence the results can be used to suggest a strategic agenda to focus data collection efforts Reducing the estimation uncertainty in the key biological-behavioural transmission parameters will have a much greater effect on increasing the prediction precision of adult AIDS cases than accurately estimating any of the subgroup sizes

However, it is also necessary to develop more realistic mathematical models Behavioural changes and additional biological complexities, (such as variable transmission efficiencies, parameter changes due to intervention and age structure) should ideally be included in future models

The formulation of realistic mathematical models that link specific risk behaviours of individuals with the seroprevalence level of a population is essential to access the epidemiological significance of behavioural intervention strategies

# Chapter 7

# Review of Results, Conclusions, and Final Recommendations

## 7.1 Review of aims and objectives

The main reason for formulating and exploring mathematical models such as that described in Chapter 6 is to investigate how the various parameters affect viral persistence and spread, and to help improve general understanding of the transmission dynamics of HIV infection The overall objective is of course to curb the growth of the epidemic Accurate estimates are important in this regard not only for developing effective strategies to prevent further spread of HIV infection, but also for assessing the potentially enormous, future demands on the health care system

## 7.2 Results of the numerical analysis

The use of deterministic models as predictive tools is still hampered by the uncertainties that surround key epidemiological parameters and processes It is still for example unclear how infectiousness varies over the incubation period of AIDS However such models do help us to understand the trends in the progress of the disease, give us important qualitative insight into the shape of the infection curve and provide a framework within which to evaluate the potential impact of different intervention programs

The results from the simulations presented in chapter 6 have strong implications for the prediction of the future course of the AIDS epidemic Even though they derive from a highly simplified model, the analyses presented here clearly show that the amount of sexual contact between the IVDUs and non-IVDU heterosexuals is a very important variable to consider when assessing the future of the epidemic in the Irish population The question as to whether the disease will become epidemic in the general population hinges critically on

accurate estimation of the amount of sexual contact between the two groups and not only on the number of sexual partners Despite the current ratio of infecteds and AIDS cases for IVDUs and non-IVDUs this will not always remain the case

Women are particularly susceptible to HIV infection As more women become infected, so too do more infants through perinatal transmission (which is not dealt with in this work) The majority of infected women are not aware of their condition They are often diagnosed **after** becoming pregnant or **after** giving birth According to a United Nations Development Programme (UNDP) study on AIDS, there are more than twice as many reported AIDS cases among 15-25 year old women in Uganda than among men of the same age (UNDP, 1994)

An appreciation of the points at which changes in sexual or drug using behaviour may dramatically reduce the burden of AIDS on its potential victims and on society at large is important Messages are more effective when they can be directed toward a specific target population Targeting education and condom distribution at high-risk groups will always be beneficial in the early stages of the epidemic, when infection in the general population is limited The projections recorded in Tables 6 26 and 6 27, which show the influence of the timing of behaviour change on the shape of the epidemic, provide a good illustration of this point With respect to data collection, they also highlight the importance of acquiring good quantitative information on sexual and drug using behaviour and temporal changes therein

## 7.3 Limitations of the model used. Developments and recommendations for future work

### 7.3.1 Data collection

The need for improved precision in estimating behavioural and population mixing variables is highlighted in Chapter 6 Data collection should therefore be extended in terms of frequency, detail and, most importantly, central collation, if rational implementation of intervention plans is to be achieved An immediate benefit would be a reduction in parameter estimation uncertainty with regard specifically to the behavioural parameters and hence improved prediction

Any worthwhile data collection presents difficulties and this is especially true in the context of research with IVDUs Nevertheless, repeat surveys of

specific data subsets undertaken during drug use surveillance or monitoring schemes would sensibly improve parameter estimates, even though some of the parameters will be impossible to measure with complete accuracy

### 7.3.2 Extensions to risk groups

Any realistic model for the spread of HIV in the population must consider all risk groups Obvious extensions to risk groups considered include homosexual and bisexual men, haemophiliacs, recipients of blood products prior to 1985, sexual contacts of haemophiliacs and transfusion recipients, and children of infected individuals

### 7.3.3 Epidemiological factors

In addition to the risk groups themselves, a number of other factors should be considered These include

- *The nature of the sexual behaviours and preventive measures taken*

As mentioned earlier certain sexual behaviour behaviours involve a higher risk of HIV transmission than others However obtaining this sort of sensitive information is not without its difficulties

- *The age distribution of the population*

Sexual behaviour is clearly age dependent, and the length of the incubation period tends to decrease with increasing age in adults Therefore a more realistic model needs to be stratified by age However this stratification involves model complications

- *Geographic location*

Chapter 1 offers a preliminary assessment of this area More interdisciplinary work is needed here as is extensive data collection

- T*he pattern of interaction of individuals within and between risk groups*

Heterogeneity in contact rates and the duration of partnerships play an important role in the spread of the HIV virus (Anderson, 1988) One should for example account for pair formation and pair separation, especially with regard to the spread of HIV in the heterosexual population There is also a need for the model to allow for proportional mixing within groups and between groups

### 7.3.4 Aetiological factors

It is also necessary to consider three main factors associated with the natural history of the disease

- *The pattern of infectivity*

This probably varies throughout the infectiousness period and the model should ideally account for this variability

- *The progression of the disease within an individual*

A more detailed calculation of the biological parameters would take into account the fact that the hazard of developing AIDS increases with time since infection There may also be a need, as suggested by Williams and Anderson (1994), to reduce the incubation rates progressively over 5 years from 1989 (by 20%) to 80% of the original rates in order to mirror the observed lengthening of incubation periods brought about by improved care of patients

- *The survival time of persons diagnosed with AIDS*

The hazard of dying also increases with time from AIDS diagnosis In addition the survival time of persons diagnosed with AIDS is constantly changing due to improvements in the care of patients

## 7.4 Discussion

Studies have indicated that knowledge of HIV serostatus may help to reduce HIV transmission from HIV-positive IVDUs to others through safer injecting and sexual behaviour However, the proportion of IVDUs reporting high-risk behaviour remains substantial Desenclos et al (1993) in a study of European injecting drug users, found that IVDUs who knew that they were HIV-seropositive were 3 1 times (95% CI, 2 3-4 2) more likely to always use condoms than were IVDUs who had never been tested (this effect was more pronounced for women and for those over 30 years of age) They also found that IVDUs with a negative test tended to inject drugs safely more often than those who had never been tested, but there was no significant difference in condom use in this regard (in fact condom use tended to be even less common among IVDUs who were negative at their last test than among never-tested IVDUs Regarding Irish IVDUs (150 respondents), they found that HIV-positive IVDUs in Ireland, were **more likely** to give their injecting equipment to other

IVDUs than were HIV-positive respondents from any of the other twelve countries, and safe injection practices of HIV seropositive IVDUs were **less likely** in Ireland than in any other country with the exception of Italy Many studies have noted more change in injection risk behaviour than in sexual risk behaviour (Klee et al , 1991a, Murphy et al , 1993, Richardson et al , 1993, Des Jarlais et al , 1992) This is particularly true of those drug users who are in long term relationships

Unfortunately, however, neither drug-abuse treatment programmes nor safer injection programmes have been successful at reaching **new** injectors It appears that most individuals inject for several years before they perceive drug misuse or AIDS as personally relevant problems requiring special attention Some reports suggest that the highest prevalence of HIV infection and lowest rates of voluntary confidential testing are found in those who have no history of treatment for their drug-use (Donoghoe et al , 1993)

In addition the availability of treatment is usually significantly less than the demand Expanding the treatment system could help to reduce IV drug injection and transmission of HIV among drug users Users who had not been exposed would reduce their chances of being exposed, and users who had already been exposed would reduce their chances of exposing others The cost of treating AIDS among drug users who are usually totally dependent on the state for their medical expenses is approximately £8,300, per case, per year for anti-viral therapy alone, (i e not including medical or hospital care or other drug costs) Therefore, the economics of the treatment of AIDS versus the provision of drug abuse treatment, also argues for expansion of the treatment network According to *AIDS in the World* (Mann et al , 1992) the cost of AIDS inpatient care per year in the UK was $25, 000 to $30, 000 for the period 1987-1989 This represents approximately **twice** the UK per capita GNP for the period 1986-1988

However the decision to expand the treatment system is in the realm of the policy makers and AIDS is a difficult area for politicians because the wisdom of present policies will often not be validated for five or more years when they may no longer be in office In addition some of the necessary language of prevention is awkward to use in the delivery of speeches

The construction of transmission models highlights how **little** we know about the major epidemiological and behavioural determinants of the pattern of the HIV epidemic in Ireland This situation is not unique to Ireland As Knox has commented

*Those who write the history of this disease will be intrigued by the contrasts which it displays the implacable deadlines of the biological hazard the still-primitive but rapidly-developing scientific foundation for understanding, predicting and controlling epidemics the urgent need to allocate resources, powers and responsibilities for its control and a disregard of all of them within a social response dominated by other concerns*

(Knox et al 1993)

Our knowledge is not likely to improve rapidly because of the practical difficulties inherent in both the study of intimate human behaviour and the assessment of infectiousness and transmissibility for a disease with a long incubation period The many uncertainties argue strongly for a precautionary approach in the delivery of public health messages about HIV and AIDS The likely extent of the heterosexual epidemic in the future is uncertain, hence education must stress that the majority are at risk while continuing to target most efforts at high risk groups

The need for continuous vigilance is also highlighted by Fitzpatrick et al (1992) in a study of 32 teenage girls attending a Dublin STD clinic which found that of 29 having intercourse without condoms, **none** considered themselves to be at risk of contracting HIV from their present partner As the Irish Times put it

*There is now a need to reach out to the non-marginalised in society who may not believe that they are at risk If only a small minority of those who have hitherto been easily recognisable as members of the marginalised groups at most risk have been persuaded to change their risk-taking behaviour, how much more daunting is the task of altering the risk behaviour of those who do not perceive themselves as being at risk? There is a great deal more to be done to contain the spread of HIV than has been done to date*

(Irish Times editorial, 30th Sept 1994)

More generally the key to reducing the spread of AIDS lies in accurate epidemiological surveillance which provides the factual base for education Transmission models produce a framework against which to interpret the factors that have generated past trends and the processes that will determine future events The stakes are very high

# Appendix A

# HIV Transmission Survey of Drug Project Clients

## A.1 Summary of principal features of AIDS in Ireland

The following represent notable features of AIDS in Ireland at present

- The proportion of AIDS cases attributed to IVDU and heterosexual transmission continues to rise
- 408 cases of AIDS were reported by the end of June 1994
- 43 4% of cases occurred among IVDUs
- 11% of cases are due to heterosexual transmission
- 31% of female AIDS cases are due to heterosexual transmission
- 49 % of all AIDS cases attributed to heterosexual transmission are women
- Heterosexually acquired AIDS increased from 29% of all women with AIDS in 1993 to 31% in 1994
- The proportion of cases due to heterosexual sex is rising far more rapidly than that of any other route of transmission
- The number of reported cases of people infected through heterosexual sex rose by 80% in the past 2 years (June 1992-June 1994)
- Many of those who acquired the virus through heterosexual sex were the sexual partners of HIV-infected IVDUs

In our study we describe differences in high-risk sexual practices among IVDUs recruited from the Drug Treatment Centre (D T C ) and from the Ana Liffey Drug Project (A L ) Our primary objective is to investigate the variability in sexual and drug using practices among IVDUs and the associations between specific high-risk sexual and drug using practices and sex

## A.2 Subjects and Methods

### A.2.1 Recruitment

Subjects were recruited from the D T C and the Ana Liffey Drug Project between 22 November 1993 and 23 August 1994 A common structured questionnaire was used with both groups A double-site strategy was employed to limit bias from single-site recruitment 133 persons were interviewed by the two different drug treatment agencies 117 of the 133 were IVDUs Of the 117, 96 were recruited by the D T C and 21 were recruited by the Ana Liffey Drug Project The D T C subjects were recruited sequentially but the Ana Liffey subjects were recruited on the threefold basis of HIV seropositive status, receptivity and lucidity Therefore the two groups are **not** strictly comparable The questions were designed to obtain data on the following age, sex, residence, attendance at a sexually transmitted disease clinic, use of intravenous drugs, sexual preference, number of sexual partners in the previous year, sexual contacts with intravenous drug users or seropositive partners, and use of condoms Individuals were asked about their injecting and drug using behaviours with IVDU and non-IVDU partners during the 12 months before interview The questionnaires were completed by trained interviewers during individual interviews Demographic details, recent drug use, syringe-sharing HIV risk behaviour, HIV testing, and awareness of HIV antibody status were compared across the two groups Given that the two groups were recruited on different bases and are not properly comparable they provide separate snapshots or cross-sectional views of the Irish HIV and drug problem Nevertheless, because numbers are small in the Ana Liffey sample, we have reported results together, indicating throughout, the likely bias introduced by the Ana Liffey group

### A.2.1 Missing values

Midpoint intervals were assumed in year and month of birth and in year of last drug injection if data were missing This was the case for two subjects where only year of birth was recorded, for 21 subjects (all those recruited by the Ana Liffey Drug Project) where only year and month of birth were available and for 5 subjects where only year of last drug injection was recorded Midpoint intervals were also assumed in year of HIV seropositive diagnosis if data were missing (9 subjects and 4 partners of subjects), but it was assumed that the diagnosis occurred on the first of the month One of those whose age

was missing and 12 whose number of sexual partners in the previous year was missing, were omitted from Tables A1, A2 and A3

### A.2.2 Statistical analysis

Descriptive analyses of data on the 117 IVDUs were carried out, and the relation of each variable to serologic status was examined Data were analysed using the SAS system (SAS Institute, 1988) The procedure TTEST, was used for comparing means Pearson's $\chi^2$, and Fisher's exact test (for when the sample size was small), were used for comparisons of proportions between groups In all cases a level of significance $\alpha$= 0 05 was used unless otherwise stated

## A.3 Results

### A.3.1 Demographic characteristics

A summary of selected characteristics of the study population, by sex, is shown in Table A1

Three quarters of the study population were men and one quarter were women

The mean age of the participants was 25 years (S D 5 97) The age distribution ranged from 17-45 years The age distribution was similar for women and men

67 individuals from the total number of IVDUs (57%) reported having a regular sexual partner Women and men did not differ significantly in respect of having a regular partner

Men were more likely to have been using IV drugs at the time of the interview than women 38 (32 5%) men were currently using compared to only 5 (4 3%) women ( $\chi^2$=6 3, df=1, p=0 012)

The mean age of first intravenous drug use was 18 years (S D 3 6) The age of first needle use ranged from 12 to 32. 70 subjects out of the 117 in the sample had used IV drugs by 18 years of age (60%)

**Table A1. Selected characteristics of 117 IVDUs recruited from the D.T.C. and the Ana Liffey Drug Treatment Program by treatment centre and sex.**

| | No (%) Treatment centre | | |
|---|---|---|---|
| | D T C | Anna Liffey | Total |
| **Men** | | | |
| No subjects | 73 | 15 | 88 |
| Age at interview | | | |
| < 24 | 44 | 00 | 44 |
| ≥ 24 | 28 | 15 | 43 |
| Regular partner | | | |
| No | 37 | 04 | 41 |
| Yes | 36 | 11 | 47 |
| IVDU at present | | | |
| No | 44 | 06 | 50 |
| Yes | 29 | 09 | 38 |
| **Women** | | | |
| No subjects | 23 | 06 | 29 |
| Age at interview | | | |
| < 24 | 13 | 00 | 13 |
| ≥ 24 | 10 | 06 | 16 |
| Regular partner | | | |
| No | 09 | 00 | 09 |
| Yes | 14 | 06 | 20 |
| IVDU at present | | | |
| No | 21 | 03 | 24 |
| Yes | 02 | 03 | 05 |

### A.3.2 Characteristics of sexual partners of subjects

26 (22%) of the sample reported having a sexual partner who was also, either at present or in the past, an IVDU

10 subjects (8 5%) reported that their regular sexual partner was seropositive, 52 (44 4%) had partners who were seronegative and 5 (4 3%) had partners whose status was unknown (42 7% had no regular partner)

When questioned regarding the HIV status of their previous partner, 8 (7 1%) reported that their previous sexual partner was seropositive, 71 (62 8%) had previous partners who were seronegative and 26 (23%) had previous partners whose status was unknown (8 (7 1%) had no previous partner)

**Table A2. Treatment centre comparisons, demographics, recent drug use and HIV risk behaviour differences in drug users.**

| | Treatment centre | | |
|---|---|---|---|
| | D T C | Anna Liffey | Total |
| | n = 96 | n = 21 | n = 117 |
| **Demographics** | | | |
| Sex | | | |
| Female (%) | 19 7 | 5 1 | 24 8 |
| Male (%) | 62 4 | 12 8 | 75 2 |
| Mean age (years) | 24 | 31 | 25 |
| Age group | | | |
| <24 years (%) | 49 1 | 0 | 49 1 |
| 24 years and over (%) | 32 8 | 18 1 | 50 9 |
| No years injecting | | | |
| <5 years (%) | 44 0 | 0 9 | 44 8 |
| ≥5 years (%) | 37 9 | 17 2 | 55 2 |
| Mean number of years injecting | 5 5 | 11 0 | 6 5 |
| **HIV risk behaviour** | | | |
| Mean injections (mth) | 63 | 86 | 67 |
| Sharing* | | | |
| Sharing within prev 3 mths(%) | 67 1 | 15 2 | 82 3 |
| Injecting but not sharing (%) | 16 5 | 1 3 | 17 7 |

* Data were missing for 38 subjects who had not injected in the previous 3 months

### A.3.3 Demographic characteristics by treatment centre

Demographic characteristics, recent drug use and syringe-sharing HIV risk behaviours by treatment centre are shown in Table A2

There were no significant differences in gender between the treatment centres

IVDUs who were recruited by the D T C were younger (mean age = 24) than those recruited by A L (mean age 31, t = -5 4, df =(94, 20), p< 0 0001) Significantly more IVDUs attending A L were 24 years of age and older (21 (100%)) than those being treated by the D T C (38 out of 95 (40%), $\chi^2$=24 8, df= 1, p< 0 0001)

Injectors attending AL also had longer injecting careers (mean = 11 years since first injection) than those attending the D T C (mean = 5 5 years, t = -4 6, df =(94,20), p< 0 0001) 51 of the IVDUs who attended the D T C (data missing for 1 subject) had less than 5 years experience of drug injecting, compared with only 1 of the 21 of those recruited by A L ($\chi^2$= 16 6, df =1, p<0 0001)

The treatment centres did not differ with respect to age of first needle use

### A.3.4 HIV risk behaviour

The study subjects were predominantly heterosexual 2 male and one female subjects were bisexual and one female subject was homosexual The proportions of women and men from each agency who had engaged in high-risk sexual and drug using practices are shown in Table A3

The mean age of first sexual intercourse for the total group was 15 7 years (S D 2 4, range 9-29 years, median 15) 70% of the total group had initiated sexual intercourse by age 16, and over half of the subjects in all agency/sex groups reported initiating sexual intercourse by age 15 51 7% of women (15 out of 29) and 52 3% of men (46 out of 88) had experienced intercourse by the time they were 15 years old There were no significant differences between the sexes, the recruiting centres, or between the different age groups regarding age of first sexual intercourse

In the group as a whole there were adequate data for 105 subjects regarding the total number of sexual partners in the previous year 46 (43 8%) of the respondents claimed to have had more than one sexual partner during the preceeding 12 months The mean number of sexual partners in the total group was 2 35 (S D 2 7, range 0-14) The median number of sexual partners was 1

There were no significant differences between the sexes, the recruiting centres, or the age groups regarding whether subjects had had more than one sexual partner in the previous year

There was a significant difference between those with a regular partner and others regarding whether subjects had had more than one sexual partner in the previous year Subjects who had a regular partner were more likely to have had at most one partner in the previous year than those who did not have a regular partner (66 7% compared to 42 2%, $\chi^2$=6 2, df =1, p=0 012)

The mean number of sexual partners for men was 2 5 (S D 2 8, range 0-14) The median number of sexual partners for men was 1 Men who did not have a regular partner were more likely than other men to have had more than one sexual partner in the previous year than those who had a regular partner (61 1% compared to 36 6%, $\chi^2$=4 6, df =1, p=0 032) This was not the case for women

The mean number of sexual partners for women was 1 9 (S D 2 1, range 0-8) The median number of sexual partners for women was 1 Women who had at most one sexual partner were more likely than other women to never use a condom (52 6% compared to 22 2%, p=0 056, Fisher's exact test)

The prevalence of sex with a non-IVDU was high in the group as a whole with 67% of subjects (n = 77, 2 missing values), reporting at least one partner who was a non-IVDU However, this differed widely between the sexes, the age-groups and between the recruiting centres Men were far more likely than women to have had a non-IVDU sexual partner in the previous year 77 9% of men (n = 67) compared to only 34 5% of women (n = 10) had a sexual partner who was a non-IVDU ($\chi^2$=18 5, df =1, p < 0 0001) Subjects recruited by the D T C were also more likely to have had a non-IVDU sexual partner in the previous year than were subjects recruited by A L 71 6% of D T C subjects compared to only 45% of A L subjects had a sexual partner who was a non-IVDU ($\chi^2$= 5 3, df =1, p = 0 022) Younger subjects too were more likely to have a non-IVDU sexual partner than were those from the older age group 75 4% of those under 24 had a non-IVDU sexual partner compared to 57 9% of those who were 24 years of age and older ($\chi^2$= 3 9, df =1, p = 0 047)

However when those who were aged 24 years and older were analysed separately, there was no significant differences between the recruiting centres regarding sex with a non-IVDU This suggests that the significant difference found in this regard in the total group may be explained by the fact that the D T C subjects were younger than those recruited by A L

On the other hand women tended to have more drug using sexual partners than men 75% of women had at least one IVDU sexual partner in the previous year compared to 41% of men (p = 0 014, Fisher's exact test) There was no significant difference between the recruiting centres regarding whether subjects had an IVDU sexual partner or not

The prevalence of anal sex was low in all agency/sex groups, with only 12 8% of the total group reporting it There were no significant differences between the sexes or between the centres regarding anal sex

Of the total group only 28 (23 9%) subjects reported that they always use condoms 53 (45 3%) reported sometimes using them and 36 (30 8%) never use them Men were less likely than women to always use condoms (22% of men compared to 31% of women, $\chi^2$= 7 1, df =2, p = 0 029) In the total group there were no significant differences between the recruiting centres, the age groups, the HIV status of subjects or between those who had a regular partner and others regarding condom use 29% of those with a regular sexual partner never use condoms, 46% sometimes use condoms and 25% always use condoms The corresponding proportions for those who do not have a regular partner are 33%, 45% and 22%

The use of condoms was also analysed by stratifying by number of sexual partners in the previous year and sexual contact with intravenous drug users There was no significant difference between those subjects who had had more than one partner in the previous year and others regarding condom use However a significantly higher proportion of women having had two or more sexual partners in the previous year reported the use of condoms, as compared with women with less than two partners (77 8% vs 47 4%, p = 0 056, Fishers exact test) In the total group no difference in condom use was seen between subjects who reported sexual contact with intravenous drug users and subjects who did not, nor between subjects who reported sexual contact with non-IVDUs and subjects who did not This also held true when the group was stratified by sex

There was a significant difference in condom use when measured against those who had been tested for HIV and those who had not been tested 26 7% of those who had been tested always use condoms compared to only 14 8% of those who had not been tested ($\chi^2$= 6 47, df =2, p = 0 039)

**Table A3. HIV risk behaviour, by sex**

| | No (%) | | |
|---|---|---|---|
| | D T C | Anna Liffey | Total |
| **Men** | 73 (83%) | 15 (17%) | 88 (100%) |
| Age at first intercourse | | | |
| ≤ 15 | 37 (42%) | 9 (10%) | 46 (52%) |
| > 15 | 36 (41%) | 6 ( 7%) | 42 (48%) |
| Total no partners in previous year (missing 11) | | | |
| ≤ 1 | 33 (43%) | 7 ( 9%) | 40 (52%) |
| > 1 | 32 (42%) | 5 ( 6%) | 37 (48%) |
| Sex with an IVDU in previous year (missing 9) | | | |
| No | 44 (56%) | 3 ( 9%) | 47 (60%) |
| Yes | 22 (28%) | 10 ( 6%) | 32 (40%) |
| Sex with a non IVDU in previous year (missing 2) | | | |
| No | 11 (13%) | 8 ( 9%) | 19 (22%) |
| Yes | 61 (71%) | 6 ( 7%) | 67 (78%) |
| **Women** | 23 (79%) | 6 (21%) | 29 (100%) |
| Age at first intercourse | | | |
| ≤ 15 | 12 (41%) | 3 (10%) | 15 (52%) |
| > 15 | 11 (38%) | 3 (10%) | 14 (48%) |
| Total no partners in previous year (missing 1) | | | |
| ≤ 1 | 15 (54%) | 4 (14%) | 19 (68%) |
| > 1 | 8 (29%) | 1 ( 4%) | 9 (32%) |
| Sex with an IVDU in previous year (missing 1) | | | |
| No | 4 (14%) | 3 (11%) | 7 (25%) |
| Yes | 19 (68%) | 2 ( 7%) | 21 (75%) |
| Sex with a non IVDU in previous year | | | |
| No | 16 (55%) | 3 (10%) | 19 (65%) |
| Yes | 7 (24%) | 3 (10%) | 10 (34%) |

### A.3.5 Injecting practices

90 6% of the IVDUs had injected drugs in the 12 months before interview and 67 5% had injected in the previous 3 months Intravenous drug users recruited by A L who had injected in the previous three months had a higher number of mean injections per month (94) than those in the D T C (59, t=-3 33, df = (12, 65), p=0 0013)

All subjects whether currently injecting or not were questioned about the number of times they injected when they were injecting Those recruited by A L had a higher number of mean injections per month (86) than those recruited by the D T C (63), (t=-2 43, df = (95, 20), p<0 017)

#### A.3.5.1 Sharing

Overall, 71 (60 7%) subjects had shared injecting equipment in the previous 6 months and 65 (55 6%) had shared in the previous 3 months There were no significant differences in needle-sharing risk behaviours by treatment centre, sex, age-group, or by the length of time that subjects were injecting

#### A.3.5.2 *Cleaning of injecting equipment*

The vast majority 93 (80 2%) of the total group reported that they always cleaned needles 21 (18 1%) said they sometimes cleaned and 2 reported that they never cleaned injecting equipment

However when questioned about the methods they employed in cleaning the equipment, only 60 (52 6%) subjects effectively cleaned the equipment

There were no significant differences in the cleaning of equipment or in the effectiveness of cleaning, between those who had shared in the previous 3 months and others, nor between those who had shared in the previous 6 months and others

Interestingly, while there was no significant difference between recruiting centres in the cleaning of equipment, they did differ regarding the effectiveness of cleaning Only 48% of those recruited by the D T C effectively cleaned injecting equipment compared to 71% of those recruited by A L ($\chi^2$= 3 65, df=1, p = 0 056)

This was also the case for the different age groups While belonging to a particular age group did not affect whether subjects cleaned equipment or not, it did influence the effectiveness of cleaning In the total group older subjects were more likely to effectively clean equipment Only 42% of those aged under 24 years effectively cleaned equipment compared to 62 5% of those aged 24 years and older ($\chi^2$= 4 7, df = 1, p = 0 03)

However when older subjects were taken separately, no significant difference was found between recruiting centres regarding the effective cleaning of equipment This suggests that the significant difference found with regard to the effective cleaning of equipment between the recruiting centres, in the total group can be explained by the difference in the age-groups between the two centres

### A.3.6 Testing for HIV

Table A4 shows that 90 of the 117 (77%) IVDUs in the total sample had been tested for HIV Rates of HIV testing were obviously significantly lower in IVDUs recruited by the D T C (69 out of 96, 71 9%) than those recruited by A L where all subjects had been tested and were seropositive This difference is an artificial one however, since A L purposely recruited seropositive clients

**Table A4. HIV testing history of IVDUs by treatment centre.**

| | Treatment centre | | |
|---|---|---|---|
| | D T C | Anna Liffey | Total |
| | n = 96 | n = 21 | n = 117 |
| **Tested** | | | |
| Yes | 69 (59%) | 21 (18%) | 90 (77%) |
| No | 27 (23%) | 00 (0%) | 27 (23%) |
| **Serostatus** | | | |
| Positive | 05 (6%) | 21 (23%) | 26 (29%) |
| Negative | 54 (60%) | 00 (0%) | 54 (60%) |
| Unknown | 10 (11%) | 00 (0%) | 10 (11%) |

Missing data testing history, 27 cases

### A.3.7 Characteristics of those who claimed to be HIV seropositive

Overall 26 (29%) were seropositive, 54 (60%) were seronegative and HIV status was unknown in 10 (11%) Considering the different bases employed in the recruitment of the two samples there were, of course, significant differences in HIV status by treatment centre 7% (5 out of 69) of IVDUs recruited in the D T C were HIV seropositive, whilst all 21 (100%) of those recruited by A L were HIV seropositive

The mean duration of time since diagnosis was 72 months, the range was from 3-116 months (S D 35 1) However with the exception of 2 individuals, all subjects had been diagnosed at least one year previously

The majority, 20 (76 9%) of those who were seropositive had a regular sexual partner, and 18 of the 20 (90%) had been with their regular partner for 4 years or more Subjects who were HIV seropositive were more likely to have a regular partner than other subjects who had been tested 76 9% of those who were seropositive had a regular partner compared to 50% who were seronegative and 40% whose serostatus was unknown ($\chi^2$= 6 4, df= 2, p=0 04)

12 (60%) of those seropositive subjects with a regular partner reported that their partner was an IVDU either at the time of the interview or in the past

9 of the 21 (45%) reported that their regular partner was also HIV seropositive

Those who reported being seropositive (N=26) were asked about their needle sharing and sexual activities since becoming seropositive

#### A.3.7.1 Sexual behaviour of subjects who reported being seropositive

In the following sections it should be remembered that the numbers of HIV seropositive subjects are small The study subjects were predominantly heterosexual 22 seropositive individuals (84 6%) were sexually active in the previous year, the majority, 16 (72 7% of those who were seropositive and sexually active) with one partner only

#### A.3.7.2 Condom use

Of those who were seropositive 10 (38 5%) claimed they used condoms always and 10 (38 5%) said they use them sometimes Although 6 (23 1%) of those who were seropositive claimed they never used condoms, only 3 of the 6 were sexually active in the previous year with a partner who was not

seropositive and one of the 3 was female whose sexual partner was female There were two sexually active individuals (7 7%) therefore, who did not use condoms who were likely to contribute to further HIV transmission

### A.3.7.3 Number of sexual partners

Since becoming HIV seropositive (n = 26), 9 (34 6%) claimed to have had fewer partners, 15 (57 7%) reported no change in the number of partners and 2 (7 7%) claimed to have had more partners Table A5 shows the number of sexual partners of HIV seropositive subjects, by IVDU status

**Table A5. Number of sexual partners by IVDU status (n = 26)**

| Number of sexual partners | IVDU | non-IVDU |
|---|---|---|
| 0 | 8 (35%) | 14 (58%) |
| 1 | 10 (43% | 9 (37%) |
| 2 | 2 (9%) | 0 ( 0%) |
| 3-9 | 2 (9%) | 1 ( 4%) |
| 10 or more | 1 (4%) | 0 ( 0%) |
| missing | 3 | 2 |

### A.3.7.4 Frequency of sexual activity

Since becoming HIV seropositive (n = 26), 17 subjects (65 4%) reported that their sexual activity was less frequent, 8 (30 8%) reported no change in the frequency of their sexual activity and 1 (3 8%) claimed that their sexual activity was more frequent

### A.3.7.5 Injecting behaviour of subjects who reported being seropositive

21 (80 8%) subjects claimed to have injected less often since becoming HIV seropositive 3 (11 5%) subjects said there was no change in their frequency of injecting and 2 (7 7%) said they inject more often since diagnosis of seropositive status

The average number of people shared with in a week when subjects were injecting, ranged from 0 to 48 with a mean of 2 9 and a standard deviation of 7 1 For females the mean was found to be 2 24 (Std Dev =2 65) and the

corresponding figure for males was 3 14 (Std Dev = 8 11) However this difference was not statistically significant

Despite being seropositive, 17 subjects (65 4%) admitted to having continued to share injecting equipment in the previous 6 months Of these, only one person said they limited sharing to one other person while 11 of the 17 (64 7%) had shared with more than one other person (data were missing for 5 subjects)

### A.3.7.6 HIV status: treatment centre comparisons by age and length of injecting career

Table A6 shows self reported HIV status by treatment centre and age All those who were HIV seropositive were 24 years of age or older Overall the HIV seropositive rate was therefore significantly higher in IVDUs aged 24 years and older (100%) than those aged < 24 years (0%, $\chi^2$=30 7, df= 2, p<0 0001) This also held true when D T C subjects were analysed separately (100%, compared to 0%, p= 0 009, Fisher's exact test)

**Table A6. Self-reported HIV status treatment centre comparisons by age group and length of drug-injecting career.**

| | Treatment centre | | |
|---|---|---|---|
| | D T C | Anna Liffey | Total |
| Age group in years (%) | | | |
| < 24 | 0 ( 0%) | 0 ( 0%) | 0 ( 0%) |
| ≥ 24 | 5 (19%) | 21 (81%) | 26 (100%) |
| No years injecting (%) | | | |
| < 5 | 1 (4%) | 1 (4%) | 2 ( 8%) |
| ≥ 5 | 4 (15%) | 20 (77%) | 24 (92%) |

Table A6 also shows the HIV seropositive rates by treatment centre and length of injecting career In the total sample of those who were tested for HIV seropositivity (n = 90, see table A4), subjects injecting for 5 or more years (n = 59), were more likely to be HIV seropositive than those injecting for less than 5 years (n = 31) (40 7% compared to 6 5%, $\chi^2$=11 7, df = 2, p=0 003)

## A.4 Discussion

Drug users recruited by D T C were younger and had shorter injecting careers than those recruited by Ana Liffey There was no difference in terms of sex, the majority being men Levels of recent equipment sharing were similar for both groups

Sexual risks for HIV infection were common in this population The use of condoms was not common among the subjects In fact, only 23 9% of them reported consistent use of condoms However, women who had more than one sexual partner in the previous year were more likely to report consistent condom use than other women

A **high** proportion of men reported sexual contact with a non-IVDU woman, indicating the potential for **widespread** heterosexual transmission of HIV to women from infected male drug users

Our data show that most IVDUs in our survey had been tested for HIV antibodies HIV seropositivity was highest in IVDUs recruited by A L but this can be explained by the different recruiting strategy employed by A L In the total group higher seropositivity was associated with older IVDUs (≥ 24 years) Higher seropositivity was also associated with IVDUs with longer injecting careers (5 years or more) However when subjects recruited by the D T C were analysed separately there was no significant difference in seropositivity between those with longer and shorter injecting careers, which is not surprising given the numbers involved

A number of recent papers have reported on risk behaviour for HIV infection among different groups of IVDUs and commented on changes in such behaviour as a result of AIDS awareness or HIV diagnosis (Hart et al , 1989, Robert et al , 1990, O'Mahony & Barry, 1992 (and references therein), Comiskey et al , 1993, Desenclos et al , 1993, Rhodes et al , 1993a, b) In particular Williams et al (1990) looked specifically at IVDUs receiving methadone maintenance and known to be seropositive (N = 48), and investigated whether they had altered their behaviour as a result of being infected They found that since diagnosis the cohort had made significant alterations in their at risk behaviour for HIV transmission Forty-two patients (88%) remained sexually active after diagnosis (the majority, 64%, with one partner) and 16 (38%) claimed they used condoms always However, **despite** this positive change, there **remained** a high level of at risk behaviour for further HIV transmission Despite being seropositive 63% of the Williams et al. survey

had **continued** to share injecting equipment (even if at a reduced risk level) and more than one third who remained sexually active, did **not** use condoms.

These results are very similar to those found in **our** HIV transmission survey described above. The similarity in the results of the two surveys suggests that they provide a reasonably accurate picture of the sexual and drug using behaviour of Dublin IVDUs who are **in contact with** a treatment centre. However, almost a third (31.6%) of IVDUs in our study were unaware of their antibody status, either because they had not sought testing at time of interview, or because they had not looked for the result once tested. This strongly indicates that only part of the problem is being assessed.

The probable levels of unreported HIV positivity in IVDU from the **D.T.C.**, consequent upon the fact that 38.5% had either not been tested or had not sought the result if tested, has important implications for epidemiological indicators of epidemic spread. Accurate information is necessary to plan and target effective prevention initiatives, to evaluate existing prevention initiatives and to allocate resources, including those for future patient care.

Knowledge of HIV-positive status may prompt changes in drug-injecting behaviour and other HIV risk behaviours, and may facilitate early diagnosis of treatable conditions, such as pulmonary tuberculosis and other opportunistic infections. Testing, irrespective of result, provides an opportunity to encourage change in HIV risk behaviour. Some studies suggest that knowledge of HIV positivity may encourage reduced risk behaviour (Desenclos & Papaevangelou, 1993).

The double-site sample discussed above included only drug users **in a treatment setting**. Consequently, data reported here reflect trends for only a proportion of all IVDUs in Dublin, and may not readily generalise to the large number of out-of-treatment IVDUs.

It is clear from the above that several sources of possible bias must be considered when interpreting these results. Recall and /or self-report bias may affect our conclusions on needle-sharing, frequency of injection and sexual behaviour. It is also possible that IVDUs in treatment may be more concerned about HIV risk behaviour, or may under-report what drug-treatment staff consider to be socially undesirable behaviour. This danger is less acute in the D.T.C. sample as 44.8% of this sample were drug free for at least one month and were questioned about their drug using behaviour retrospectively.

Our results emphasise that behavioural intervention programs targeted at IVDU in particular must focus equally on changes in risky sexual behaviours and drug-injection practices. The necessity of such a focus is emphasised by

evidence suggesting that drug-related behaviour change is more readily achieved and maintained than sex-related behaviour change In addition, the high prevalence of subjects in our study who had engaged in sexual intercourse by 15 years of age emphasises the importance of educating young people about safer sexual practices at an early age, before they become sexually active

The high rates of equipment sharing and the low rates of consistent condom use reported in this high-risk population also indicates the need for new and more effective strategies designed to promote safer drug usage and sexual activity among intravenous drug users

Further research is urgently needed for understanding and characterising the sexual behaviours in the populations currently at higher risk IVDUs and their partners This will aid the development of more effective and accessible intervention programs

# Appendix B

# Mathematica Program for Perturbation Method

☐Clear Functions and Parameter Set

```
Clear[Pm, Pf, Xm ,Xf, Ym, Yf, Am, Af, Xmt ,Xft, Ymt, Yft, Amt, Aft],
Clear[XmTemp ,XfTemp, YmTemp, YfTemp, AmTemp, AfTemp],
Clear[XmnTemp ,XfnTemp, YmnTemp, YfnTemp, AmnTemp, AfnTemp],

Clear[a, del, eps, Lm, Lf, mm, mf, tmax, Xm0, Xf0, Ym0, Yf0, Am0, Af0],

Pm[n_] .= Pm[n] = Xm[n] + Ym[n] + Am[n];
Pf[n_] := Pf[n] = Xf[n] + Yf[n] + Af[n];

(* dummy variables for integration up to fifth order*)
Clear [tau, tau0],
tau={t1,t2,t3,t4,t5},
```

☐Generate Series Procedure

```
Clear[GenSeries],
GenSeries[Xser_,n_] .= Module [{ans,t1},
        if [n<3,
                ans = Simplify[Xser],
                (* n>=3 simplifying takes too long *)
                ans = Collect [Xser, eps],
                ans = Coefficient [ans, eps, 0],
                ans = Together[ans],
                t2 = Numerator[ans],
                ans = Simplify[t2]/ Denominator [ans],],
                Return[ans],],
```

■Xm

```
Clear[Xmt, Xm, Xm0, XmTemp, XmnTemp],
Xmt[0] = Lm - mm Xm[0],
Xmt[n_] := Xmt[n] = 1/(eps^n *Pf[0]) (
        - Sum[eps^k Sum[Xmt[k-j] Pf[j], {j,0,k}], {k,0,n-1}] -
        eps^n Sum[Xmt[n-j] Pf[j], {j,1,n}] +
        Lm Sum[eps^k Pf[k], {k,0,n}] -
        mm Sum[eps^k Sum[Xm[k-j] Pf[j], {j,0,k}], {k,0,n}] -
        eps Sum[eps^k Sum[Xm[k-j] Yf[j], {j,0,k}], {k,0,n-1}] ),

(* Anlyatical Solution n=0*)
XmTemp[0] = z[t] /
        DSolve[{z'[t]==(Xmt[0] /  {Xm[0]->z[t]}),z[0]==Xm0},
                z[t],t] [[1]],

(* Exp[-mm t] Xm0 +
         Integrate [Exp[-mm(t-tau0)] Lm, {tau0,0,t}],*)

(* Numerical Solution n>0*)
XmnTemp[n_]  =  z[t] /
        NDSolve[{z'[t]==(Xmt[n] /  {Xm[n]->z[t]}) ,z[0]==0 0},
                z[t], {t,0 0,tmax}] [[1]],
```

## Xf

```
Clear[Xft, Xf, Xf0, XfTemp, XfnTemp],
Xft[0] = Lf - mf Xf[0],
Xft[n_] := Xft[n] = Xft[n] = 1/(eps^n *Pm[0]) (
        - Sum[eps^k Sum[Xft[k-j] Pm[j], {j,0,k}], {k,0,n-1}] -
        eps^n Sum[Xft[n-j] Pm[j], {j,1,n}] +
        Lf Sum[eps^k Pm[k], {k,0,n}] -
        mf Sum[eps^k Sum[Xf[k-j] Pm[j], {j,0,k}], {k,0,n}] -
        8 eps Sum[eps^k Sum[Xf[k-j] Ym[j], {j,0,k}], {k,0,n-1}] ),

(* Anlyatical Solution n=0 *)
XfTemp[0] = z[t] /
        DSolve[{z'[t]==(Xft[0] /. {Xf[0]->z[t]}) ,z[0]==Xf0},
                z[t], t] [[1]],

(* Exp[-mf t] Xf0 +
         Integrate [Exp[-mf(t-tau0)] Lf, {tau0,0,t}], *)

(* Numerical Solution n>0*)
XfnTemp[n_] := z[t] /
        NDSolve[{z'[t]==(Xft[n] /  {Xf[n]->z[t]}) ,z[0]==0 0},
                z[t], {t,0 0,tmax}] [[1]],
```

## Ym

```
Clear[Ymt, Ym, Ym0, YmTemp, YmnTemp],
Ymt[0] =  - (a+mm) Ym[0],
Ymt[n_]  = 1/(eps^n *Pf[0]) (
        - Sum[eps^k Sum[Ymt[k-j] Pf[j], {j,0,k}], {k,0,n-1}] -
        eps^n Sum[Ymt[n-j] Pf[j], {j,1,n}] -
        (a+mm) Sum[eps^k Sum[Ym[k-j] Pf[j], {j,0,k}], {k,0,n}] +
        eps Sum[eps^k Sum[Xm[k-j] Yf[j], {j,0,k}], {k,0,n-1}] ),

(* Anlyatical Solution n=0 *)
YmTemp[0] = Exp[-(a+mm) t] Ym0,

(* Numerical Solution n>0*)
YmnTemp[n_]  =  z[t] /
        NDSolve[{z'[t]==(Ymt[n] /  {Ym[n]->z[t]}) ,z[0]==0 0},
                z[t], {t,0 0,tmax}] [[1]],
```

## Yf

```
Clear[Yft, Yf, Yf0, YfTemp, YfnTemp],
Yft[0] = - (a+mf) Yf[0],
Yft[n_]  = Yft[n] = 1/(eps^n *Pm[0]) (
        - Sum[eps^k Sum[Yft[k-j] Pm[j], {j,0,k}], {k,0,n-1}] -
        eps^n Sum[Yft[n-j] Pm[j], {j,1,n}] -
        (a+mf) Sum[eps^k Sum[Yf[k-j] Pm[j], {j,0,k}], {k,0,n}] +
        8 eps Sum[eps^k Sum[Xf[k-j] Ym[j], {j,0,k}], {k,0,n-1}] );

(* Anyatical Solution n=0*)
YfTemp[0] = Exp[-(a+mf) t] Yf0 ,

(* Numerical Solution n>0*)
YfnTemp[n_] := z[t] /
        NDSolve[{z'[t]==(Yft[n] /  {Yf[n]->z[t]}) ,z[0]==0 0},
                z[t], {t,0.0,tmax}] [[1]];
```

## ■Am

```
Clear[Amt, Am, Am0, AmTemp, AmnTemp],
Amt[n_] = a Ym[n] - (del+mm) Am[n],

(* Anlyatıcal Solution n=0*)
AmTemp[0] = z[t] /
        DSolve[{z'[t]==(Amt[0] /  {Ym[0]->YmTemp[0], Am[0]->z[t]}) ,
                                   z[0]==Am0},  z[t], t] [[1]],

(*Exp[-(del+mm) t] Am0 + _
         Integrate [Exp[-(del+mm) (t-tau0)] * a *
                (Ym[0] /  {t->tau0}), {tau0,0,t}],*)

(* Numerical Solution n>0*)
AmnTemp[n_]  =  z[t] /.
        NDSolve[{z'[t]==(Amt[n] /  {Am[n]->z[t]}) ,z[0]==0 0},
                z[t], {t,0 0,tmax}] [[1]],
```

## ■Af

```
Clear[Aft, Af, Af0, AfTemp, AfnTemp],
Aft[n_] = a Yf[n] - (del+mf) Af[n],

(* Anlyatıcal Solutıon *)
AfTemp[0] = z[t] /
        DSolve[{z'[t]==(Aft[0] /  {Yf[0]->YfTemp[0], Af[0]->z[t]}) ,
                                  z[0]==Af0}, z[t], t] [[1]],

(* Exp[-(del+mf) t] Af0 +
         Integrate [Exp[-(del+mf) (t-tau0)] * a *
                (Yf[0] /  {t->tau0}), {tau0,0,t}], *)

(* Numerical Solution *)
AfnTemp[n_] .= AfnTemp[n] = z[t] /
        NDSolve[{z'[t]==(Aft[n] /  {Af[n]->z[t]}) ,z[0]==0 0},
                z[t], {t,0 0,tmax}] [[1]],
```

### ☐Calculate Series Expansions

```
(* 'remember' expansions up to order 3 *)
n=0,
Xmt[n]=GenSerıes[Xmt[n],n],     Xft[n]=GenSerıes[Xft[n],n],
Ymt[n]=GenSeries[Ymt[n],n],     Yft[n]=GenSeries[Yft[n],n],
Amt[n], Aft[n];

n=1,
Xmt[n]=GenSerıes[Xmt[n],n],     Xft[n]=GenSerıes[Xft[n],n],
Ymt[n]=GenSeries[Ymt[n],n],     Yft[n]=GenSeries[Yft[n],n],
Amt[n], Aft[n],

n=2,
Xmt[n]=GenSeries[Xmt[n],n],     Xft[n]=GenSerıes[Xft[n],n],
Ymt[n]=GenSerıes[Ymt[n],n],     Yft[n]=GenSeries[Yft[n],n],
Amt[n], Aft[n],

n=3;
Xmt[n]=GenSerıes[Xmt[n],n];     Xft[n]=GenSeries[Xft[n],n];
Ymt[n]=GenSerıes[Ymt[n],n],     Yft[n]=GenSeries[Yft[n],n],
Amt[n], Aft[n],
```

☐ Remember Series Expansions

**Zero order**

```
Xmt[0] = Lm - mm*Xm[0],

Xft[0] = Lf - mf*Xf[0],

Ymt[0] = -((a + mm)*Ym[0]),

Yft[0] = -((a + mf)*Yf[0]),

Amt[0] = -((del + mm)*Am[0]) + a*Ym[0],

Aft[0] = -((del + mf)*Af[0]) + a*Yf[0];
```

**First order**

```
Xmt[1] = -((mm*Af[0]*Xm[1] + mm*Xf[0]*Xm[1] + Xm[0]*Yf[0] + mm*Xm[1]*Yf[
    (Af[0] + Xf[0] + Yf[0])),

Xft[1] = -((mf*Am[0]*Xf[1] + mf*Xf[1]*Xm[0] + 8*Xf[0]*Ym[0] + mf*Xf[1]*Y
    (Am[0] + Xm[0] + Ym[0])),

Ymt[1] = (Xm[0]*Yf[0] - a*Af[0]*Ym[1] - mm*Af[0]*Ym[1] - a*Xf[0]*Ym[1] -
    mm*Xf[0]*Ym[1] - a*Yf[0]*Ym[1] - mm*Yf[0]*Ym[1])/
  (Af[0] + Xf[0] + Yf[0]),

Yft[1] = (-(a*Am[0]*Yf[1]) - mf*Am[0]*Yf[1] - a*Xm[0]*Yf[1] -
    mf*Xm[0]*Yf[1] + 8*Xf[0]*Ym[0] - a*Yf[1]*Ym[0] - mf*Yf[1]*Ym[0])/
  (Am[0] + Xm[0] + Ym[0]),

Amt[1] = -((del + mm)*Am[1]) + a*Ym[1],

Aft[1] = -((del + mf)*Af[1]) + a*Yf[1],
```

**Second order**

```
Xmt[2] = (-(mm*Af[0]^2*Xm[2]) - 2*mm*Af[0]*Xf[0]*Xm[2] - mm*Xf[0]^2*Xm[2
    Af[1]*Xm[0]*Yf[0] + Xf[1]*Xm[0]*Yf[0] - Af[0]*Xm[1]*Yf[0] -
    Xf[0]*Xm[1]*Yf[0] - 2*mm*Af[0]*Xm[2]*Yf[0] -
    2*mm*Xf[0]*Xm[2]*Yf[0] - Xm[1]*Yf[0]^2 - mm*Xm[2]*Yf[0]^2 -
    Af[0]*Xm[0]*Yf[1] - Xf[0]*Xm[0]*Yf[1])/(Af[0] + Xf[0] + Yf[0])^2,

Xft[2] = (-(mf*Am[0]^2*Xf[2]) - 2*mf*Am[0]*Xf[2]*Xm[0] - mf*Xf[2]*Xm[0]^
    8*Am[1]*Xf[0]*Ym[0] - 8*Am[0]*Xf[1]*Ym[0] -
    2*mf*Am[0]*Xf[2]*Ym[0] - 8*Xf[1]*Xm[0]*Ym[0] -
    2*mf*Xf[2]*Xm[0]*Ym[0] + 8*Xf[0]*Xm[1]*Ym[0] -
    8*Xf[1]*Ym[0]^2 - mf*Xf[2]*Ym[0]^2 - 8*Am[0]*Xf[0]*Ym[1] -
    8*Xf[0]*Xm[0]*Ym[1])/(Am[0] + Xm[0] + Ym[0])^2,

Ymt[2] = (-(Af[1]*Xm[0]*Yf[0]) - Xf[1]*Xm[0]*Yf[0] + Af[0]*Xm[1]*Yf[0] +
    Xf[0]*Xm[1]*Yf[0] + Xm[1]*Yf[0]^2 + Af[0]*Xm[0]*Yf[1] +
    Xf[0]*Xm[0]*Yf[1] - a*Af[0]^2*Ym[2] - mm*Af[0]^2*Ym[2] -
    2*a*Af[0]*Xf[0]*Ym[2] - 2*mm*Af[0]*Xf[0]*Ym[2] -
    a*Xf[0]^2*Ym[2] - mm*Xf[0]^2*Ym[2] - 2*a*Af[0]*Yf[0]*Ym[2] -
    2*mm*Af[0]*Yf[0]*Ym[2] - 2*a*Xf[0]*Yf[0]*Ym[2] -
    2*mm*Xf[0]*Yf[0]*Ym[2] - a*Yf[0]^2*Ym[2] - mm*Yf[0]^2*Ym[2])/
  (Af[0] + Xf[0] + Yf[0])^2,

Yft[2] = (-(a*Am[0]^2*Yf[2]) - mf*Am[0]^2*Yf[2] - 2*a*Am[0]*Xm[0]*Yf[2]
    2*mf*Am[0]*Xm[0]*Yf[2] - a*Xm[0]^2*Yf[2] - mf*Xm[0]^2*Yf[2] -
    8*Am[1]*Xf[0]*Ym[0] + 8*Am[0]*Xf[1]*Ym[0] +
    8*Xf[1]*Xm[0]*Ym[0] - 8*Xf[0]*Xm[1]*Ym[0] -
    2*a*Am[0]*Yf[2]*Ym[0] - 2*mf*Am[0]*Yf[2]*Ym[0] -
    2*a*Xm[0]*Yf[2]*Ym[0] - 2*mf*Xm[0]*Yf[2]*Ym[0] +
    8*Xf[1]*Ym[0]^2 - a*Yf[2]*Ym[0]^2 - mf*Yf[2]*Ym[0]^2 +
    8*Am[0]*Xf[0]*Ym[1] + 8*Xf[0]*Xm[0]*Ym[1])/
  (Am[0] + Xm[0] + Ym[0])^2,

Amt[2] = -((del + mm)*Am[2]) + a*Ym[2],

Aft[2] = -((del + mf)*Af[2]) + a*Yf[2],
```

☐Parameter Set 1

```
        a = 0 1,
        del = 0 6329,
        eps = 0 0104,
        Lm = 9577.0,
        Lf = 9568.0,
        mm = 0 04;
        mf = 0 04,

(* initial conditions *)
        Xm0 = 214257 0;
        Xf0 = 223764 0,
        Ym0 = 1 83691,
        Yf0 = 59.0501,
        Am0 = 0 146069;
        Af0 = 5.01905,

(* maximum time interval *)
        tmax = 30.0,
```

☐Zero order - Anlyatical

```
(* anlyatical *)
n=0,
Xm[n] = XmTemp[n],      Xf[n] = XfTemp[n],
Ym[n] = YmTemp[n];      Yf[n] = YfTemp[n],
Am[n] = AmTemp[n],      Af[n] = AfTemp[n],
```

☐First order - Numerical

```
(* numerical *)
n=1,
Xm[n] = XmnTemp[n],     Xf[n] = XfnTemp[n],
Ym[n] = YmnTemp[n],     Yf[n] = YfnTemp[n],
Am[n] = AmnTemp[n],     Af[n] = AfnTemp[n],
```

☐Second order - Numerical

```
(* numerical *)
n=2,
Xm[n] = XmnTemp[n],     Xf[n] = XfnTemp[n],
Ym[n] = YmnTemp[n],     Yf[n] = YfnTemp[n],
Am[n] = AmnTemp[n],     Af[n] = AfnTemp[n],
```

# Appendix C

# Numerical Analysis

The NAG library routine D02EBF was used to solve the system of non-linear differential equations described in Chapter 6 The fortran program which calls on the NAG routine follows

```
C     IVDU/HETERO HIV TRANSMISSION MODEL SOLVER, D02EBF
C     Ni LOW, DUBL POP ESTIMATES, Pi MIX WITH IV, 1980 TO
      2005
C
      IMPLICIT NONE
C     SCALARS IN COMMON
      REAL*8 H, XEND
      INTEGER I
C
C     LOCAL SCALARS
      REAL*8 TOL, X
      INTEGER IFAIL, IR, IW, J, MPED, N, NOUT
C
C     LOCAL ARRAYS
      REAL*8 W(16,498), Y(16)
C
C     SUBROUTINE REFERENCES
C     D02EBF
C
      EXTERNAL FCN, OUT, PEDERV
      COMMON XEND, H, I
      DATA NOUT /2/
      WRITE (NOUT, 99996)
      WRITE (NOUT, 99994)
      N=16
```

```
      IW=498
      MPED=0
      IR=0
      DO 20 J=10,12
      TOL=10 0D0**(-J)
      WRITE (NOUT,99999) TOL
      WRITE (NOUT,99998)
      X=0 0D0
      XEND=25 0D0
      Y(1)=2999 0D0
      Y(2)=1000 0D0
      Y(3)=205363 0D0
      Y(4)=218663 0D0
      Y(5)=1 0D0
      Y(6)=0 0D0
      Y(7)=0.0D0
      Y(8)=0 0D0
      Y(9)=0 0D0
      Y(10)=0 0D0
      Y(11)=0 0D0
      Y(12)=0 0D0
      Y(13)=3000 0D0
      Y(14)=1000 0D0
      Y(15)=205363 0D0
      Y(16)=218663 0D0
      H=1 0D0
      I=24
      IFAIL=0
      CALL D02EBF(X, XEND, N, Y, TOL, IR, FCN, MPED, PEDERV,
     +    OUT, W, IW, IFAIL)
      WRITE (NOUT,99997) IFAIL
      IF (TOL LT 0 0D0) WRITE (NOUT, 99995)
 20   CONTINUE
      STOP
C
99999 FORMAT (1X,'CALCULATION WITH TOL=', 1PD11 4)
99998 FORMAT (1X,'X AND SOLUTION AT EQUALLY SPACED
      POINTS')
```

```
99997  FORMAT (1X,'IFAIL=', I2)
99996  FORMAT (4(1X/),1X,'D02EBF HIVSYS2 PROGRAM RESULTS',/)
99995  FORMAT (1X,'RANGE TOO SHORT FOR TOL')
99994  FORMAT (1X,'CALCULATING JACOBIAN INTERNALLY')
C
       END
C
       SUBROUTINE FCN(T, Y, F)
C
       IMPLICIT NONE
C      SCALAR ARGUMENTS
       REAL*8 T
C
C      ARRAY ARGUMENTS
       REAL*8 F(16), Y(16)
C
 REAL*8BETA12,BETA14,BETA21,BETA23,BETA32,BETA34,BETA41,
 BETA43,
+      BETAHT,N1,N2,C12,C14,C21,C23,C32,C34,C41,C43,
+      LAMDA1,LAMDA2,LAMDA3,LAMDA4,MU1,MU2,MU3,MU4,GA,
+      ALPHA,D
C
       BETA12=0 007D0
       BETA14=0 007D0
       BETA32=0 007D0
       BETA34=0 0054D0
       BETA21=0 1015D0
       BETA23=0 1015D0
       BETA41=0 1015D0
       BETA43=0 0783D0
       BETAHT=0 19D0
       N1=6 280D0
       N2=4 48D0
       C12=0 72D0
       C14=1 76D0
       C21=1 29D0
       C23=0 59D0
       C32=0 0046D0
```

```
      C34=1 9254D0
      C41=0 0148D0
      C43=1 1152D0
      LAMDA1=396 0D0
      LAMDA2=132 0D0
      LAMDA3=9577 0D0
      LAMDA4=9568 0D0
      MU1=0 15D0
      MU2=0 15D0
      MU3=0 0333D0
      MU4=0 0333D0
      GA=0 007D0
      ALPHA=0 1D0
      D=0 6329D0
      F(1)=LAMDA1-N1*BETAHT*Y(1)*(Y(5)+Y(6))/(Y(13)+Y(14))
     +     -C12*BETA12*Y(1)*Y(6)/Y(14)-C14*BETA14*Y(1)*Y(8)/Y(16)
     +     -(MU1+GA)*Y(1)
      F(2)= LAMDA2-N2*BETAHT*Y(2)*(Y(5)+Y(6))/(Y(13)+Y(14))
     +     -C21*BETA21*Y(2)*Y(5)/Y(13)-C23*BETA23*Y(2)*Y(7)/Y(15)
     +     -(MU2+GA)*Y(2)
      F(3)=LAMDA3-C32*BETA32*Y(3)*Y(6)/Y(14)
     +     -C34*BETA34*Y(3)*Y(8)/Y(16)
     +     -(MU3+GA)*Y(3)
      F(4)=LAMDA4-C41*BETA41*Y(4)*Y(5)/Y(13)
     +     -C43*BETA43*Y(4)*Y(7)/Y(15)
     +     -(MU4+GA)*Y(4)
C
      F(5)=N1*BETAHT*Y(1)*(Y(5)+Y(6))/(Y(13)+Y(14))
     +     +C12*BETA12*Y(1)*Y(6)/Y(14)+C14*BETA14*Y(1)*Y(8)/Y(16)
     +     -(MU1+GA+ALPHA)*Y(5)
      F(6)=N2*BETAHT*Y(2)*(Y(5)+Y(6))/(Y(13)+Y(14))
     +     +C21*BETA21*Y(2)*Y(5)/Y(13)+C23*BETA23*Y(2)*Y(7)/Y(15)
     +      -(MU2+GA+ALPHA)*Y(6)
      F(7)=C32*BETA32*Y(3)*Y(6)/Y(14)
     +     +C34*BETA34*Y(3)*Y(8)/Y(16)
     +     -(MU3+GA+ALPHA)*Y(7)
      F(8)=C41*BETA41*Y(4)*Y(5)/Y(13)
     +     +C43*BETA43*Y(4)*Y(7)/Y(15)
```

```
+       -(MU4+GA+ALPHA)*Y(8)
C
        F(9)=ALPHA*Y(5)-(D+GA)*Y(9)
        F(10)=ALPHA*Y(6)-(D+GA)*Y(10)
        F(11)=ALPHA*Y(7)-(D+GA)*Y(11)
        F(12)=ALPHA*Y(8)-(D+GA)*Y(12)
C
        F(13)=F(1)+F(5)+F(9)
        F(14)=F(2)+F(6)+F(10)
        F(15)=F(3)+F(7)+F(11)
        F(16)=F(4)+F(8)+F(12)
        RETURN
        END
C
        SUBROUTINE PEDERV(X, Y, PW)
C       CAN OMIT THIS SECTION
        RETURN
        END
C
        SUBROUTINE OUT(X, Y)
        IMPLICIT NONE
C       SCALAR ARGUMENTS
        REAL*8 X
C       ARRAY ARGUMENTS
        REAL*8 Y(16)
C       SCALARS IN COMMON
        REAL*8 H, XEND
        INTEGER I
C       LOCAL SCALARS
        INTEGER J, NOUT
        COMMON XEND, H, I
        DATA NOUT /2/
        WRITE (NOUT,99999) X, (Y(J), J=1,16)
        X=XEND - FLOAT(I)*H
        I=I-1
        RETURN
99999   FORMAT (1X,1PD11 4,/,4(4(2X,1PE12 5)/))
        END
```

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