Mathematical Models For The Transmission Dynamics of HIV and its Progression to AIDS in Ireland.

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Submitted in fulfillment of a PhD degree

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July 1991

Declaration

I declare that this dissertation is entirely my own work and that it has not been submitted to any other University as an exercise for a degree

Acknowledgements

I wish to express my warmest and sincerest thanks to my supervisors, Professor Alastair Wood and Ms Heather Ruskin for all their encouragement and support during my period of research at Dublin City University Both were a constant source of helpful discussion and inspiration when progress and the way forward was not always clear to me

I would like to thank Dr Fiona Mulcahy and her staff at The Genito Urinary Clinic at St James Hospital Dublin for their useful discussions and co-operation with the administration of the HIV survey I would also like to thank Dr Louise Pomeroy formerly of St James Hospital for administering the pilot HIV survey I would like to thank Dr James Walsh, AIDS Co-ordinator at The Department of Health and Professor Irene Hillary at The Virus Reference Laboratory, University College Dublin, the former for supplying data on AIDS cases and deaths in Ireland and the latter for data on the numbers testing HIV positive In addition I would like to thank Di Valerie Isham for useful discussions on Chapter 3, the Society of Actuaries in Ireland, AIDS Working Party, Doctors Zachary and Howard Johnson, Dr Derek Freidman and Fr Paul Lavel all of whom gave of their time when I first started researching AIDS in Ireland

Finally I wish my fellow research students, Fiona, Colm, Pauline, Stephen, Lansen, Aisling (honorary research student!) and the staff of the School of Mathematical Sciences well and thank each of them for their many helpful suggestions and kindnesses

This research would not have been possible without generous financial support from The AIDS Fund and The Health Research Board

For Peter,
friend, soulmate and husband For listening, supporting and loving and for my family whom I love very much

Abstract

Despite advances in understanding the basic biology of HIV the aetiological agent of AIDS, medical, public health and health education planning is plagued by uncertainties Mathematical models of the dynamics of HIV transmission and its progression to AIDS can clarify what data must be collected in order to predict future prevalence, make predictions about the likely effect of future intervention policies and provide predictions for several decades ahead The motivation of this research is to provide reliable estimates of the incidence of HIV infection and AIDS in the Irish population

In Chapters 1 and 2 we discuss the background to the disease in Ireland and the role of mathematical modelling in the spread AIDS From this we show where key epidemiological data is lacking and how models to date have concentrated on the spread of the disease within the homosexual population In Chapter 3 we describe the adjustment of the number of AIDS cases to allow for reporting delays Subsequently we consider the solution of the integral equation models generated by the back-projection method for the adjusted AIDS cases In Chapter 4 we improve upon the estimates of the incidence of HIV infection found in Chapter 3 by evaluating the integral arising in back-projection, in terms of a gamma function plus a remainder in the form of a series in t We also provide error bounds for the remainder This new solution allows us to predict new and more reliable estimates of the level of HIV infection in Ireland

In Chapter 5 we provide estimates of the minimum number of deaths from AIDS, based on the number of AIDS cases known to the Department of Health and the distribution of the length of survival times after the onset of AIDS

The results of a HIV transmission survey are presented in Chapter 6 These provide detailed information on the habits and behaviour of those at risk of HIV infection and allow us to derive preliminary model parameters Finally in Chapter 7 we develop and implement a nonlinear deterministic differential equation model for the spread of HIV and its progression to AIDS in the Irish IVDU and homosexual populations We examine the effects of likely intervention policies on the extent and spread of the disease and we make recommendations based on our thesis findings

Contents

Chapter 1

AIDS in Ireland.

'The AIDS epidemic is considered the most serious epidemic of the last 50 years The word epidemic conjures up a picture of the Black Death sweeping across Europe in the 14th century ' *Science, 21st November 1986*
'AIDS Depressing news from Paris ' *Nature, 3rd July 1986*
'Grim Projections for AIDS Epidemic By 1991, some 270,000 people in the United States will have AIDS or will have died from the disease, how many others will be infected is uncertain, ' *Science, 27th June 1986*
'AIDS - Ireland moves into European second division ' *Irish Medical Times, 1st May 1989*

1.1 Introduction

The Director of The AIDS Program, at The Centres for Disease Control (CDC) Atlanta, has stated that the first cases of acquired immune deficiency syndrome (AIDS) were reported in the U S A in mid 1981, J W Curran et al (1985) [17] The initial occurrence of the syndrome among homosexual men and intravenous drug users suggested a transmissible agent as the cause The transmissible hypothesis became more widely accepted by early 1983, with the well documented occurrence of the syndrome in persons with haemophilia and recipients of blood transfusions During the next year a retrovirus variously termed lymphadenopathy-associated virus (LAV), human T-lymphotropic virus type III (HTLV-III), or AIDS-associated retovirus (ARV) was isolated and shown to be the cause of AIDS

Despite these considerable advances in understanding the basic biology of the human immuno-deficiency virus, the aetiological agent of AIDS, we can see from the cross section of quotes above that medical, public health and health education planning continues to be plagued by uncertainties There remain many questions of an epidemiological nature to be answered The questions to be addressed include

How many people are HIV positive now, or will become positive?
Will the proportion HIV positive be the same in A) the total population, B) homosexual and C) drug users?
How many HIV positives will develop full blown AIDS and how soon?
How will this proportion and rate of development be affected by therapy with new drugs?
Will reporting delays play an important role in data collection?

How many deaths can we expect from AIDS over the next few years?
How widespread and prevalent is AIDS at present?

The objective of this thesis is to provide some of the answers to these questions within the Irish situation To achieve this aim we implement and modify internationally recognised mathematical models of mathematicians and statisticians in the U K and U S A

An obvious way to predict the future course of any epidemic is to extrapolate figures from the immediate past Such empirical predictions are useful only up to two or three years into the future, after which they become too imprecise In the medium term, mathematical models of the dynamics of HIV infection and its progression to AIDS can facilitate the indirect assessment of the essential epidemiological parameters, clarify what data must be collected in order to predict future prevalence and make predictions about the likely effect of alternative intervention policies These models can provide predictions for several decades ahead

In order to model any situation be it epidemiological or otherwise, one must first have a thorough and in depth knowledge of the phenomena to be modelled One must know the crucial aspects of the problem and its essential parameters It is also important to have a global picture of the problem and to remind oneself regularly of the aims and objectives It is all too easy to become engrossed in detail and lose sight of the objectives In our next section we provide in detail a global picture of HIV and AIDS in Ireland

1 2 The Irish Situation

In this section we aim to provide a global view of AIDS in Ireland We shall compare the spread of the disease with other western European and African countries We shall see how the pattern of spread in Ireland is very different to that of our closest European partner, Britain and our trans-atlantic partner, the United States We shall provide a detailed look at the distribution of cases of the HIV virus in Ireland and finally we shall discuss the difficulties associated with data collection in Ireland and how these affect attempts at modelling

P A Sato, J Chin and J M Mann (1989) [46] review the global epidemiology and statistics of AIDS and HIV infection They discuss distinctive global epidemiological patterns as identified by WHO Three main patterns have emerged They are as follows,

- **Pattern I**
  - Extensive spread from the late 1970's to the early 1980's
  - Most cases in homosexual/bisexual men and urban intravenous drug users
  - Only small percentage of infections heterosexually transmitted
  - Transmission via blood/blood products largely under control
  - Male female ratio about 10 1, thus paediatric AIDS uncommon
  - Transmission through inadequately sterilised needles and syringes not a significant mode of spread except among intravenous drug users

- Overall HIV prevalence is < 1% but may exceed 50% in groups at high risk for infection

- **Pattern II**

  - Extensive spread beginning from the late 1970's to the early 1980's
  - Most cases among heterosexual men and women
  - Transmission via contaminated blood/blood products remains significant in many of these countries
  - Transmission via inadequately sterilised needles and syringes although small, remains of concern
  - National prevalence of HIV infections can exceed 1%, in some urban areas up to 25% of those aged 15-49 years are infected

- **Pattern III**

  - HIV first introduced in the early to mid 1980's
  - Only a small number of AIDS cases reported
  - Cases recorded among homosexuals, bisexuals, heterosexuals intravenous drug users, transmission through blood/blood products has also occurred
  - Cases mostly in people who have travelled to higher prevalence areas, also in people exposed to individuals who have been to such areas

Pattern I areas are primarily comprised of western industrialised countries In some pattern I areas, HIV infection continues to increase in the most socially and economically vulnerable segments of society Pattern II areas are comprised of sub-Saharan Africa and parts of the Caribbean Here transmission remains predominantly heterosexual and the prevalence of HIV infection continues to rise Pattern III regions are characterised epidemiologically by the recent onset of the HIV/AIDS pandemic In consequence most countries that exhibit this pattern have not as yet shown predominant modes of transmission, this is however slowly changing

Ireland is classified as a Pattern I country, yet the first cases of AIDS in Ireland were not identified until 1981 We shall also see that paediatric AIDS is not uncommon compared with other European countries This is a direct result of the male female ratio of HIV cases Table 1 1 summarises this ratio for 1985, when testing first started in Ireland to the year 1989 In this table figures for males include, homosexuals, bisexuals, intravenous drug users and haemophiliacs Females include intravenous drug users only As information on the sex of those classified as 'others' (representing 7% of the total HIV positive at the end of 1989) was not available, they are not included in the table

Table 1 1
Male Female ratio of HIV cases

Year	Numbers	Ratio
1985	251 48	5 2 1
1986	412 75	5 5 1
1987	490 93	5 3 1
1988	545 110	5 0 1
1989	623 125	5 0 1

We see from Table 1 1 that the male female ratio of HIV infections is well below that estimated for pattern I countries This is largely explained by the following table, which shows the distribution of known cases of the virus as of December 1989

Table 1 2

Distribution of known HIV cases to the end of December 1989

Risk Group	Number Positive	% of Total Cases
I V D U		
Male	390	42 86
Female	125	13 74
Sex Unknown	5	0 55
Total I V D U	520	57 15
Babies	63	6 92
Homo/Bisexual	121	13 30
Haemophiliac	112	12 30
Blood Donors	15	1 65
Prisoners	12	1 32
Hetero/Unspecified	67	7 36
Total Cases	910	100 00

We see from the table above that there were a total of 910 known cases of the HIV virus in Ireland at the end of 1989, 57 15% of which were identified in the intravenous drug using group, while the homosexual and bisexual group represents only 13 30% of all cases This is a direct contradiction of the WHO Pattern I countries description In addition, we note that paediatric cases comprise almost 7% of the total identified

If we examine the distribution of AIDS cases at the same time we see that the total number of AIDS cases amongst the I V drug users is lower than that of male homosexual and bisexuals This is because the first cases of AIDS in Ireland were identified in the homosexual/bisexual group in 1981 The first case of AIDS in an I V D U was not identified until the second half of 1985 It is interesting to note that the first paediatric case also appeared at this time The distribution of reported AIDS cases is given in Table 1 3 below

Table 1 3

Distribution of known AIDS cases to the end of December 1989

Risk Group	Number of Cases	% of Total Cases
I V D U	41	33 06
Homo/Bisexual	48	38 71
Homo/Bi and IVDU	7	5 65
Haemophiliac	16	12 90
Hetero Contact	4	3 23
Paediatric	5	4 03
Other/Unspecified	3	2 42
Total Cases	124	100 00

Given the distribution of both HIV and AIDS cases in Ireland and the fact that

first cases were identified relatively late it may be prudent to describe a specific pattern of spread for the Irish situation In addition within Ireland, homosexuality, abortion and the sale of condoms to those under 18 years of age is illegal The Irish situation may then be summarised as follows

- **Irish Pattern**
  - Spread early to mid 1980's
  - Majority of cases amongst male and female Dublin city I V D U
  - Few cases heterosexually spread though this is increasing
  - Paediatric cases common and increasing
  - Male to female ratio approximately 5 1
  - Transmission via blood/sterilised needles nil excluding early transmission amongst haemophiliacs

Now that we have examined the Irish situation in detail we are in a position to begin to consider the modelling of the spread of HIV infection and AIDS in Ireland We are also aware of the difficulties that this will involve due to the sensitivity of the data and the lack of key data on the life-styles of the Irish IVDU's and homosexuals

In Chapter 2 we begin the modelling process by a careful examination of the models currently in the literature We begin with the preliminary compartment models of Anderson, Medley, May and Johnson (1986) [5], then we look at the further developments by Blythe and Anderson (1988) [9], and finally we look at the review of current models by Isham (1988a) [26] In later chapters we shall also refer to models by Dietz (1988) [18]

In Chapter 3 we model the probability distribution of the reporting delay, based on the work of Brookmeyer and Damiano (1989) [10] Reporting of diagnosed AIDS cases is frequently subject to considerable time lag This reporting delay (or difference between date of diagnosis and entry in national AIDS records) has important implications both for the provision of resources and for modelling the progression of the disease In Chapter 3 we also make preliminary estimates of the incidence of HIV infection in Ireland using the back projection method and some new forms for the growth in AIDS cases, $a(t)$ Knowledge of the distribution of the incubation period enables us to work forwards and backwards, i e to predict future AIDS cases from those currently HIV positive and, alternatively, to use current adjusted figures for AIDS cases to derive estimates for those previously infected with the HIV virus This alternative use of the incubation probability distribution is known as 'back-projection' We show how results derived depend upon, not only the choice of incubation period chosen but also the form of $a(t)$

In Chapter 4 we extend this work and improve on the estimates provided in Chapter 3, by the use of the exact incubation distribution as fitted by Anderson and Medley (1988) [4] We show how the integral equation model can be changed to an Abel integral equation, the solution of which is given in terms of the gamma function plus a remainder This new solution allows us to predict new and more reliable estimates of the level of HIV infection in the Irish population

In Chapter 5 we provide estimates of the number of deaths each year and prevalence of AIDS within the Irish population Given estimates for the number of AIDS cases in Ireland after adjustment for reporting delays, we can provide estimates for the likely number of deaths arising from these AIDS cases based on a particular choice of the survival function as fitted by Cox (1988) [16] and Reeves and Overton

(1988) [43] In addition estimates for the prevalence of AIDS in Ireland are provided based on the results for deaths

In Chapter 6 we discuss the results from a comprehensive behavioural survey of HIV positive patients from the various risk groups The survey was administered at the primary Dublin Genito-Urinary Clinic at St James Hospital The survey provides us with an in-depth look at the life-style and behaviour of HIV positive patients From the survey we shall also estimate the parameters required for the transmission model in Chapter 7

Finally in Chapter 7 we provide preliminary estimates of the model parameters, we also develop our transmission models and describe the results obtained We provide predictions on the spread of the HIV virus and AIDS in the Irish IVDU population Current models concentrate on the progression of the disease within the homosexual population We develop a model centred on the male and female drug using populations, which, as we have seen earlier, comprise the main route of transmission in Ireland Our results describe the changes in the susceptible, HIV infected and AIDS IVDU and homosexual populations

We conclude with our results and we make recommendations to both mathematicians and those concerned with public health on future research needs based on the findings of our thesis

Chapter 2

Modelling The Transmission Dynamics of HIV and its Progression to AIDS.

2.1 Introduction

Mathematical models of epidemics have a long and varied history First recorded accounts of epidemics go back as far as the ancient Greeks of approximately 400 BC Hippocrates (459 - 377 BC) in his essay on 'Airs, Waters and Localities' wrote that ones temperament, personal habits and environment were important factors in the cause and spread of epidemics In the light of the current AIDS epidemic, many would say that his words still ring true

In recent times Kermack and McKendrick (1927) [28] have provided more detailed and elaborate studies of infectious diseases N T J Bailey (1957) [7] provides one of the first comprehensive mathematical studies of infectious diseases and of host-vector and venereal disease models The monograph by Hethcote and Yorke (1984) [24] gives a very good survey of models used for the spread and control of gonorrhea In the U S A it is believed that more than 2 million people contract gonorrhea annually Finally Murray (1989) [37] discusses modelling venereal diseases in general

In this chapter we shall first, critically discuss some general models for the spread of the HIV virus and its progression to AIDS We shall then move on to examine a more comprehensive model as described by Blythe and Anderson (1988) [9] Finally we shall comment on the relevance of these models within the Irish context

2.2 Preliminary Models

Some of the most comprehensive models to date are proposed by Anderson(1988) [2], Bailey(1988) [6] and Isham (1988a) [26] Anderson proposes a simple deterministic model representing a closed male homosexual population of size N This model consists of three compartments, the susceptible, denoted by X, infectious and diseased (AIDS), denoted by Y and A respectively This is a closed community with no recruitments of susceptibles and no mortality other than those deaths from the disease AIDS We have

$$\frac{dX}{dt} = -\lambda X$$

$$\begin{aligned} \frac{dY}{dt} &= \lambda X - vY \\ \frac{dA}{dt} &= vY - \alpha A \\ \frac{dN}{dt} &= -\alpha A \end{aligned} \tag{2 1}$$

with the following definitions,
λ is the per capita force of infection, $\lambda = \beta cY/N$,
β is the probability of infecting a susceptible partner,
c is the average number of sexual partners per unit time,
D is the average duration of stay in Y, $v = 1/D$ defines the rate of leaving the infected class Y to join the AIDS class A and
α is the rate of mortality in the AIDS class

HIV will persist once introduced into the community provided $R_0 \geq 1$ where R_0 defines the average number of secondary cases of infection generated by one primary case in a totally susceptible community For the model described above $R_0 = \beta cD$ with the assumption that infectious individuals are infectious throughout their stay in the Y class That is, the model assumes that the incubation period is the same as the infectious period

In the above it was assumed that individuals infected had constant infectivity throughout the long incubation period Recent studies invalidate this assumption Anderson models for one hypothesis, the hypothesis that there are 2 phases of peak infectiousness In the intervening period between the peaks infectiousness may be very low or zero With this assumption Anderson constructs the following model, which is similar to the simple model described earlier but with extra compartments given by Y_1, Y_2 and Y_3, corresponding to the three phases of infectiousness described above We have

$$\begin{aligned} \frac{dY_1}{dt} &= \lambda X - v_0 Y_1 \\ \frac{dY_2}{dt} &= v_0 Y_1 - sY_2 \\ \frac{dY_3}{dt} &= sY_2 - v_1 Y_3 \end{aligned} \tag{2 2}$$

with

$$\frac{dA}{dt} = v_1 Y_3 - \alpha A \tag{2 3}$$

In the first phase the probability of infecting a susceptible partner is β_0 In the second phase one is non infectious and in the third phase probability of infecting a susceptible partner is β_1 In the above model we have

$$\lambda = c(\beta_0 Y_1 + \beta_1 Y_3)/N, \tag{2 4}$$

where

$$N = X + Y_1 + Y_2 + Y_3 + A \tag{2 5}$$

and c is the average number of sexual partners

In summary Anderson says that the early exponential phase of the epidemic depends mainly on the first episode of infectiousness However both episodes are important in setting saturation levels later in the epidemic

Isham (1988a) [26] reviews some of the mathematical models currently in use In addition she also discusses the use of a deterministic model as opposed to a stochastic one She says that, in general, for large populations, once the disease is established, the deterministic model should give solutions that are approximately valid In this paper Isham first discusses a simple model for the spread of HIV within a closed male homosexual community She then moves on to discuss a model which incorporates two classes, those who do and those who do not develop AIDS Finally she produces a model which involves heterogeneity in sexual activity

With a heterogeneous model the early exponential increase in the incidence of seropositivity or of AIDS is expected to be rapidly replaced by a more slowly increasing function In the initial period the rapid spread of infection is through the highly active individuals but most of the subsequent infections will be from the less active individuals amongst whom the epidemic will progress at a slower rate An important point to note at this stage is that the slowing up in the rate of increase of the incidence is an inevitable consequence of heterogeneity and not a consequence of people changing their behaviour Thus in a highly promiscuous homosexual community it may be reasonable to approximate the transmission probability per partner by a constant but it is less likely to be appropriate for a population where long lasting partnerships are common This should be remembered in the context of the Irish male homosexual population where, due to legislation, homosexuals tend to have fewer partners

For transmission between heterosexuals Isham complicates her model further since there are now 2 groups of individuals with the infectives in one group spreading the infection to the susceptibles in the other Isham denotes the numbers of female susceptibles and infectives by $x^f(t), y^f(t)$ with $x^m(t), y^m(t)$ being the corresponding quantities for males In a 2 group analogue of the simple homogeneous mixing model the quantities satisfy the following

$$\begin{aligned}
\frac{dx^m(t)}{dt} &= -\beta_f k_m x^m(t)\frac{y^f(t)}{n^f(t)} \\
\frac{dy^m(t)}{dt} &= -\frac{dx^m(t)}{dt} - v^m y^m(t) \\
\frac{dx^f(t)}{dt} &= -\beta_m k_f x^f(t)\frac{y^m(t)}{n^m(t)} \\
\frac{dy^f(t)}{dt} &= -\frac{dx^f(t)}{dt} - v^f y^f(t)
\end{aligned} \tag{2 6}$$

Here mean incubation periods $1/v^m, 1/v^f$ and the transmission coefficients β_m, β_f for the spread of the infection from male to female and from female to male are not assumed to be the same Anderson and May (1988) [3] have suggested that $\beta_f < \beta_m < \beta$, where β is for homosexual men Similarly the rates of partner change k_m, k_f are probably not the same In the model given above only the spread of HIV is modelled To extend these equations to include the incidence of AIDS and of non infectious seropositivity together with immigration of susceptibles and natural mortality extra variables and parameters must be introduced

2.3 Blythe and Anderson Model

In this section we discuss a particular paper of Blythe and Anderson (1988) [9] and the use of the model they discuss in the context of the Irish situation We shall also briefly discuss the parameters of this model and shall give details on how we propose to obtain the data which will enable us to estimate these parameters

Blythe and Anderson derive from a series of risk or hazard functions distributions describing the variation in the infectious and incubation periods of the human immunodeficiency virus (HIV) Recent studies of the incubation period of AIDS in patients infected via blood transfusions and blood products reveal great variability among patients Current estimates of the incubation period range from 4 to 8 years The relationship between the incubation and infectious period is also uncertain but is taken by Blythe and Anderson to be of equal length Blythe and Anderson start with the development of a simple compartmental model which describes the transmission dynamics of HIV within a male homosexual community The model is given in terms of a set of differential equations that describe changes in the number of persons in a series of classes which denote different states of susceptibility and infection This model was first proposed by Anderson et al (1986) [5] We have the following system,

$$\frac{dX}{dt} = \Lambda - c\lambda X(t) - \mu X(t), \tag{2 7}$$

$$\frac{\partial y(u,t)}{\partial t} + \frac{\partial y(u,t)}{\partial u} = -(v_Y(u) + \mu)y(u,t), \tag{2 8}$$

$$\frac{\partial i(u,t)}{\partial t} + \frac{\partial i(u,t)}{\partial u} = -(v_I(u) + \mu)i(u,t), \tag{2 9}$$

$$\frac{dA}{dt} = V_Y(t) - (d+\mu)A(t), \tag{2 10}$$

$$\frac{dZ}{dt} = V_I(t) - \mu Z(t), \tag{2 11}$$

with the following initial conditions,

$$X(0) = \Lambda/\mu, \tag{2 12}$$

$$y(0,t) = pc\lambda(t)X(t) + J(t), \tag{2 13}$$

$$i(0,t) = (1-p)c\lambda(t)X(t), \tag{2 14}$$

$$A(0) = 0, \tag{2 15}$$

$$Z(0) = 0, \tag{2 16}$$

and where

$$\lambda(t) = \beta\frac{Y(t) + I(t)}{X(t) + Y(t) + I(t) + A(t) + Z(t)}, \tag{2 17}$$

$$V_Y(t) = \int_0^t v_Y(u)y(u,t)du, \tag{2 18}$$

$$V_I(t) = \int_0^t v_I(u)i(u,t)du \tag{2 19}$$

With $X(t)$ denoting the number of susceptibles, $A(t)$ the number of AIDS patients and $Z(t)$ the number of post-infectious seropositives (from the non-AIDS stream) at time t $y(u,t)$ denotes the number of infected and infectious persons who eventually develop AIDS (total $Y(t)$), and $i(u,t)$ the number of infected and infectious persons

who do not develop AIDS (total $I(t)$), who have been in their respective classes for the infinitesimal interval $(u, u+du)$ at time t The parameters are as follows,
$\Lambda > 0$ is the recruitment rate,
$\mu > 0$ is the normal per capita death rate,
$\lambda(t)c$ is the force of infection, where, $c > 0$ is a measure of sexual activity (new partners per unit time),
$\beta > 0$ is the transmission coefficient, that is the average probability that an infected person will pass on the infection, per partner,
$d > 0$ is the AIDS related death rate,
$p > 0$ is the fraction of those infected who enter the $Y(t)$ class (and hence the pre AIDS stream,
$1 - p$ is the remaining fraction who enter the $I(t)$ class (and hence the non AIDS stream),
$v_Y(u), v_I(u)$ are the rates at which individuals of residence time u are removed by the development of AIDS or loss of infectiousness, respectively and
$V_Y(t), V_I(t)$ are the rates of recruitment of individuals to the AIDS and post infectious classes respectively
We can solve equations (2 8) and (2 9) by using characteristic equations to give,

$$y(u,t) = y(0,t-u)\exp(-\mu u)\exp(-\int_0^u v_Y(u')du'), \quad (2\ 20)$$

$$i(u,t) = i(0,t-u)\exp(-\mu u)\exp(-\int_0^u v_I(u')du'), \quad (2\ 21)$$

We can then write equations (2 18) and (2 19) as,

$$V_Y(t) = \int_0^t f_Y(u)e^{-\mu u}[pc\lambda(t-u)X(t-u) + J(t-u)]du \quad (2\ 22)$$

$$V_I(t) = \int_0^t f_I(u)e^{-\mu u}[(1-p)c\lambda(t-u)X(t-u) + J(t-u)]du \quad (2\ 23)$$

where

$$f_Y(u) = v_Y(u)\exp(-\int_0^u v_Y(u')du') \quad (2\ 24)$$

$$f_I(u) = v_I(u)\exp(-\int_0^u v_I(u')du') \quad (2\ 25)$$

We can now integrate over all u in equations (2 8) and (2 9) to obtain ordinary differential equation forms for pre-AIDS and non-AIDS populations, giving

$$\frac{dY}{dt} = pc\lambda(t)X(t) + J(t) - V_Y(t) - \mu Y(t), \quad (2\ 26)$$

$$\frac{dI}{dt} = (1-p)c\lambda(t)X(t) - V_I Y(t) - \mu I(t) \quad (2\ 27)$$

Equations (2 7), (2 10), (2 26) and (2 27) specify our distributed incubation period model for $t \geq 0$, with $X(0) = \Lambda/\mu$ and $Y(0) = I(0) = A(0) = Z(0) = 0$ The functions $f_Y(u)$ and $f_I(u)$ are the probability density functions for the duration of the pre-AIDS class and non-AIDS class The quantities $v_Y(u)$ and $v_I(u)$ are the risk or hazard functions and are related to $f_Y(u)$ and $f_I(u)$ through equations (2 24) and (2 25)

Blythe and Anderson (1988) [9] then discuss four probability density functions and their underlying hazard functions These are the exponential, Weibull, Erlang

and rectangular They also examine the steady state behaviour of the model given these distributions and find that the errors in X^*, (the equilibrium point of the system), deriving from the use of different distributions around the same mean incubation period are negligible

We shall use the Blythe and Anderson model as a basis for our two population transmission model in Chapter 7 We shall see that in order to find actual estimates of the numbers HIV positive and with AIDS we need to simplify the existing model as proposed by these authors In Chapter 6 we shall discuss the parameters in more detail and shall provide estimates for these from our survey

Chapter 3

Estimating The Incidence of HIV Infection using the Back Projection Method.

3.1 Introduction

The Department of Health in Ireland acts as the centre for the collation of national data on AIDS, with diagnosed cases being reported directly to the AIDS Co-ordinator A considerable time lag may occur between the time that a case is diagnosed and the time at which it is recorded in the national AIDS figures, (the difference between these times being known as the reporting delay) It is at the time of diagnosis and not the time of reporting that the patient will need treatment and it is therefore necessary to plan for and work with the number of diagnosed cases Recently Brookmeyer and Damiano (1989)[10] have described a method, based on the reporting delay distribution, for adjustment of the numbers of AIDS cases with respect to reporting delays, and we have adapted their method here for our investigation of the Irish figures

Knowledge of the numbers infected with the HIV virus and of the incubation period distribution allow us to predict the number of AIDS cases we can expect in the future from these HIV patients Similarly, if the number of AIDS cases (after adjustment for reporting delays) is known and information on the incubation period distribution is available, we may derive estimates for those previously infected with the HIV virus This method is known as back-projection It must be stressed, however, that since the proportion of those infected who eventually go on to develop AIDS is unknown, and as we are working from the number of diagnosed AIDS cases, this method provides estimates only for those infected who will eventually go on to develop the disease

The relationship between the incidence of AIDS cases, the incidence of HIV infections and the distribution of the incubation period is well documented by Brookmeyer and Gail (1986), (1987), (1988),[13,12,11], Isham (1988)[25] and Anderson (1989)[1] and may be expressed in the form,

$$a(t) = \int_0^t h(t-u)f(u)du, \tag{3 1}$$

where $a(t)$ is the rate of new diagnoses of AIDS cases, $h(t)$ is the rate of acquiring HIV infection and $f(t)$ is the distribution of the incubation period Intuitively, if

we take t in years, equation (3.1) above says that the number of AIDS cases to be diagnosed in any one year arises via the incubation period distribution from the number of HIV infecteds in all previous years back to the start of the epidemic.

3.2 Adjusting the number of diagnosed AIDS cases for reporting delays.

For every AIDS case reported, data is supplied on the risk group (and other demographic features) of the patient and the date that he/she was diagnosed as falling within the CDC definition of an AIDS case. 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). Within Group IV, subgroup classification is independent of the presence or absence of lymphadenopath. Subgroup IV C1 defines an AIDS case. It consists of patients with secondary infectious diseases defined as the diagnosis of an infectious disease associated with HIV infection and/or at least moderately indicative of a defect in cell-mediated immunity. Included are patients with symptomatic or invasive disease due to one of a number of specified secondary infectious diseases.

Reporting delays may occur for a variety of reasons, such as pressure of work or delay for the accumulation of several cases. Typically, figures for any quarter will not be completed for anything from one to forty two months due to reporting delays. Demands for services provided in the form of special care or hospital resources, for example, may well be immediate. In the most recent Department of Health reports the total number of cases diagnosed to date will clearly not be known due to reporting delays. Predictions however must ideally be based on the numbers of diagnosed cases and we must therefore adjust the number of diagnosed cases to take account of the time lag.

The problem of reporting delays is discussed by Brookmeyer and Daminano (1989)[10], who base their method on a conditional likelihood for estimation of the reporting delay distribution. Calendar time is divided into intervals defined by the calendar dates,

$$T_0, T_1, \ldots, T_R,$$

i.e. the jth calendar interval is

$$[T_{j-1}, T_j), j = 1, \ldots, R.$$

T_R is the most recent report date. Reporting delays are classified into intervals $[d_{i-1}, d_i), i = 1, \ldots, I$. For each case we know the date of diagnosis and the date of the report. AIDS cases are cross classified by their date of diagnosis and the length of their reporting delay. Brookmeyer and Damiano essentially define a matrix with rows and columns equal to reporting delays and date of diagnosis respectively with elements equal to the numbers of AIDS cases. This procedure may be modified to be used with the data of a single risk group where appropriate but since numbers in any particular risk group are small for Irish data, we concentrate on the general approach.

We let X_{ij} represent the number of AIDS cases diagnosed in the jth calendar interval $[T_{j-1}, T_j)$ who had a reporting delay in the interval $[d_{i-1}, d_i), i = 1, \ldots, I$. We must remember that we may not have all the information on X_{ij}. For a given j

we have complete information on $X_{i,j}$ if

$$1 \leq i \leq L_j,$$

where L_j is the largest value of i such that

$$T_j + d_{L_j} \leq T_R$$

The total number of cases diagnosed in the jth interval who were reported at or before the report date T_R, is

$$X_{\cdot j} = \sum_{i=1}^{L_j} X_{i,j} \tag{3.2}$$

We are interested in estimating the reporting delay distribution

Let p_i represent the probability that an AIDS case has a reporting delay in the interval $[d_{i-1}, d_i)$ Thus the reporting delay distribution $\mathbf{p} = \{p_1, p_2, p_3, \quad, p_I\}$ refers to cases which are reported with delays less than or equal to d_I For each j the observed counts $X_{i,j}$, when conditioned on the total $X_{\cdot j}$ have a multinomial distribution with sample size $X_{\cdot j}$ and cell probabilities

$$p_{i,j} = p_i \Big| \sum_{i=1}^{L_j} p_i \;, i = 1, \quad, L_j \tag{3.3}$$

The conditional likelihood for $\{X_{i,j}, i = 1, \quad, L_j, j = 1, \quad, R\}$ conditional on $X_{\cdot j}$ is,

$$L_c = \prod_{j=1}^{R} \frac{X_{\cdot j}!}{\prod_{i=1}^{L_j} X_{i,j}!} \prod_{i=1}^{L_j} p_{i,j}^{X_{i,j}} \tag{3.4}$$

This likelihood function is the same as the joint probability density function of the response variables $X_{i,j}$, but viewed primarily as a function of the parameters, p_i, conditional on the observations A computational advantage of L_c is that we can use GLIM [41] to estimate the parameters by declaring $X_{i,j}$ to have a Poisson distribution with mean $\exp(\alpha_i + \beta_j)$, (Poisson error, log link) Once the maximum likelihoods of the parameters $\hat{\alpha}_i$ and $\hat{\beta}_j$ are found the estimate of p_i is given by

$$\hat{p}_i = e^{\alpha_i} \Big| \sum e^{\alpha_i} \tag{3.5}$$

Details of the method given in Brookmeyer and Damiano (1989) [10] describe the use of the estimated reporting delay distribution $\mathbf{p}$ to adjust the observed numbers of diagnosed AIDS cases In practice the number actually diagnosed in the interval of calendar time $(T_R - d_m, T_R - d_{m-1})$ is found by multiplying the reported number diagnosed in this interval by the factor $\left[\sum_{i=1}^{m-1} \hat{p}_i + \hat{p_m}/2\right]^{-1}$

3.3 The Method of Back-projection.

The method of back calculating from British and American AIDS incidence data has been discussed by Anderson (1989) [1], Brookmeyer and Damiano (1989) [10] and Isham (1988) [25] New cases of HIV are assumed to occur in a Poisson process denoted $h(t)$ The lengths of the incubation periods (i e the time between infection with the HIV virus and diagnosis of AIDS) are considered to be independent identically distributed variables with probability density function f New cases of

diagnosis of AIDS then occur in a Poisson process rate $a(t)$, given by equation (3 1) above If we know any two of $a(t)$, $h(t)$ or $f(t)$ then the third can be derived

It has been shown by Downs et al (1987) [20] that in Europe the numbers of new AIDS cases grew rapidly in the early years of the epidemic This has since been followed by a period of slower growth with doubling times increasing To describe the rate of new diagnosis of AIDS cases we consider four forms for $a(t)$ We have,

$$a(t) = d_0 \exp(d_1 t) \tag{3 6}$$

$$a(t) = a_0 \exp(a_1 t - a_2 t^2) \tag{3 7}$$

$$a(t) = (b_0 + b_1 t)/\exp(1 - t) + b_2 \tag{3 8}$$

$$a(t) = c_0 + c_1 t + c_2 t^2 \tag{3 9}$$

These four reflect empirical results which suggest that an initial period of exponential growth in AIDS cases is followed by a period where growth is slower Similar $a(t)$ have been employed by Isham (1988) [25] in her work on the U K figures We choose these not to model the future incidence of AIDS cases but rather to model over the range of values for which we wish to estimate $h(t)$

The gamma and Weibull distributions have been used to model the incubation period distribution, as suggested by Blythe and Anderson (1988) [9] and Medley et al (1987) [35] The gamma distribution we denote by $\Gamma(\alpha, \lambda)$ with probability density function,

$$f(t) = \lambda(\lambda t)^{\alpha-1} \exp(-\lambda t)/\Gamma(\alpha), \tag{3 10}$$

with $t \geq 0$ and mean $\mu = \alpha/\lambda$ The Weibull we denote by $W(\beta, \rho)$ with probability density,

$$f(t) = \beta\rho(\rho t)^{\beta-1} \exp\{-(\rho t)^{\beta}\}, \tag{3 11}$$

for $t \geq 0$ and mean $\mu = \rho^{-1}\Gamma(1 + 1/\beta)$

If $a(t)$ is given by equations (3 6) to (3 9) and $f(t)$ is the gamma distribution then $h(t)$ can be determined analytically

Consider the case where $f(t)$ is given by $\Gamma(2, \lambda)$, we then have,

$$a(t) = \int_0^t h(t - u)\lambda^2 u \exp(-\lambda u) du \tag{3 12}$$

To solve this integral for $h(t)$ we make a change of variables Let $s = t - u$, when $u = 0$, $s = t$ and when $u = t$, $s = 0$ We also have $-ds = du$ Substituting these into the above gives,

$$a(t) = \int_0^t h(s)\lambda^2 (t - s) \exp(-\lambda(t - s)) ds \tag{3 13}$$

Using Leibnitz's rule for the derivative of an integral gives us,

$$\frac{da(t)}{dt} = \int_0^t h(s)\lambda^2 (t - s)(-\lambda) \exp(-\lambda(t - s)) + h(s)\lambda^2 \exp(-\lambda(t - s)) ds \tag{3 14}$$

Differentiating a second time, dividing across by λ^2 and rearranging gives,

$$h(t) = \frac{1}{\lambda^2}\frac{d^2 a}{dt^2} + \int_0^t -\lambda^2 h(s)(t - s) \exp(-\lambda(t - s)) + 2\lambda h(s) \exp(-\lambda(t - s)) ds \tag{3 15}$$

From equation (3 14) above we have,

$$h(t) = \frac{1}{\lambda^2}\frac{d^2a}{dt^2} - a(t) + \left[\frac{da}{dt} + \lambda a(t)\right]\frac{2}{\lambda} \tag{3 16}$$

and adding the coefficients of $a(t)$ gives,

$$h(t) = \frac{1}{\lambda^2}\frac{d^2a}{dt^2} + \frac{2}{\lambda}\frac{da}{dt} + a(t) \tag{3 17}$$

Using the same approach we can show that for $f(t) = \Gamma(1, \lambda)$ we have,

$$h(t) = \frac{1}{\lambda}\frac{da}{dt} + a(t) \tag{3 18}$$

For $f(t) = \Gamma(3, \lambda)$ we have,

$$h(t) = \frac{1}{\lambda^3}\frac{d^3a}{dt^3} + \frac{3}{\lambda^2}\frac{d^2a}{dt^2} + \frac{3}{\lambda}\frac{da}{dt} + a(t) \tag{3 19}$$

while for $f(t) = \Gamma(4, \lambda)$ we have,

$$h(t) = \frac{1}{\lambda^4}\frac{d^4a}{dt^4} + \frac{4}{\lambda^3}\frac{d^3a}{dt^3} + \frac{6}{\lambda^2}\frac{d^2a}{dt^2} + \frac{4}{\lambda}\frac{da}{dt} + a(t) \tag{3 20}$$

From equations (3 17) to (3 20) we see that the order of $h(t)$ is given by the value of α and the coefficients of $h(t)$ are binomial in form

If we choose to use the Weibull distribution to model the incubation period than analytical determination of $h(t)$ is not possible as we require the integral of a quadratic exponential Equation (3 1) must be solved numerically, to do this we again make a change of variables by letting $s = t - u$ For $f(t) = W(2, \rho)$ this gives

$$a(t) = \int_0^t h(s)2\rho^2(t-s)\exp(-\rho^2(t-s)^2), \tag{3 21}$$

a linear Volterra equation of the first kind Equation (3 21) may be viewed as the convolution of $h(t)$ and $f(t)$, which could be solved using Laplace transforms This would then require finding the Laplace transform of $a(t)$, this however cannot be derived analytically when $a(t)$ is given by equation (3 7) Alternatively if we differentiate equation (3 21) twice this gives,

$$\frac{1}{2\rho^2}\frac{d^2a}{dt^2} = \int_0^t [-6\rho^2(t-s) + 4\rho^4(t-s)^3]\exp(-\rho^2(t-s)^2)h(s)ds + h(t) \tag{3 22}$$

This integral equation is now a Volterra equation of the second kind The NAG (1984) [38] library of routines can then be used to numerically solve the integral equation We choose routine D05ABF, which solves Fredholm equations of the second kind (similar to Volterra equations but with fixed limits of integration) by finding an approximation to the solution in the form of a Chebyshev series, as described by El-gendi (1969) [21]

3.4 Results

Our analysis was based on cases reported to the Department of Health up to March 1990 We decided to look at the reporting delays in all cases diagnosed up to the

31st of December 1989. As of 31st of March 1990 131 cases of AIDS had been reported to the Department. Of these 4 were diagnosed in 1990 and two cases were incorrectly recorded. This left 125 diagnosed AIDS cases up to the end of December 1989. The case number, date of diagnosis and date of report was recorded for each of the 125 cases. The reporting delay and the dates of diagnosis were grouped into three month intervals. The first case of AIDS was diagnosed in 1980. No cases were diagnosed in 1981 and the second Irish case of AIDS was diagnosed in late 1982. For ease of manipulation we assumed that the first case of AIDS occurred in 1981. As data was grouped into three month intervals we had delays of up to fourteen quarters (maximum delay was forty two months). All cases from the third quarter of 1986 were adjusted by multiplying the reported numbers of diagnosed cases in that quarter by the appropriate factor. For example cases in the first quarter of interest (1986, third quarter) were multiplied by 1.004. The number of cases in the second quarter was multiplied by 1.012 and so on until the number of cases in the final quarter (the thirteenth) was multiplied by 1.232. Table 3.1 shows the reporting delay probabilities when the model $E(Y_{ij}) = exp(\alpha_i + \beta_j)$ was fitted to the data using GLIM [41].

TABLE 3.1
Estimated Reporting Delay Probabilities.

Delay(months)	p_i	$\sum p_i$
0 - 3	0.776	0.776
4 - 6	0.072	0.848
7 - 9	0.048	0.896
10 - 12	0.056	0.952
13 - 15	0.016	0.968
16 - 18	0.008	0.976
19 - 21	0.000	0.976
22 - 24	0.000	0.976
25 - 27	0.000	0.976
28 - 30	0.000	0.976
31 - 33	0.000	0.976
34 - 36	0.008	0.984
37 - 39	0.008	0.992
40 - 42	0.008	1.000

It is interesting to note that almost 85% of all cases are reported within six months of diagnosis. This is due to the fact that most cases appear in the Dublin genito urinary clinics and are reported almost immediately. Brookmeyer and Damiano (1989) [10] in their work on the United States data show that 78.9% of all cases are reported within six months of diagnosis and 88.9% are reported within a year. We see also that there has been up to a 42 month reporting delay in the Irish data, this was a case that was diagnosed early in the epidemic. A maximum delay of 48 months is reported in the U.S. data.

As cases are reported promptly and numbers are small, very little adjustment was made to the quarterly figures. There were no differences in the reported numbers of diagnosed cases and the adjusted numbers of cases for 1981 to 1988. There was a difference of plus four cases between the reported and adjusted numbers for 1989. The adjusted numbers of cases is provided in Table 3.3.

The functions (3 6) to (3 9) which describe the rate of appearance of new AIDS cases were then fitted to the adjusted AIDS incidence data for 1981 to 1989 The parameter estimates along with R^2 (a crude measure of how well the regression equation fits the data, with 100% indicating a perfect fit R^2 =100(SS due to regression)/(SS total)) are given below in Table 3 2

TABLE 3 2
Parameter estimates obtained for $a(t)$

Exponential	$d_0 = 0\ 336$	$d_1 = 0\ 558$		$R^2 = 94\ 4\%$
Quadratic				
Exponential	$a_0 = 0\ 573$	$a_1 = 0\ 267$	$a_2 = -0\ 029$	$R^2 = 96\ 4\%$
Linear				
Logistic	$b_0 = 0\ 145$	$b_1 = -0\ 014$	$b_2 = 0\ 658$	$R^2 = 98\ 9\%$
Quadratic	$c_0 = 10\ 905$	$c_1 = -8\ 465$	$c_2 = 1\ 445$	$R^2 = 97\ 6\%$

The expected annual AIDS incidence these parameters give rise to is given in Table 3 3

TABLE 3 3
Expected and Observed Annual AIDS Incidence

Year	Exponential	Quadratic Exponential	Linear Logistic	Quadratic	Observed Cases (Adjusted)
1981	0 59	0 77	0 79	3 88	1
1982	1 03	1 10	0 98	-0 25	1
1983	1 79	1 66	1 41	-1 49	1
1984	3 14	2 66	2 43	0 16	3
1985	5 48	4 52	4 70	4 70	6
1986	9 57	8 13	9 53	12 13	6
1987	16 72	15 50	19 05	22 45	22
1988	29 21	31 34	35 09	35 65	35
1989	51 04	67 14	51 93	51 75	54

Isham (1988) [25] cites work done by Anderson and Medley (1988) [4] on modelling the incubation period distribution They fitted both the gamma and Weibull distributions given by equations (3 10) and (3 11) to data from transfusion recipients available up to April 1988 and obtained the following parameter estimates, $\Gamma(\alpha, \lambda)$ $\alpha = 2\ 70$, $\lambda = 0\ 19$ with mean $\mu = 14\ 3$ years $W(\beta, \rho)$ $\beta = 2\ 33$, $\rho = 0\ 12$ with mean $\mu = 7\ 3$ years

For ease of manipulation we have solved above for $h(t)$, when $f(t)$ is given by the gamma distribution with α =2 or 3 and the Weibull distribution with $\beta = 2$ Since exact progression rates are unknown, we choose to work with a spread of three different progression rates to estimate rate of new cases of infection, $h(t)$ slow progression given by $\Gamma(3, 0\ 21)$, mean incubation period $\mu = 14\ 3$ years, 38% of all infected individuals progress to the disease after 10 years, moderate progression given by $\Gamma(2, 0\ 14)$, mean incubation period, $\mu = 14\ 3$ years, 44% progress after 10 years and rapid progression given by W(2, 0 12), mean incubation period, $\mu = 7\ 4$ years, 79% progress to the disease after 10 years A comparison of these assumed progression rates with those fitted by Anderson and Medley (1988)[4] can be seen in Figure 3 1 and Figure 3 2

For each of the four choices of $a(t)$ and using equations (3 17) and (3 19) and using the NAG (1984) [38] routine D05ABF with 10 Chebychev coefficients, we estimate

FIGURE 3.1

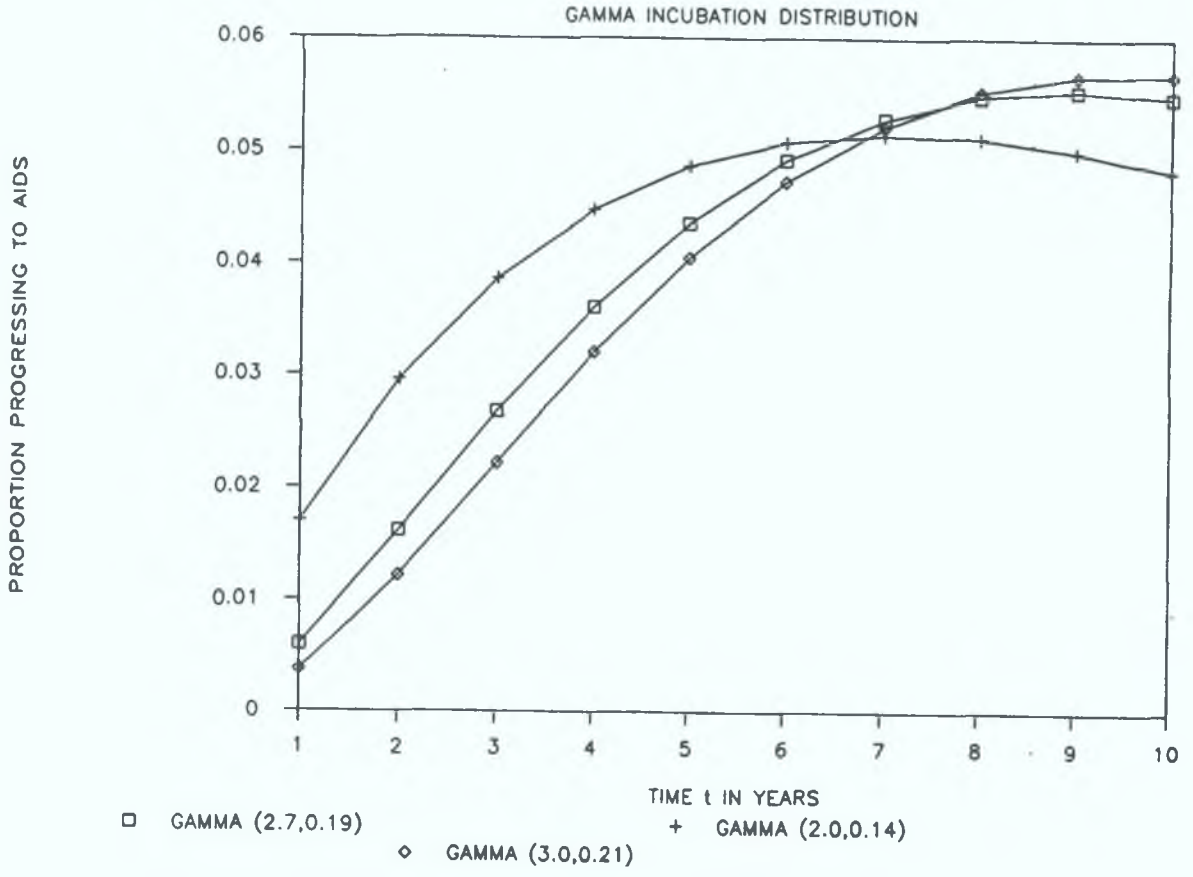
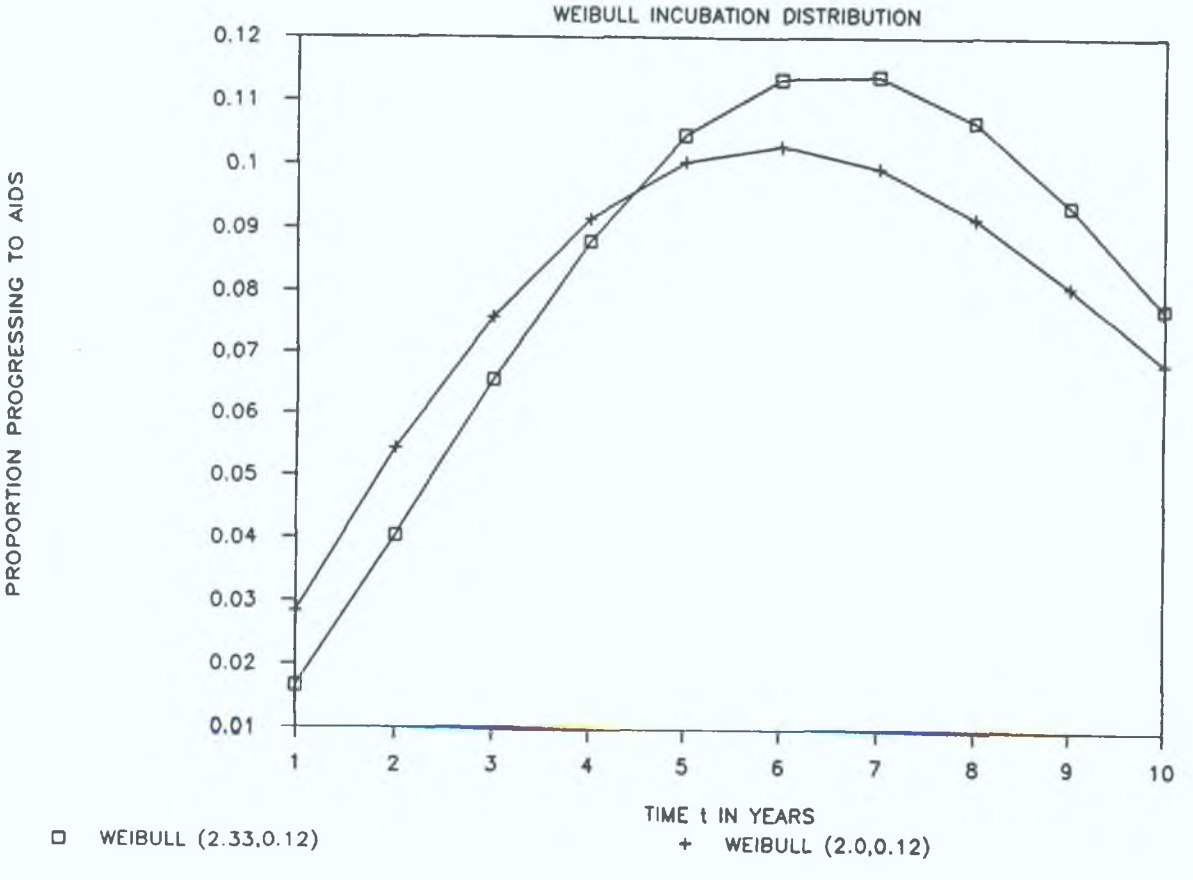


FIGURE 3.2



the expected annual incidence of HIV infections given each of the three progression rates. Expected annual incidence of HIV infection given slow progression is provided in Table 3.4. Expected annual incidence given moderate and rapid progression is provided in Tables 3.5 and 3.6 respectively. In addition the cumulative numbers infected given certain conditions (described in the footnotes at the bottom of Tables 3.4, 3.5 and 3.6) up to the end of 1989 are provided.

TABLE 3.4

Expected annual incidence of HIV infections given slow progression rates, $f(t) = \Gamma(3, 0.21)$, $a(t)$ from equations (3.6) to (3.9).

Year	Exponential	Quadratic Exponential	Linear Logistic	Quadratic
1981	29	21	19	121
1982	51	42	43	158
1983	88	89	96	198
1984	154	189	204	241
1985	269	413	405	287
1986	470	937	697	336
1987	821	2206	795	388
1988	1434	5413	-822	442
1989	2506	13876	-10343	499
1990	4380	37244	-50157	560
1991	7654	104831	-196255	623
1992	13377	309834	-696336	689
Total to 1989	5822	23186	3849[1]	2670

[1] *Assuming 795 cases in 1988 and in 1989.*

TABLE 3.5

Expected annual incidence of HIV infections given moderate progression rates, $f(t) = \Gamma(2, 0.14)$, $a(t)$ as previously.

Year	Exponential	Quadratic Exponential	Linear Logistic	Quadratic
1981	15	11	8	72
1982	26	19	18	109
1983	45	34	42	149
1984	79	64	93	192
1985	137	126	200	238
1986	239	262	403	287
1987	417	571	713	338
1988	729	1311	904	393
1989	1274	3168	-351	450
1990	2226	8063	-8589	511
1991	3890	21625	-44096	574
1992	6799	61146	-176269	640
Total to 1989	2961	5566	3285[1]	2228

[1] *Assuming 904 cases in 1989.*

TABLE 3.6
Expected annual incidence of HIV infections given rapid progression rates, $f(t) = W(2, 0.12)$, $a(t)$ as previously.

Year	Exponential	Quadratic Exponential	Linear Logistic	Quadratic
1981	7	5	4	105
1982	12	9	9	116
1983	22	16	20	131
1984	37	30	43	144
1985	61	59	85	152
1986	102	119	153	156
1987	172	259	222	159
1988	297	601	96	162
1989	520	1486	-1107	166
1990	917	3880	-6771	171
1991	1621	10655	-28775	178
1992	2861	30730	-106656	184
Total to 1989	1230	2580	980[1]	1286

[1] *Assuming 222 cases in 1988 and in 1989.*

3.5 Discussion

We see from Tables 3.4, 3.5 and 3.6 that the estimated total number of individuals infected with the HIV virus from 1st January 1981 to 31st December 1989 ranges from 980 to 23186 depending on the assumptions made about $a(t)$ and $f(t)$. This is not surprising, as a wide interval is inevitable given the amount of data we are working with. Isham (1988) [25] in her work on applying the back projection method to HIV cases in the United Kingdom estimates between 19,578 and 60,269 cases of the virus between 1980 and 1887 inclusive. Some further comments are discussed below in explanation of the seemingly wide interval in the Irish data.

Describing $a(t)$ by an exponential gives totals of 5822, 2961 and 1230 cases of the HIV virus in Ireland up to the end of 1989, given slow moderate and rapid progression rates respectively. After 1989 there is a large increase in the predictions for the numbers HIV positive. This would seem to imply that the plateau phase following exponential growth that A.M. Downs et al (1987) [20] speak of starts at the beginning of 1990 in the Irish case. This is a reasonable assumption as first cases of AIDS in Ireland were not identified until the early to mid eighties, as opposed to some other European countries where first cases were identified in the late seventies and early eighties.

Describing $a(t)$ by a quadratic exponential gives a large increase in the fitted values for the number of AIDS cases between 1988 and 1989. This is then reflected in the predictions for the HIV figures from 1988 to 1992, (illustrated in Table 3.4 where the predicted annual incidence given slow progression for 1988 is 5413 cases and 13,876 cases in 1989). We have said earlier that the experiences of other countries suggest that the epidemic reaches a plateau after the initial phase of exponential growth (Downs et al (1987) [20]). If then, we assume approximately the same number of individuals infected in 1989 as in 1988, then a total of 14,723 cases will be observed given slow progression rates, giving an overall interval of 980 to 14,723

HIV cases in Ireland from 1981 to 1989 inclusive This is a reasonable assumption as we know from test centres in Ireland that we had an increase of 229 in the known numbers of HIV positive cases in 1986, 143 in 1987, 116 in 1988 and an increase of 116 cases again in 1989

Also, slow progression assumes that only 38% of all individuals infected with the virus progress to the disease after ten years Consequently this progression rate will predict that the current AIDS cases came from a large pool of HIV infected individuals

Looking at moderate and rapid progression rates with $a(t)$ described by the quadratic exponential we note that the total number of HIV infected individuals up to 31st December 1989 are 5566 and 2580 respectively These would appear to be far more realistic figures given that we know from Irish testing centres that we have at least 910 individuals infected at this time Again however there are large increases in the predictions for 1990, 1991 and 1992 As more data on the numbers of AIDS cases and reporting delays becomes available these projections can be re-estimated based on the new estimates for $a(t)$

The linear logistic form for $a(t)$ gives negative values for $h(t)$ in later years This problem was also encountered by Isham (1988) [25] in her analysis of the U K data Although the linear logistic describes the number of AIDS cases well over the years 1981 to 1989, it predicts low values for $a(t)$ in later years as can be seen in Table 3 3 This is then reflected in the predictions for $h(t)$ given in Tables 3 4,3 5 and 3 6 However, on the basis of the known increases in the numbers of HIV cases given above, we can make the assumption that we have at least the same number of HIV cases in 1988 and 1989 as predicted in 1987 for slow and rapid progression and at least the same number of cases in 1989 as we had in 1988 for moderate progression then we arrive at estimates of 3849, 3285 and 980 cases for slow, moderate and rapid progression respectively

The figure of 980 cases with rapid progression still appears to be unrealistically low This may be explained by the fact that with rapid progression rates we are assuming that 79% of all infected individuals progress to the disease within ten years This low prediction of HIV cases may also reflect the extent of under reporting of AIDS cases

Finally the quadratic form for $a(t)$ provides estimates of 2670, 2228 and 1286 cases up to 1989 for slow, moderate and rapid progression rates These figures are encouragingly similar to those predictions of HIV arising from both the linear logistic and exponential forms of $a(t)$

For planning purposes it would seem prudent to assume the moderate progression rates of 44% progressing to the disease within ten years This would then give estimates of 2961, 5566, 3285 and 2228 individuals infected with the HIV virus in Ireland as of 31st December 1989 given each of the four forms for $a(t)$ However it must be stressed that, as yet, exact progression rates are unknown and as such all estimates should be viewed with caution Further research into this area of modelling the disease is imperative if reliable estimates for $h(t)$ are to be provided

Chapter 4

Improved Estimates of the Incidence of HIV Infection.

4.1 Introduction

We saw in Chapter 3 how estimates of the incidence of HIV infection were provided A method known as 'Back-Projection' was employed to predict annual incidence of HIV infection This method is based upon the knowledge of the distribution of AIDS cases and the distribution of the incubation period We provided estimates for the level of HIV infection from 1981 to 1989 given slow, moderate and rapid progression rates from HIV infection to the onset of AIDS

The time taken to progress from infection to disease is known as the incubation period Much work has been carried out in the United Kingdom by Anderson and Medley (1988) [4] on the study of the incubation period distribution We have seen in the Anderson and Medley work that the distribution is well described by a gamma distribution with a mean of 14 3 years and 48% of all those infected progressing to AIDS within 10 years In this chapter we shall implement their exact choice of incubation distribution into our integral equation model for back projection and in so doing we shall considerably improve our estimates of the incidence of HIV infection in Ireland from 1981 to 1989

4.2 Methods

We have seen that the integral equation model arising in Back-Projection is a linear Volterra equation of the first kind with a difference kernel We have

$$a(t) = \int_0^t h(t-u)f(u)du \tag{4 1}$$

When $f(t)$ is given by a gamma distribution with parameter $\alpha \in \mathbf{R}$ as opposed to $\alpha \in \mathbf{N}$ in the previous chapter, then equation (4 1) becomes increasingly difficult to solve Although (4 1) may be viewed as the convolution of $h(t)$ and $f(t)$ we cannot find a solution by means of inverse Laplace transforms

We show how (4 1) can be changed into an generalised Abel integral equation by differentiation The solution of this equation is then given in terms of an integral in the two known functions $a(t)$ and $f(t)$ We then proceed to solve the the resulting integral in terms of incomplete and complete gamma functions We also provide error bounds for all solutions

4.3 Exponential Growth in AIDS Cases.

We shall first consider the solution of (4 1) given exponential growth in the number of AIDS cases We have seen in Chapter three that the exponential model fits the Irish data well We have

$$a(t) = d_0 \exp(d_1 t) \tag{4 2}$$

and

$$f(t) = \frac{\lambda^\alpha}{\Gamma(\alpha)} t^{\alpha-1} \exp(-\lambda t), \tag{4 3}$$

with $2 < \alpha < 3$ Substituting (4 3) into (4 1) and making the change of variable $t - u = s$ gives

$$a(t) = \int_0^t h(s) \frac{\lambda^\alpha}{\Gamma(\alpha)} (t-s)^{\alpha-1} \exp(-\lambda(t-s)) ds \tag{4 4}$$

Differentiating with respect to t gives

$$\begin{aligned} a(t) &= \int_0^t h(s) \frac{\lambda^\alpha}{\Gamma(\alpha)} (t-s)^{\alpha-1} (-\lambda) \exp(-\lambda(t-s)) \\ &\quad + h(s) \frac{\lambda^\alpha}{\Gamma(\alpha)} (\alpha-1)(t-s)^{\alpha-2} \exp(-\lambda(t-s)) ds, \end{aligned} \tag{4 5}$$

which can be rearranged to give

$$a(t) = -\lambda a(t) + \int_0^t h(s) \frac{\lambda^\alpha}{\Gamma(\alpha)} (\alpha-1)(t-s)^{\alpha-2} \exp(-\lambda(t-s)) ds \tag{4 6}$$

Differentiating with respect to t a second time gives

$$\begin{aligned} a(t) &= -\lambda a(t) + \int_0^t h(s) \frac{\lambda^\alpha}{\Gamma(\alpha)} (\alpha-1)(t-s)^{\alpha-2} (-\lambda) \exp(-\lambda(t-s)) \\ &\quad + h(s) \frac{\lambda^\alpha}{\Gamma(\alpha)} (\alpha-2)(\alpha-1)(t-s)^{\alpha-3} \exp(-\lambda(t-s)) ds, \end{aligned} \tag{4 7}$$

which we can rearrange to give

$$\begin{aligned} a(t) + 2\lambda a(t) + \lambda^2 a(t) &= \frac{\lambda^\alpha}{\Gamma(\alpha)} (\alpha-2)(\alpha-1) \exp(-\lambda t) \\ &\quad \int_0^t h(s)(t-s)^{\alpha-3} \exp(\lambda s) ds \end{aligned} \tag{4 8}$$

Letting $1/C = \lambda^\alpha(\alpha-2)(\alpha-1)/\Gamma(\alpha)$ and $\alpha - 3 = -p$ gives

$$C \exp(\lambda t)[a(t) + 2\lambda a(t) + \lambda^2 a(t)] = \int_0^t \frac{h(s) \exp(\lambda s)}{(t-s)^p} ds, \tag{4 9}$$

where $0 < p < 1$ Equation (4 9) is now a generalised Abel integral equation of the form

$$F(t) = \int_0^t \frac{U(s)}{(t-s)^p} ds, \tag{4 10}$$

with $U(s)$ as the required unknown

The solution of (4 10) is well documented A J Jerri (1985) [27, pages 82–87] in his book 'Integral Equations with Applications' discusses generalised Abel integral equations the solution of which is given by

$$U(t) = \frac{sin(p\pi)}{\pi}\frac{d}{dt}\int_0^t (t-s)^{p-1}F(s)ds \tag{4 11}$$

We can now say that the solution of (4 9) is given by

$$h(t) = \frac{sin(p\pi)}{\pi}\exp(-\lambda t)\frac{d}{dt}\int_0^t (t-s)^{p-1}F(s)ds \tag{4 12}$$

where

$$F(t) = C\exp(\lambda t)[a(t) + 2\lambda a(t) + \lambda^2 a(t)] \tag{4 13}$$

When $a(t)$ is given by the simple exponential in (4 2) we have

$$F(s) = C\exp(\lambda s)[d_0 d_1^2\exp(d_1 s) + 2\lambda d_0 d_1\exp(d_1 s) + \lambda^2 d_0\exp(d_1 s)] \tag{4 14}$$

which when adding the coefficients and combining the exponentials gives

$$F(s) = Cg\exp[(d_1 + \lambda)s], \tag{4 15}$$

with

$$g = d_0 d_1^2 + 2\lambda d_0 d_1 + \lambda^2 d_0 \tag{4 16}$$

We can now say that the required solution of $h(t)$ is given by

$$h(t) = Cg\frac{sin(p\pi)}{\pi}\exp(-\lambda t)\frac{d}{dt}\int_0^t (t-s)^{p-1}\exp[(\lambda + d_1)s]ds \tag{4 17}$$

and we wish to solve the integral on the right hand side of (4 17)

We have

$$I = \int_0^t (t-s)^{p-1}\exp[(\lambda + d_1)s]ds \tag{4 18}$$

where $-1 < p-1 < 0$ Let $u = t - s$ when $s = 0, u = t$ and when $s = t, u = 0$ also $-du = ds$ Then we obtain

$$I = \exp[(\lambda + d_1)t]\int_0^t u^{p-1}\exp[-(\lambda + d_1)u]du \tag{4 19}$$

Making a further change of variables by letting $v = (\lambda + d_1)u$ gives

$$I = \frac{\exp[(\lambda + d_1)t]}{(\lambda + d_1)^p}\int_0^{(\lambda+d_1)t} v^{p-1}\exp(-v)dv, \tag{4 20}$$

which we can write as,

$$I = \frac{\exp[(\lambda + d_1)t]}{(\lambda + d_1)^p}\left[\int_0^\infty v^{p-1}\exp(-v)dv - \int_{(\lambda+d_1)t}^\infty v^{p-1}\exp(-v)dv\right] \tag{4 21}$$

We can now say that

$$I = \frac{\exp[(\lambda + d_1)t]}{(\lambda + d_1)^p}\{\Gamma(p) - \Gamma[p, (\lambda + d_1)t]\} \tag{4 22}$$

We are required to find dI/dt This we can compute using Leibnitz's rule for the derivative of an integral in order to find the derivative of the incomplete gamma function $\Gamma[p,(\lambda+d_1)t]$ We have,

$$\begin{aligned}\frac{d}{dt}\Gamma[p,(\lambda+d_1)t] &= \frac{d}{dt}\int_{(\lambda+d_1)t}^{\infty} v^{p-1}e^{-v}dv \\ &= -(\lambda+d_1)^p t^{p-1}e^{-(\lambda+d_1)t} \end{aligned} \tag{4 23}$$

We can now say that

$$\begin{aligned}\frac{dI}{dt} &= e^{(\lambda+d_1)t}\frac{\Gamma(p)}{(\lambda+d_1)^{p-1}} + t^{p-1} - \frac{\Gamma[p,(\lambda+d_1)t]e^{(\lambda+d_1)t}}{(\lambda+d_1)^{p-1}} \\ &= e^{(\lambda+d_1)t}\frac{\Gamma(p)}{(\lambda+d_1)^{p-1}} + t^{p-1} - R, \end{aligned} \tag{4 24}$$

where

$$R = \Gamma[p,(\lambda+d_1)t]\frac{e^{(\lambda+d_1)t}}{(\lambda+d_1)^{p-1}} \tag{4 25}$$

We can easily compute $\Gamma(p)$ numerically and Olver (1974) [40, pages 66–67] provides us with bounds for $\Gamma(z,t)$ when $z \leq 1$ and $t > 0$ We have

$$\Gamma[p,(\lambda+d_1)t] \leq \exp[-(\lambda+d_1)t](\lambda+d_1)^{p-1}t^{p-1}, \tag{4 26}$$

as $p \leq 1$ and $(\lambda+d_1)t > 0$ We have then from (4 17), (4 24) and (4 26)

$$R \leq t^{p-1} \tag{4 27}$$

and

$$h(t) = Cg\frac{sin(p\pi)}{\pi}e^{-\lambda t}\left[e^{(\lambda+d_1)t}\frac{\Gamma(p)}{(\lambda+d_1)^{p-1}} + t^{p-1}\right] - \hat{R}, \tag{4 28}$$

where

$$0 \leq \hat{R} \leq Cg\frac{sin(p\pi)}{\pi}e^{-\lambda t}t^{p-1} \tag{4 29}$$

In our results section we shall compute all constants and provide a table of estimates for $h(t)$, the number of HIV cases in Ireland in year t, based on equations (4 28) and (4 29) above

4.4 Quadratic Exponential Growth in AIDS Cases.

Our objective in this section is to solve the integral equation (4 1) when $a(t)$ is of the form

$$a(t) = a_0\exp(a_1t - a_2t^2) \tag{4 30}$$

and $f(t)$ is given by the gamma distribution as previously with $2 < \alpha < 3$ To do this we proceed as in section 4 3 and change (4 1) into a generalised Abel equation the solution of which is given by

$$h(t) = \frac{sin(p\pi)}{\pi}\exp(-\lambda t)\frac{d}{dt}\int_0^t (t-s)^{p-1}F(s)ds \tag{4 31}$$

where

$$F(t) = C\exp(\lambda t)[a(t) + 2\lambda a(t) + \lambda^2 a(t)] \tag{4 32}$$

and $C = \Gamma(\alpha)/\lambda(\alpha)(\alpha-2)(\alpha-1)$ as previously With $a(t)$ given by (4 29) we can write

$$F(t) = C\exp(\lambda t)[4a_3^2t^2 + (4a_1a_3 + 4\lambda a_3)t + (a_1^2 + 2a_3 + 2\lambda a_1 + \lambda^2)]a_0\exp(a_1t + a_3t^2), \tag{4 32}$$

where we write $a_3 = -a_2$ for convenience Letting

$$\begin{aligned} a_4 &= 4a_0a_3^2, \\ a_5 &= a_0(4a_1a_3 + 4\lambda a_3) \\ a_6 &= a_0(a_1^2 + 2a_3 + 2\lambda a_1 + \lambda^2) \end{aligned}$$

and combining the exponentials gives

$$F(t) = C(a_4t^2 + a_5t + a_6)\exp[(a_1 + \lambda)t + a_3t^2] \tag{4 33}$$

Completing the square on the exponential gives

$$F(t) = C(a_4t^2 + a_5t + a_6)exp[a_3(t + \frac{a_1 + \lambda}{2a_3})^2]exp[-a_3(\frac{a_1 + \lambda}{2a_3})^2] \tag{4 34}$$

Writing $\delta = (a_1 + \lambda)/2a_3$ gives

$$F(t) = C(a_4t^2 + a_5t + a_6)exp[a_3(t + \delta)^2]\exp[-a_3\delta^2] \tag{4 35}$$

From equation (4 30) we can now say that

$$\begin{aligned} h(t) &= C\exp[-a_3\delta^2]\frac{sin(p\pi)}{\pi}\exp(-\lambda t) \\ &\quad \frac{d}{dt}\int_0^t (t-s)^{p-1}(a_4s^2 + a_5s + a_6)exp[a_3(s+\delta)^2]ds \end{aligned} \tag{4 36}$$

We now wish to evaluate the integral on the right hand side of (4 36) above To do this we make the change of variable $v = s + \delta$ Substituting into the integral above gives

$$I(t) = \int_\delta^{t+\delta} (t - v + \delta)^{p-1}[a_4(v-\delta)^2 + a_5(v-\delta) + a_6]e^{a_3v^2}dv \tag{4 37}$$

Expanding $(v-\delta)^2$ and adding coefficients gives

$$I(t) = \int_\delta^{t+\delta} (t - v + \delta)^{p-1}[a_4v^2 + (a_5 - 2a_4\delta)v + (a_4\delta^2 - a_5\delta + a_6)]e^{a_3v^2}dv \tag{4 38}$$

Writing $a_7 = a_4, a_8 = (a_5 - 2a_4\delta)$ and $a_9 = (a_4\delta^2 - a_5\delta + a_6)$ gives

$$I(t) = \int_\delta^{t+\delta} (t - v + \delta)^{p-1}(a_7v^2 + a_8v + a_9)e^{a_3v^2}dv \tag{4 39}$$

As we have a squared term in the exponential component of the integral above we cannot proceed as we did in the previous case Instead we choose to evaluate the above integral $I(t)$ by numerical means To do this we employ the NAG [38] library routine D01AJF, a general purpose integrator which calculates an approximation to the integral of the function $F(x)$ over a finite integral (A, B) This provides us with $I(t)$ evaluated at the points of interest to us We shall provide the results from this routine below

In order to estimate $h(t)$ we see from equation (4 37) that we require dI/dt Using results obtained for $I(t)$ from the integration above we shall proceed to numerically differentiate $I(t)$ at the required points We first employ a forward-difference formula discussed in Burden and Faires (1985) [14, pages 136–141] to estimate dI/dt for $t \in [1, 12]$, the times of interest here We have

$$\frac{dI(t_0)}{dt} = \frac{I(t_0 + h) - I(t_0)}{h} \tag{4 41}$$

For small values of h, the difference quotient $[I(t_0 + h) - I(t_0)]/h$ can be used to approximate $dI(t_0)/dt$ with an error of order h This formula is known as a forward-difference formula if $h > 0$ We then compare these results for dI/dt with those obtained by the central difference formula

$$\frac{dI(t_0)}{dt} = \frac{I(t_0 + h) - I(t_0 - h)}{2h} \tag{4 42}$$

which has an error of order h^2 To assess the accuracy of results we then compare the output from the two methods with a small step size h The values derived for dI/dt using this method will then be used to obtain estimates for $h(t)$ The results obtained are given in Tables 4 3 to 4 5 in section 4 7

4.5 Linear Logistic Growth in AIDS Cases.

We now consider the solution of (4 1) when the growth in AIDS cases is given by the linear logistic function

$$a(t) = \frac{b_0 + b_1 t}{\exp(1 - t)} + b_2 \tag{4 43}$$

To do this we again change (4 1) into a generalised Abel integral equation, the solution of which is given by (4 12) where $F(s)$ is now given by

$$F(s) = C \exp(\lambda s)\{[(1 + \lambda)^2 b_0 + 2(1 + \lambda)b_1 + (1 + \lambda)^2 b_1 t]e^{-1}e^s + \lambda^2 b_2\} \tag{4 44}$$

The required solution $h(t)$ is now given by

$$h(t) = C \exp(-\lambda t)\frac{sin(p\pi)}{\pi}\frac{dI}{dt} \tag{4 45}$$

where

$$I = \int_0^t (t - s)^{p-1} \exp(\lambda s)[(a + bs)e^{-1}e^s + \lambda^2 b_2]ds, \tag{4 46}$$

with $b_3 = (1 + \lambda)^2 b_0 + 2(1 + \lambda)b_1$ and $b_4 = (1 + \lambda)^2 b_1$ For ease of manipulation we split I into $I = I_1 + I_2 + I_3$ with

$$\begin{aligned} I_1 &= \int_0^t (t - s)^{p-1} \exp(\lambda s) b_3 e^{-1} e^s ds, \\ I_2 &= \int_0^t (t - s)^{p-1} \exp(\lambda s) b_4 s e^{-1} e^s ds, \\ I_3 &= \int_0^t (t - s)^{p-1} \exp(\lambda s) \lambda^2 b_2 ds \end{aligned}$$

Returning to I_1, we make the change of variables $u = t - s$ Then when $s = t, u = 0$ and when $s = 0, u = t$ and $-du = ds$ Substituting into I_1 gives

$$I_1 = b_3 e^{-1} e^{(1+\lambda)t} \int_0^t u^{p-1} \exp[-(1+\lambda)u] du \tag{4 47}$$

Making a further change of variables $v = (1+\lambda)u$ gives

$$\begin{aligned} I_1 &= \frac{b_3 e^{-1}}{(1+\lambda)^p} e^{(1+\lambda)t} \int_0^{(1+\lambda)t} v^{p-1} e^{-v} dv \\ &= \frac{b_3 e^{-1}}{(1+\lambda)^p} e^{(1+\lambda)t} [\Gamma(p) - \Gamma(p,(1+\lambda)t)] \end{aligned} \tag{4 48}$$

Differentiating I_1 with respect to t and rearranging gives,

$$\begin{aligned} \frac{dI_1}{dt} &= \frac{b_3 e^{-1}}{(1+\lambda)^{p-1}} \Gamma(p) e^{(1+\lambda)t} + b_3 e^{-1} t^{p-1} - \Gamma[p,(1+\lambda)t] \frac{b_3 e^{-1}}{(1+\lambda)^{p-1}} e^{(1+\lambda)t} \\ &= \frac{b_3 e^{-1}}{(1+\lambda)^{p-1}} \Gamma(p) e^{(1+\lambda)t} + b_3 e^{-1} t^{p-1} - R_1, \end{aligned} \tag{4 49}$$

where

$$R_1 = \Gamma[p,(1+\lambda)t] \frac{b_3 e^{-1}}{(1+\lambda)^{p-1}} e^{(1+\lambda)t} \tag{4 50}$$

But we know from (4 26) that

$$\Gamma(p,(1+\lambda)t) \leq \exp[-(1+\lambda)t](1+\lambda)^{p-1} t^{p-1} \tag{4 51}$$

for $p \leq 1$ and $(1+\lambda)t > 0$ We can now say that dI_1/dt is given by (4 49) where

$$0 \leq R_1 \leq b_3 e^{-1} t^{p-1} \tag{4 52}$$

We have seen that I_2 is given by

$$I_2 = \int_0^t (t-s)^{p-1} \exp(\lambda s) b_4 s e^{-1} e^s ds \tag{4 53}$$

Making the same substitution $u = t - s$ we can say that $I_2 = I_{21} + I_{22}$ where

$$\begin{aligned} I_{21} &= b_4 e^{-1} e^{(1+\lambda)t} \int_0^t t u^{p-1} \exp[(-1+\lambda)u] du, \\ I_{22} &= -b_4 e^{-1} e^{(1+\lambda)t} \int_0^t u^p \exp[(-1+\lambda)u] du \end{aligned} \tag{4 54}$$

Making the change of variables $v = (1+\lambda)u$ as previously gives

$$\begin{aligned} I_{21} &= \frac{b_4 e^{-1}}{(1+\lambda)^p} t e^{(1+\lambda)t} \int_0^{(1+\lambda)t} v^{p-1} e^{-v} dv \\ &= \frac{b_4 e^{-1}}{(1+\lambda)^p} t e^{(1+\lambda)t} [\Gamma(p) - \Gamma(p,(1+\lambda)t)] \end{aligned} \tag{4 55}$$

Proceeding as before we can show that

$$\frac{dI_{21}}{dt} = \frac{b_4 e^{-1}}{(1+\lambda)^p} \Gamma(p) e^{(1+\lambda)t} [(1+\lambda)t + 1] + b_4 e^{-1} t^p - R_{21}, \tag{4 56}$$

where

$$0 \leq R_{21} \leq b_4 e^{-1} t^p + \frac{b_4 e^{-1}}{(1+\lambda)} t^{p-1} \tag{4 57}$$

Similarly we can show that

$$I_{22} = \frac{-b_4 e^{-1}}{(1+\lambda)^{p+1}} e^{(1+\lambda)t} \int_0^{(1+\lambda)t} v^p e^{-v} dv \tag{4 58}$$

Integrating by parts in order to reduce the power on v above gives

$$\begin{aligned} I_{22} &= \frac{-b_4 e^{-1}}{(1+\lambda)^{p+1}} e^{(1+\lambda)t} \left[-(1+\lambda)^p t^p e^{-(1+\lambda)t} + p \int_0^{(1+\lambda)t} v^{p-1} e^{-v} dv \right], \\ &= \frac{-b_4 e^{-1}}{(1+\lambda)^{p+1}} e^{(1+\lambda)t} \left[-(1+\lambda)^p t^p e^{-(1+\lambda)t} + p\left[\Gamma(p) - \Gamma(p,(1+\lambda)t)\right] \right] \end{aligned} \tag{4 59}$$

Proceeding as for dI_{21}/dt, we can show that,

$$\frac{dI_{22}}{dt} = \frac{-b_4 p e^{-1}}{(1+\lambda)^p} \Gamma(p) e^{(1+\lambda)t} + R_{22}, \tag{4 60}$$

where

$$0 \leq R_{22} \leq \frac{b_4 p e^{-1}}{(1+\lambda)} t^{p-1} \tag{4 61}$$

Similarly we can show that

$$I_3 = \frac{b_2}{\lambda^{p-2}} e^{\lambda t} [\Gamma(p) - \Gamma(p, \lambda t)] \tag{4 62}$$

and

$$\frac{dI_3}{dt} = \frac{b_2}{\lambda^{p-3}} \Gamma(p) e^{\lambda t} + \frac{b_2 t^{p-1}}{\lambda^{-2}} - R_3, \tag{4 63}$$

where

$$0 \leq R_3 \leq \lambda^2 b_2 t^{p-1} \tag{4 64}$$

Adding equations (4 49), (4 56), (4 60) and (4 63) gives,

$$\begin{aligned} \frac{dI}{dt} &= \Gamma(p) e^{(1+\lambda)t} \left[\frac{b_3 e^{-1}}{(1+\lambda)^{p-1}} + \frac{b_4 e^{-1}}{(1+\lambda)^p} [(1+\lambda)t + 1] - \frac{b_4 p e^{-1}}{(1+\lambda)^p} \right] \\ &+ \Gamma(p) e^{\lambda t} \frac{b_2}{\lambda^{p-3}} + b_4 e^{-1} t^p + (b_3 e^{-1} + b_2 \lambda^2) t^{p-1} - R, \end{aligned} \tag{4 65}$$

where R is derived from equations (4 52), (4 57), (4 61) and (4 64) and is given by

$$\begin{aligned} R &= R_1 + R_{21} - R_{22} + R_3 \\ &\leq b_4 e^{-1} t^p + \left[b_3 e^{-1} + \frac{b_4 e^{-1}}{(1+\lambda)} - \frac{b_4 e^{-1} p}{(1+\lambda)} + \lambda^2 b_2 \right] t^{p-1} \end{aligned} \tag{4 66}$$

From equation (4 45) and equations (4 65) and (4 66) we have

$$\begin{aligned} h(t) &= C \frac{sin(p\pi)}{\pi} \\ &\left\{ \Gamma(p) e^t \left[\frac{b_3 e^{-1}}{(1+\lambda)^{p-1}} + \frac{b_4 e^{-1}}{(1+\lambda)^p} [(1+\lambda)t + 1] - \frac{b_4 p e^{-1}}{(1+\lambda)^p} \right] \right. \\ &+ \left. \Gamma(p) \frac{b_2}{\lambda^{p-3}} + b_4 e^{-1} e^{-\lambda t} t^p + (b_3 e^{-1} + b_2 \lambda^2) e^{-\lambda t} t^{p-1} \right\} - \hat{R}, \end{aligned} \tag{4 67}$$

where

$$0 \leq \hat{R} \leq C\frac{sin(p\pi)}{\pi}e^{-\lambda t} \left\{ b_4 e^{-1} t^p + \left[b_3 e^{-1} + \frac{b_4 e^{-1}}{(1+\lambda)} - \frac{b_4 e^{-1} p}{(1+\lambda)} + \lambda^2 b_2 \right] t^{p-1} \right\} \quad (4\,68)$$

The values of all parameters and the incidence of HIV infection arising from equations (4 67) and (4 68) will be provided below in Tables 4 6 and 4 7

4.6 Quadratic Growth in AIDS Cases.

We now consider the case when $a(t)$ is given by

$$a(t) = c_0 + c_1 t + c_2 t^2 \quad (4\,69)$$

We can easily show that $h(t)$ is as in (4 12) with $F(s)$ given by

$$F(s) = C\exp(\lambda s)[c_3 s^2 + c_4 s + c_5] \quad (4\,70)$$

where $c_3 = \lambda^2 c_2, c_4 = 4\lambda c_2 + \lambda^2 c_1$ and $c_5 = 2c_2 + 2\lambda c_1 + \lambda^2 c_0$ Making the change of variables $s = t - u$ as previous gives

$$I = \exp(\lambda t) \int_0^t u^{p-1} \exp(-\lambda u)[c_3 u^2 - (c_4 + 2c_3 t)u + f(t)]du, \quad (4\,71)$$

where $f(t) = c_3 t^2 + c_4 t + c_5$ and I is the integral of interest Using the same approach to evaluating the integral as in the previous case we can show that

$$\begin{aligned} h(t) &= C\frac{sin(p\pi)}{\pi} \left\{ \left[c_3 t^{p+1} + (c_4 + c_3(1-p)\lambda^{-1})t^p + c_5 t^{p-1} \right] e^{-\lambda t} \right. \\ &+ \left. \left[\frac{c_3}{\lambda^{p-1}} t^2 + \left[\frac{c_4}{\lambda^{p-1}} + \frac{2c_3(1-p)}{\lambda^p} \right] t + \frac{c_3 p(p-1)}{\lambda^{p+1}} + \frac{c_4(1-p)}{\lambda^p} + \frac{c_5}{\lambda^{p-1}} \right] \Gamma(p) \right\} \\ &+ \hat{R}, \end{aligned} \quad (4\,72)$$

where

$$\begin{aligned} 0 \leq \hat{R} \leq C\frac{sin(p\pi)}{\pi} e^{-\lambda t} \left\{ -c_3 t^{p+1} + (2c_3(p-1)\lambda^{-1} - c_4)t^p \right. \\ \left. + (c_3 p(1-p)\lambda^{-2} + c_4(p-1)\lambda^{-1} - c_5)t^{p-1} \right\} \end{aligned} \quad (4\,73)$$

Parameter estimates and results for this choice of $a(t)$ are provided in Tables 4 8 and 4 9

4.7 Results

For each of the four cases the parameters for $a(t)$, the number of AIDS cases in year t is as given in chapter 3, where the number of AIDS cases diagnosed and reported in any one year from 1981 to 1989 were adjusted for reporting delays Throughout this chapter we have chosen to start with $t = 1$ corresponding to the first year (1981) that AIDS cases were reported The incubation period distribution, $F(t)$ which we work with is that observed by Anderson and Medley (1988) [4] $F(t)$ is given by the Gamma distribution $\Gamma(\alpha, \lambda)$ with $\alpha = 2\,7$ and $\lambda = 0\,19$ This corresponds as we

have seen to a mean incubation period of $\mu = 14\ 3$ years and approximately 40% of all infected individuals progressing to AIDS within 10 years

For $a(t)$ given by an exponential we have $h(t)$ given by (4 28) with parameters given in Table 4 1 below

Table 4 1
Parameter Estimates Used to Evaluate $h(t)$ in (4 28)

Parameter	Value
C	115 0130
g	0 1884
$\Gamma(0\ 3)$	2 9920
$\Gamma(2\ 7)$	1 5450
$sin(p\pi)/\pi$	0 2575

These parameters along with those given earlier in Chapter 3 for d_0 and d_1 and equation (4 28) give rise to the estimates in Table (4 2) below for the incidence of HIV infection in Ireland from 1981 to 1992

Table 4 2
Expected Annual Incidence of HIV Infections,
$a(t)$ exponential, equation (4 2)

Year	Without Error Bound	With Error Bound
1981	28	24
1982	44	42
1983	74	73
1984	128	127
1985	223	222
1986	389	388
1987	679	679
1988	1186	1186
1989	2073	2073
1990	3623	3623
1991	6331	6331
1992	11065	11065
Total to 1989	4824	4814

When $a(t)$ is given by the quadratic exponential (4 30) $h(t)$ is found from (4 37) and the NAG (1984) [38] library program D01AJF Parameter values for $a(t)$ are as previous and the values of other parameters are given below in Table 4 3

Table 4 3
Parameter Estimates Used to Evaluate $h(t)$ in (4 37)

Parameter	Value
a_4	0 0019
a_5	0 0304
a_6	0 1529
δ	7 8793
a_7	0 0019
a_8	0 0005
a_9	0 0313

In order to estimate $h(t)$ from (4 37) we required the values of dI/dt where $I(t)$ was given in terms of the integral (4 40) We estimated dI/dt using the forward-difference and central-difference formulae described above with step size of $h = 0\ 001$ The values of $I(t)$, $I(t+h)$ and $I(t-h)$ along with an estimate of the associated error obtained from (4 40) and the NAG (1984) [38] library program D01AJF are given in Tables 4 4a and 4 4b below

Table 4 4a
Evaluating the Integral $I(t)$ in (4 40)

t	$I(t)$	Error
1	5 27022	$0\ 73\text{x}10^{-8}$
2	11 8058	$0\ 84\text{x}10^{-7}$
3	25 8227	$0\ 51\text{x}10^{-6}$
4	57 9752	$0\ 25\text{x}10^{-5}$
5	135 5830	$0\ 11\text{x}10^{-4}$
6	332 2450	$0\ 46\text{x}10^{-4}$
7	855 4990	$0\ 19\text{x}10^{-3}$
8	2318 2300	$0\ 78\text{x}10^{-3}$
9	6617 3900	$0\ 32\text{x}10^{-2}$
10	19911 9000	$0\ 13\text{x}10^{-1}$
11	63193 4000	$0\ 60\text{x}10^{-1}$
12	211620 0000	$0\ 46\text{x}10^{-1}$

Table 4 4b
Evaluating the Integrals $I(t-h), I(t+h)$ in (4 40)

t	$I(t-h)$	Error	$I(t+h)$	Error
1	5 26565	$0\ 76\text{x}10^{-8}$	5 27479	$0\ 74\text{x}10^{-8}$
2	11 7966	$0\ 85\text{x}10^{-7}$	11 8150	$0\ 85\text{x}10^{-7}$
3	25 8022	$0\ 52\text{x}10^{-6}$	25 8431	$0\ 51\text{x}10^{-6}$
4	57 9272	$0\ 25\text{x}10^{-5}$	58 0232	$0\ 25\text{x}10^{-5}$
5	135 4650	$0\ 11\text{x}10^{-4}$	135 7010	$0\ 11\text{x}10^{-4}$
6	331 9390	$0\ 45\text{x}10^{-4}$	332 5510	$0\ 46\text{x}10^{-4}$
7	854 6690	$0\ 19\text{x}10^{-3}$	856 3310	$0\ 19\text{x}10^{-3}$
8	2315 8600	$0\ 78\text{x}10^{-3}$	2320 6000	$0\ 78\text{x}10^{-3}$
9	6610 2800	$0\ 33\text{x}10^{-2}$	6624 5100	$0\ 32\text{x}10^{-2}$
10	19885 5000	$0\ 14\text{x}10^{-1}$	19934 4000	$0\ 13\text{x}10^{-1}$
11	63118 8000	$0\ 61\text{x}10^{-1}$	63268 2000	$0\ 60\text{x}10^{-1}$
12	211359 0000	$0\ 47\text{x}10^{-1}$	211882 0000	$0\ 46\text{x}10^{-1}$

Using the values for $I(t)$, $I(t-h)$ and $I(t+h)$ given above along with the central-difference and forward-difference formulae we arrive at the estimates for dI/dt given in Table 4 4c below

Table 4 4c
Values Obtained For dI/dt

t	Forward Difference	Central Difference
1	5	5
2	9	9
3	20	20
4	48	48
5	118	118
6	306	306
7	832	831
8	2370	2370
9	7120	7115
10	22500	24450
11	74801	74699
12	262000	261500
Error	$O(h)$	$O(h^2)$

Using the central-difference estimates for dI/dt and equation (4 37) we arrive at the following estimates for $h(t)$

Table 4 5
Expected Annual Incidence of HIV Infections,
$a(t)$ quadratic exponential, equation (4 30)

Year	$h(t)$
1981	18
1982	31
1983	57
1984	110
1985	223
1986	479
1987	1075
1988	2536
1989	6297
1990	17895
1991	45212
1992	130885
Total to 1989	10826

When $a(t)$ is given by the linear logistic (4 43) we see that $h(t)$ is given by (4 67) with $a(t)$ as previous and the following parameter estimates,

Table 4 6
Parameter Estimates Used to Evaluate $h(t)$ in (4 67)

Parameter	Value
b_3	0 1720
b_4	-0 0198

We are now in a position to provide estimates of $h(t)$, the annual incidence of HIV cases in Ireland from 1981 to 1992, given a linear logistic growth in the annual numbers of AIDS cases

Table 4 7
Expected Annual Incidence of HIV Infections,
$a(t)$ linear logistic, equation (4 43)

Year	Without Error Bound	With Error Bound
1981	13	11
1982	24	24
1983	49	48
1984	90	90
1985	136	136
1986	75	75
1987	-594	-594
1988	-3778	-3778
1989	-16151	-16151
1990	-59887	-59887
1991	-206236	-206236
1992	-678703	-678703

When $a(t)$ is given by the quadratic (4 69), with parameters as given previously then parameters for $h(t)$ in (4 72) are as given below in Table 4 8

Table 4 8
Parameter Estimates Used to Evaluate $h(t)$ in (4 72)

Parameter	Value
c_3	0 0522
c_4	0 7926
c_5	0 0670

Table 4 9
Expected Annual Incidence of HIV Infections,
$a(t)$ quadratic, equation (4 69)

Year	Without Error Bound	With Error Bound
1981	135	40
1982	173	108
1983	212	160
1984	253	210
1985	297	260
1986	343	312
1987	393	366
1988	445	422
1989	500	480
1990	558	541
1991	620	605
1992	684	671
Total to 1989	2751	2358

4.8 Discussion

We see from Tables 4 2, 4 5, and 4 9 that estimates of the total number HIV infectious in Ireland from 1981 to 1989 inclusive ranges from 2751 to 10,826 This ia a considerable narrowing of the range estimated in Chapter 3, where approximations to the fitted incubation distribution were used in all calculations From HIV testing centres we know that there were approximately 1000 HIV individuals testing positive during the same time period However predictions diverge considerably for 1990, 1991 and 1992 This is also the case with the predictions of Isham (1988) [25] based on approximations of the incubation period distribution We saw in Chapter 3 that this divergence in predictions for later years is directly related to the nature of $a(t)$ at these time points

If we look at each of the four cases individually, for predictions up to and including 1989 we see that in the exponential case the is a large increase in the numbers becomming HIV positive in 1989 and the years thereafter This is a direct result of the choice of $a(t)$ and is also evident in the quadratic exponential case In the latter we estimate 2536 cases in 1988 and 6297 cases in 1989 In the case of the linear logistic we have negative numbers predicted from 1987 This is due to $a(t)$ itself predicting low figures for these years With the quadratic case figures for the numbers of HIV positives increase evenly over the 9 years

Overall there is good improvement on the Chapter 3 estimates If we decide to look only at the totals to 1988, due to the large increases in the 1989 figures, we arrive at estimates of the numbers of HIV positives ranging from 2251 to 4529, representing the quadratic and quadratic exponential respectively This is a very encouraging improvement on all previous estimates and would lead one to believe that the methods discussed in this Chapter can be applied with increasing confidence as time progresses and we have more data with which to estimate $a(t)$

Chapter 5

Estimating Deaths and Prevalence.

5.1 Introduction

In this Chapter we attempt to estimate the annual death rate from AIDS We are interested in the number of deaths arising from all associated AIDS illnesses and complications and not just those deaths where AIDS has been recorded on the death certificates In Ireland the National AIDS Co-ordinator regularly scans death certificates in order to identify AIDS related deaths (personal communication, Dr J Walsh, Department of Health) It is often the case that AIDS has not been recorded on the death certificate in order to respect the feelings of the deceased's family All AIDS related deaths must be estimated in order to give a true picture of the extent of the disease

We also intend in this Chapter to estimate the prevalence of AIDS in Ireland by providing estimates of the numbers of AIDS cases alive each year This we shall accomplish by looking at the numbers of new AIDS cases each year, as described earlier in Chapter 3, and combine these with estimates of the annual death rate We shall provide predictions for the actual numbers of diagnosed cases as opposed to the reported numbers, as it is the actual number of diagnosed cases that the health services will have to provide for

5.2 Methods

There are two ways in which estimates of the annual death rate can be derived One consists of the extrapolation from current figures on AIDS related deaths obtained by the Department of Health Using this approach one could in principle extrapolate the figures for the combined cases and for each risk group, so providing estimates of the annual death rate within each group Those most at risk could then be clearly identified and targeted by the health services

While this appears to be a reasonable approach in theory, this is not feasible within the Irish situation There are few deaths in the early eighties and cases recorded in the mid to late eighties are sparse and erratic This can be seen in Table 5 1 below

Table 5 1
Reported deaths from AIDS in Ireland from 1981 to 1989 by year of diagnosis

Year of Diagnosis	Male Homo/ Bisexual	IV Drug User	Homo/Bi IVDU	Haemo- philia	Hetero /Others	Mother To Child
Pre 1981						
1981						
1982	2					
1983			1			
1984	1		1	1		
1985	1	1	1		1	1
1986	1	1		3		1
1987	6	7	1	2	1	
1988	4	1		1	1	2
1989	7	1	1	1	4	1
Total	22	11	5	8	7	5

Also, if we plot the figures on deaths for the IVDU or homosexual/bisexual group we find no apparent pattern in the profiles For these reasons we seek a different approach to the estimation of annual death rates

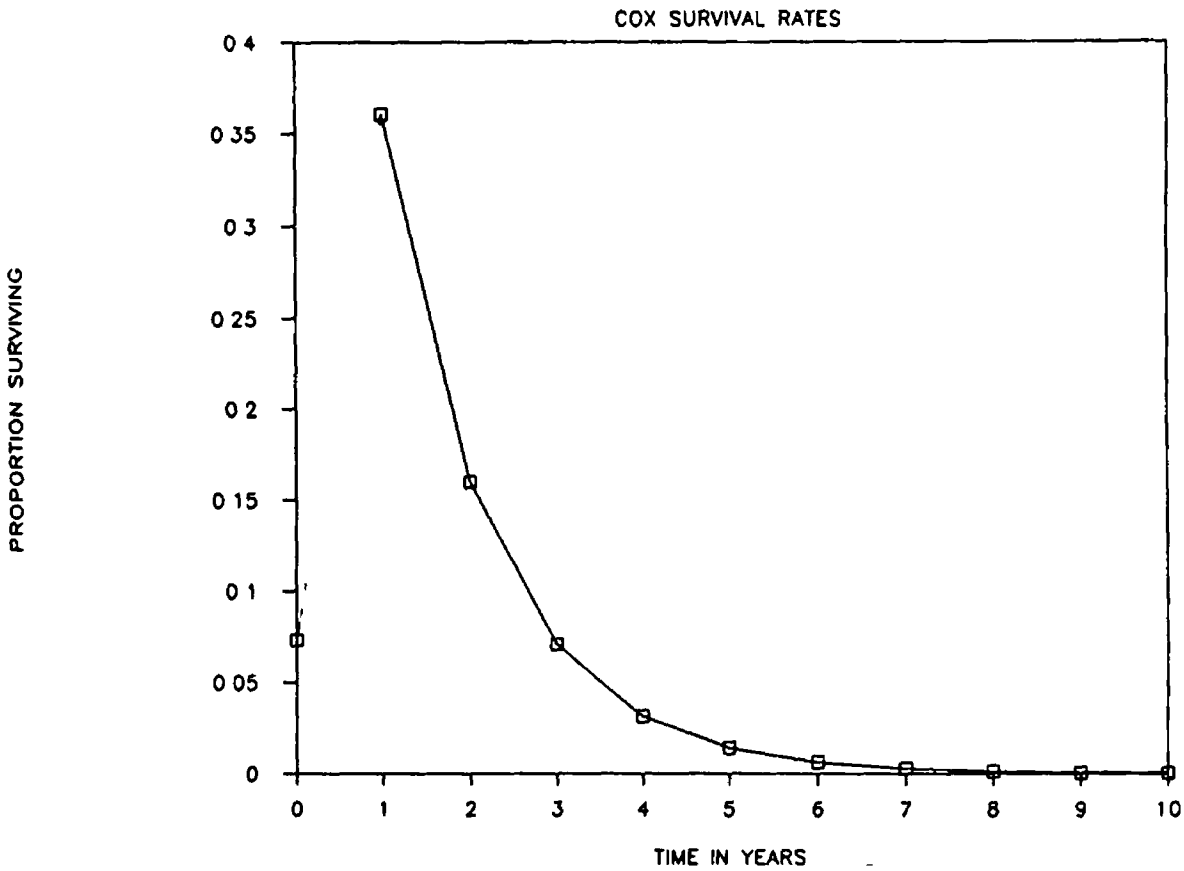
Sir David Cox (1988) [16] provides predictions of deaths and prevalence based on estimates of the number of new AIDS cases per year and the distribution of survival times from the onset of AIDS to death We implement this approach here and again in Chapter 7, when we discuss our transmission models which predict from the number of susceptible through infectious to death This approach depends upon reliable estimates of survival rates of AIDS patients and the estimates of $a(t)$ as derived in Chapter 3

5.3 Estimating Survival Times

Data on the initial diagnosis of AIDS to date of death has not as yet been collated and analysed for Irish AIDS patients Data on survival times is not available in any single center Some patient information on these dates is available in the Dublin Genito Urinary Clinic at St James' Hospital, Dublin These files are in the process of computerisation Some information on rural cases is available in the Department of Health, where G P s report new diagnoses of AIDS Indeed it can be the case that diagnosis of AIDS and death are simultaneous The computerisation of records at St James's Hospital will, when completed, enable one to analyse Irish survival rates However estimates of annual death rates depend upon estimates of survival rates, so for this reason we choose to work with estimates of survival rates as discussed by Reeves and Overton (1988) [43] and Cox (1988) [16] but we are aware of this implications this has on our final estimates of the Irish annual death rates

Reeves and Overton (1988) [43] performed a preliminary survival analysis of 725 U K AIDS patients This was then compared with an analysis of trends by Marasca and McEnvoy (1987) [31] in 725 patients from the United Kingdom and 5833 patients from New York City The median survival time for selected subgroups was computed and found to be very similar to that of the New York group No major differences in survival times between male homosexual and IVDU groups were found For our

FIGURE 5 1



prediction purposes it is the overall distribution of survival time (from diagnosis to death) that is of interest Reeves (1988) [44] updates original predictions on survival times with the analysis of 997 U K AIDS patients It was found that a two parameter exponential model given by $S(t) = \alpha \exp(\beta t)$ fitted the data well, with 0 08 equalling the probability of death and diagnosis being simultaneous, a median survival time of 9 2 months and a mean survival time of 1 14 years

Cox (1988) [16] when estimating the ratio of death and diagnosis rate, report and diagnosis rate assumes a probability of 0 073 of diagnosis and death being simultaneous, a median survival time of 7 2 months and a mean survival time of 1 22 years This distribution of survival times is plotted in Figure 5 1

Finally, the main point of interest from an Irish point of view of the Reeves and Overton (1988) [43] research is that the analysis of U K and New York City data gave similar results and that no major differences in median survival times were observed between risk groups We can therefore be more confident in using the predictions of survival times of others in order to estimate Irish annual death rates

5.4 Estimating the Number of Deaths

Assuming the distribution of survival times discussed in the previous section the rate of occurrence of deaths at time t is given by

$$d(t) = \gamma_0 a(t) + (1 - \gamma_0) \int_0^t a(u)\gamma \exp[-\gamma(t-u)]du \qquad (5\ 1)$$

Intuitively this says that the rate of occurrence of deaths at time t depends upon those cases where diagnosis of AIDS and death are simultaneous plus all cases that

were diagnosed in the past and have survived up to the present time

If we assume that $S(t)$ is as discussed above and $a(t)$ is given by one of the four forms,

$$a(t) = d_0 \exp(d_1 t), \tag{5 2}$$

$$a(t) = a_0 \exp(a_1 t - a_2 t^2), \tag{5 3}$$

$$a(t) = \frac{b_0 + b_1 t}{\exp(1-t)} + b_2, \tag{5 4}$$

$$a(t) = c_0 + c_1 t + c_2 t^2, \tag{5 5}$$

then $d(t)$ can easily be derived analytically Here and throughout this chapter Greek and Roman letters denote constants which have been or will be estimated from the data If $a(t)$ is given by equation (5 3) then $d(t)$ may be derived numerically

Case 0 if $a(t)$ is given by equation (5 2) then,

$$d(t) = \gamma_0 d_0 \exp(d_1 t) + (1-\gamma_0) \int_0^t d_0 \exp(d_1 u) \gamma \exp[-\gamma(t-u)] du \tag{5 6}$$

When integrated this gives,

$$d(t) = d_0 \exp(d_1 t) \frac{\gamma_0 d_1 + \gamma}{d_1 + \gamma} - \frac{1-\gamma_0}{d_1+\gamma} d_0 \gamma \exp(-\gamma t) \tag{5 7}$$

Case 1 if $a(t)$ is given by equation (5 3) then,

$$d(t) = \gamma_0 a_0 \exp(a_1 t - a_2 t^2) + (1-\gamma_0) \int_0^t a_0 \exp(a_1 u - a_2 u^2) \gamma \exp[-\gamma(t-u)] du \tag{5 8}$$

Taking terms containing t outside the integral gives,

$$d(t) = \gamma_0 a_0 \exp(a_1 t - a_2 t^2) + (1-\gamma_0) a_0 \gamma \exp(-\gamma t) \int_0^t \exp[(a_1+\gamma)u - a_2 u^2] du \tag{5 9}$$

The integral on the right hand side of equation (5 9) must be solved numerically for t, as we are looking for the integral of a quadratic exponential We are interested in values of t from 1 to 12 in order to estimate the number of deaths from 1981 to 1992 To do this we employed the NAG (1984) [38] routine D01AJF This is a general purpose integrator which calculates an approximation to the integral of a function $F(x)$ over a finite interval (A, B)

Case 2 if $a(t)$ is given by equation (5 4) then,

$$d(t) = \gamma_0 a(t) + (1-\gamma_0) \gamma \exp(-\gamma t) \int_0^t a(u) \exp(\gamma u) du \tag{5 10}$$

Consider first the integral on the right hand side of equation (5 10) above, which we denote by I We have

$$I = \int_0^t \frac{b_0 + b_1 u}{\exp(1-u)} \exp(\gamma u) + b_2 \exp(\gamma u) du \tag{5 11}$$

Splitting the above into the sum of three integrals gives,

$$I = \int_0^t \frac{b_0}{\exp(1-u)} \exp(\gamma u) du + \int_0^t \frac{b_1 u \exp(\gamma u)}{\exp(1-u)} du + \int_0^t b_2 \exp(\gamma u) du \tag{5 12}$$

We can now say that $I = I_1 + I_2 + I_3$ with the definitions of I_1, I_2, I_3 obvious Evaluating I_1 we have,

$$I_1 = \int_0^t b_0 \exp[(\gamma + 1)u - 1]du, \tag{5 13}$$

integrating gives,

$$I_1 = \frac{b_0}{\gamma + 1} \exp[(\gamma + 1)t - 1] - \frac{b_0}{\gamma + 1} e^{-1} \tag{5 14}$$

To compute I_2 we use integration by parts, starting from,

$$I_2 = \int_0^t b_1 u \exp[(\gamma + 1)u - 1]du, \tag{5 15}$$

to obtain,

$$I_2 = \left[\frac{b_1 t}{(\gamma + 1)} - \frac{b_1}{(\gamma + 1)^2}\right] \exp[(\gamma + 1)t - 1] + \frac{b_1 e^{-1}}{(\gamma + 1)^2} \tag{5 16}$$

I_3 may be evaluated directly as,

$$I_3 = \frac{b_2}{\gamma}[\exp(\gamma t) - 1] \tag{5 17}$$

By combining equation (5 10) with the sum of I_1, I_2 and I_3 we have,

$$\begin{aligned} d(t) \;=\; & \gamma_0 a(t) + (1 - \gamma_0)\gamma \exp(-\gamma t) \left[\frac{b_2}{\gamma} \exp(\gamma t) + \left(\frac{b_0 + b_1 t}{\gamma + 1} - \frac{b_1}{(\gamma + 1)^2}\right)\right. \\ & \left. \exp[(\gamma + 1)t - 1] + \left(\frac{b_1}{(\gamma + 1)^2} - \frac{b_0}{\gamma + 1}\right) e^{-1} - \frac{b_2}{\gamma}\right] \end{aligned} \tag{5 18}$$

Case 3 if $a(t)$ is given by equation (5 5) then $d(t)$ is given by,

$$d(t) = \gamma_0 a(t) + (1 - \gamma_0)\gamma \exp(-\gamma t) \int_0^t (c_0 + c_1 u + c_2 u^2) \exp(\gamma u) \tag{5 19}$$

Again the integral on the right hand side of equation (5 19) can be calculated by splitting the integral into the sum of three integrals and integrating by parts We have,

$$I_1 = \int_0^t c_0 \exp(\gamma u)du \tag{5 20}$$

which when integrated simply gives,

$$I_1 = \frac{c_0}{\gamma}[\exp(\gamma t) - 1] \tag{5 21}$$

$$I_2 = \int_0^t c_1 u \exp(\gamma u)du, \tag{5 22}$$

which when integrated gives,

$$I_2 = \exp(\gamma t)\left[\frac{c_1 t}{\gamma} - \frac{c_1}{\gamma^2}\right] + \frac{c_1}{\gamma^2} \tag{5 23}$$

Finally I_3 is given by,

$$I_3 = \int_0^t c_2 u^2 \exp(\gamma u) du, \tag{5.24}$$

which when integrated by parts twice gives,

$$I_3 = \left[\frac{c_2 t^2}{\gamma} - \frac{2c_2 t}{\gamma^2} - \frac{2c_2}{\gamma^3}\right] \exp(\gamma t) + \frac{2c_2}{\gamma^3}. \tag{5.25}$$

Adding equations for I_1, I_2 and I_3 and combining with equation (5.19) gives,

$$\begin{aligned} d(t) &= \gamma_0 a(t) + (1-\gamma_0)\left[c_2 t^2 + (c_1 - \frac{2c_2}{\gamma})t + (c_0 - \frac{c_1}{\gamma} + \frac{2c_2}{\gamma^2})\right] \\ &\quad + (1-\gamma_0)\exp(-\gamma t)\left[-\frac{2c_2}{\gamma^2} + \frac{c_1}{\gamma} - c_0\right]. \end{aligned} \tag{5.26}$$

5.5 Estimating The Prevalence

The second objective of this chapter is to provide predictions of prevalence of AIDS in Ireland. The number of live cases will be the difference between the number of diagnosed cases and the number of deaths. We define $p(t)$ to be the number of patients alive and diagnosed as having AIDS at time t. This is then given by

$$p(t) = \int_0^t [a(u) - d(u)] du. \tag{5.27}$$

We consider the four cases where $a(t)$ is given by equations (5.2) to (5.5) above.

Case 0: if $a(t)$ is given by the simple exponential form (5.2) then,

$$p(t) = \int_0^t \left[1 - \frac{\gamma_0 d_1 + \gamma}{\gamma + d_1}\right] d_0 \exp(d_1 u) + \frac{(1-\gamma_0)}{\gamma + d_1} d_0 \gamma \exp(-\gamma u) du. \tag{5.28}$$

This is easily integrated to give

$$p(t) = d_0 \frac{1-\gamma_0}{\gamma + d_1} \left[\exp(d_1 t) - \exp(-\gamma t)\right]. \tag{5.29}$$

Case 1: when $a(t)$ is given by the quadratic exponential (5.3) we have,

$$p(t) = \int_0^t [a(u) - d(u)] du, \tag{5.30}$$

but this integration cannot be performed analytically as we do not know the explicit form of $d(u)$. To solve we split (5.30) into the difference of two integrals given by

$$p(t) = \int_0^t a(u) du - \int_0^t d(u) du. \tag{5.31}$$

The first integral we can solve numerically by using a modified version of the NAG (1984) [38]library routine D01AJF. The second can be solved by implementing the NAG routine D01GAF which integrates a function which is specified numerically at four or more points over the whole of its range. This routine uses third order finite difference formula with error estimates, according to a method due to Gill and Miller (1972) [22]. We are interested in values of the integral when t takes on values from $t = 1$ to $t = 12$, corresponding to the years 1981 to 1992. This is straightforward as we have d(u) specified at at least four points when $t \geq 4$. To evaluate the integral

between 0 and 1, 0 and 2 and 0 and 3, two further values of $d(u)$ between 0 and 3 had first to be computed When all required values of the integral were found, these were then subtracted from the corresponding values of $\int_0^t a(u)du$ to provide the estimates of $p(t)$

Case 2 if $a(t)$ is given by the linear logistic type function in equation (5 4) then $p(t)$ is given by,

$$\frac{p(t)}{(1-\gamma_0)} = \int_0^t a(u) - \gamma e^{-\gamma u}\left[\frac{b_2}{\gamma}e^{\gamma u} + \left(\frac{b_0+b_1 u}{\gamma+1} - \frac{b_1}{(\gamma+1)^2}\right)e^{(\gamma+1)u-1} + \left(\frac{b_1}{(\gamma+1)^2} - \frac{b_0}{\gamma+1}\right)e^{-1} - \frac{b_2}{\gamma}\right]du \quad (5\ 32)$$

The solution of the integral may be found by splitting the integral into a sum of several smaller integrals The calculations are straightforward but tedious Integrating equation (5 32) above gives,

$$\begin{aligned}\frac{p(t)}{(1-\gamma_0)} = {} & \left[b_0 + b_1(t-1) - \gamma\left[\frac{b_0}{\gamma+1} - \frac{b_1}{(\gamma+1)^2}\right] - \gamma\frac{b_1}{\gamma+1}(t-1)\right]e^{t-1} \\ & + \left[b_1 - b_0 + \gamma\left[\frac{b_0}{\gamma+1} - \frac{b_1}{(\gamma+1)^2}\right] - \gamma\frac{b_1}{\gamma+1}\right]e^{-1} \\ & + \left[\gamma\left[\frac{b_0}{\gamma+1} - \frac{b_1}{(\gamma+1)^2}\right]e^{-1} + b_2\right]\left[-\frac{1}{\gamma}e^{-\gamma t} + \frac{1}{\gamma}\right] \quad (5\ 33)\end{aligned}$$

The values of $p(t)$ using the parameter estimates discussed earlier are given in Table 5 2

Case 3 when $a(t)$ is given by the quadratic in equation (5 5) we have,

$$\frac{p(t)}{(1-\gamma_0)} = \int_0^t a(u) - \gamma e^{-\gamma u}\left[\frac{1}{\gamma}e^{\gamma u}\left(c_2u^2 + (c_1 - \frac{2c_2}{\gamma})u + c_0 - \frac{c_1}{\gamma} + \frac{2c_2}{\gamma^2}\right) - \frac{2c_2}{\gamma^3} + \frac{c_1}{\gamma^2} - \frac{c_0}{\gamma}\right]du \quad (5\ 34)$$

Again this integral is cumbersome but straightforward and may be solved by splitting into more managable parts The solution of $p(t)$ is given by,

$$\frac{p(t)}{1-\gamma_0} = \left[\frac{c_1}{\gamma} - \frac{2c_2}{\gamma^2}\right]t + \left[\frac{c_2}{\gamma}\right]t^2 + \left[e^{-\gamma t} - 1\right]\left[-\frac{2c_2}{\gamma^3} + \frac{c_1}{\gamma^2} - \frac{c_0}{\gamma}\right] \quad (5\ 35)$$

5.6 Results

We use Table 3 2 as discussed in Chapter 3 for parameter estimates of $a(t)$ Using Cox's estimates on survival rates, and equation (5 7), equation (5 9) with routine D01AJF and equations (5 18) and (5 26) we can provide estimates for the rate of occurrence of AIDS related deaths at time t These are provided in Table 5 1 below

Table 5 1
Predictions of Number of Deaths

Year	Case 0	Case 1	Case 2	Case 3	Known
1981	1	0	0	4	0
1982	1	1	1	2	2
1983	1	1	1	0	1
1984	2	2	2	0	3
1985	3	3	3	2	5
1986	6	5	5	6	6
1987	10	9	11	13	17
1988	18	18	21	23	9
1989	32	37	36	36	15
1990	56	82	40	52	
1991	97	191	-44	70	
1992	170	474	-534	92	

The values of $p(t)$ for equation (5 29), equation (5 31) with routine D01AJF and D01GAf and equations (5 33) and (5 35) with parameter estimates discussed above can be found in Table 5 2 below

Table 5 2
Predictions of Prevalence

Year	Case 0	Case 1	Case 2	Case 3
1981	0	0	0	4
1982	1	1	1	3
1983	1	1	1	0
1984	2	2	2	0
1985	4	3	3	1
1986	6	6	6	6
1987	11	10	12	14
1988	20	19	22	25
1989	34	40	38	39
1990	60	87	43	57
1991	105	201	-46	78
1992	184	496	-562	102

5.7 Discussion

The predictions of the number of deaths and prevalence of AIDS are based on the form of $a(t)$ and the assumption that there is no major change in the distribution of times between diagnosis and death Obviously as there are improvements in the treatment of AIDS patients, the lengths of survival times will increase and the distribution will have to be reassessed

The total number of deaths to the end of 1989 given exponential growth in the number of new AIDS cases, is 71 This compares with 58 deaths known to the Department of Health at that time After 1990 the number of deaths increases more rapidly as would be expected from the exponential distribution The total number of deaths in the same period for $a(t)$ described by the quadratic exponential is 76 The figures for the number of deaths then increase very rapidly from 1990 to 1992 and cannot be considered as predicative in any way If $a(t)$ is given by the linear logistic form we arrive at a total of 80 deaths to the end of 1989 We then

obtain negative results for 1991 and 1992 This is a direct consequence of $a(t)$ itself becoming negative at this time for this form Finally, the quadratic form for $a(t)$ gives a total of 86 deaths up to the end of 1989 This is a slightly higher estimate than the others due to the nature of the quadratic which predicts a larger number of deaths in the initial stages of the epidemic

Comparing the total number of deaths predicted from each of the $d(t)$ with the known number of deaths in the same period we see that predictions differ with the known by factors ranging from 1 22 to 1 48 This we may use to obtain a more accurate picture of the actual numbers as opposed to the reported numbers of deaths in any period

All estimates on deaths are derived directly from the fits for $a(t)$ which are in turn derived from those AIDS cases reported to the Department of Health As a result when we estimate $p(t)$ from both $a(t)$ and $d(t)$ we arrive at figures lower than those given by the Department of Health According to the department there was a total of 124 known cases of AIDS up to and including 1989 During the same period there were 58 known deaths This would lead us to believe that there were 66 live cases of AIDS in Ireland at the end of 1989 However we believe, based on our calculations, that the figures for the numbers of deaths as published by the Department of Health are under-reported Our estimates of prevalence are then lower than those of the Department because we are working from the number of AIDS cases reported to the Department adjusted for reporting delays and subtracting the higher estimates for the numbers of deaths

Chapter 6

HIV Transmission Survey.

6.1 Introduction

The aim of this survey was to investigate the social, sexual and drug habits of those at risk from the Human Immunodeficiency Virus (HIV). It was our intention to look particularly at the rate of needle use in the drug abusing population and the rate of sexual partner change amongst all individuals at risk. In addition to this we aimed to estimate the rate of introduction to each of the at risk populations. This information is essential to the construction of any mathematical or statistical models for the transmission dynamics of the disease. It was our original intension to administer the survey at several centres, to encompass both HIV positive and negative individuals. Unfortunatly this was not possible at the time as a European study was already in progress at one of the planned administration centres. Given this obvious limitation, to our knowledge this is still the most comprehensive survey of this type, to date, in the Irish population at risk of HIV. Research on sexual behaviour has been carried out in America and Britain [29] but results from these countries cannot necessarily be applied to the Irish situation.

The participants in the survey were drawn from the Genito Urinary Clinic at St. James Hospital Dublin. All patients attending the clinic have been tested HIV positive. At the time of our initial pilot survey there was a total of approximately 300 patients registered at the clinic, although not all of these were regular attenders. For the purposes of the pilot survey it was agreed with the clinic that twenty patients would be surveyed initially and we hoped to survey approximately two hundred patients in the final survey. Due to clinic difficulties and pressures of time a total of nineteen patients were questioned in the pilot and 187 patients questioned in the final survey. Details of the pilot survey report is provided in Appendix A. A copy of the final survey form is given in Appendix B.

The information collected in the final survey can be broken down into five categories. These were;

Section 0: Interview Details.

In this section the date and place of the interview was recorded. To check for interviewer bias the interviewers' initials were also noted.

Section 1: Personal Details.

This section included the patients initials, data of birth, sex, primary risk category, cohabitation status and information on where else the patient was under regular care. This final question was included to enable us to check for duplications, if the survey were to be administered at another centre at a later date.

Section 2: HIV Details.

In this section the patient was asked how many times he/she had been tested for the HIV virus Each patient was then asked to give the dates of their last negative test and their first positive test We know from the Virus Reference Laboratory that many people have had more than one HIV test He/she was then asked if they had a regular partner and if so they were questioned on the HIV status of their partner and date of their partners first positive test He/she was also requested to state their CDC classifications and if they were classified as stage CDC 4 they were asked to state when they progressed to stage 4

Section 3a Heterosexual Partner Details

Within this section patients were asked to describe their sexual activity pattern and if this pattern had changed since becoming HIV positive They were then asked to give their average number of partners per month and per year (as a check), the age at which they first became heterosexually active, if they used contraceptives and if so we asked what type of contraception was used We would consider the age at which a patient first became sexually active a key question This information may be used to estimate a transmission model parameter describing the introduction rate to the heterosexually active population

Section 3b Homosexual Partner Details

This section requested those who engaged in homosexual and bisexual activity to answer questions on their sexual activity similar to those asked of heterosexuals They were also asked to list their types of sexual activity

Section 4 Drug Use Details

Patients were asked if they had used intravenous drugs in the past If so they were then requested to give information on why and when they had stopped, estimates on the extent of their drug use, per day and per week, frequency of needle sharing and the lifetime of their needles Patients were also asked at what age they first used intravenous drugs This is also a key question and information from replies will be used to estimate the introduction rate to the male and female drug using populations Patients were then asked if their drug use pattern had changed since becoming HIV positive Female patients in this section were asked if they had given birth since becoming HIV positive and if so they were then asked to provide details on the HIV status of their children Finally patients were asked to list any other relevant information

The data described above was collected by the medical staff at the clinic This included the consultant, the senior house officers and a research nurse The survey was administered by the staff while patients were attending the clinic for reasons associated with their HIV status The 187 patients involved in the survey were questioned on a first come first served basis

Finally the primary aim of the survey was two fold firstly to provide a comprehensive picture of the behaviour of those at risk from and capable of transmitting the HIV virus and secondly to generate the necessary data for the estimation of the essential epidemiological parameters used in our transmission models of HIV within the Irish IVDU and homosexual populations, discussed in Chapter 7

6.2 Methods

Descriptive statistics in the form of mean, mode, median, ranges and distribution of replies to questions were prepared Key questions, necessary for parameter estimation, were identified and looked at in more detail In this section we shall also give a brief description of the steps followed to ensure accuracy

All questionnaires were read and checked prior to data entry For ease of reference each questionnaire was then assigned a case number and a batch number, completed questionnaires were returned in several batches on an ongoing basis Each questionnaire was also assigned a record number from 1 to 20, depending on the description of the patient and the number of variables to be recorded for that patient For example record type one referred to male drug abusers and record type twenty referred to female bisexuals who used intravenous drugs and had no children Data was entered in fixed format with each variable assigned a short variable name and fixed position Hardcopy records of the variable names and positions were kept, details of these along with a description of record types are available in Appendix D, (see file, Survey sps) Approximately one hundred variables were identified and from these, others, including the length of time the patient had been positive and the minimum length of the incubation period of those at CDC stage 4 were computed SPSSX the statistical package for the social sciences was used to analyse the data In order to shorten subsequent command files all data definitions and derived variables were stored in system files These could then be readily accessed

The statistical analysis of the survey was broken down into several sections which followed along the lines of the sections within the survey itself

6.3 Results

In this section we shall briefly summarise our main findings In relation to key questions we shall first provide the overall findings and shall then split the results by risk group

Section 0 Interview Details

A total of 187 surveys were administered to the patients between November 1989 and May 1991 To check for duplication of patients interviewed, the patients' initials with the age they were at the time of the statistical analysis (May 1991) were cross tabulated From this we found that six patients were interviewed twice For each of these six, the second interview was deleted from the file and all subsequent analysis was carried out on the remaining 181 patients There was a total of ten interviewers identified, of these, one, a research nurse trained in survey and clinical trial administration, carried out the majority, 75% or 135 of the interviews The senior consultant at the clinic administered the majority of the remaining 46 questionaires

Section 1 Personal Details

Initials, date of birth and sex of the patient were recorded Of the 181 patients surveyed 119 or 65 7% were male and 62 or 34 3% were female, giving a male/female ratio of 1 9/1,in agreement with the male/female ratio at the clinic Patients were classified into one of six risk groups 92 or 50 8% were identified as male IVDU, 51 or 28 2% as female IVDU, 20 or 11 0% as male homosexual only, 3 or 1 7% as male bisexual only, 2 or 1 1% as male homosexual or bisexual and IVDU and 13 or 7 2% as other risk The age of the 181 patients surveyed ranged from 18 years to 40 years with 3 missing observations The distribution of ages for male and female IVDU's and homosexuals is provided in the form of a stacked bar chart in Figure 6 1 Summary statistics are provided in Table 6 1

FIGURE 6 1

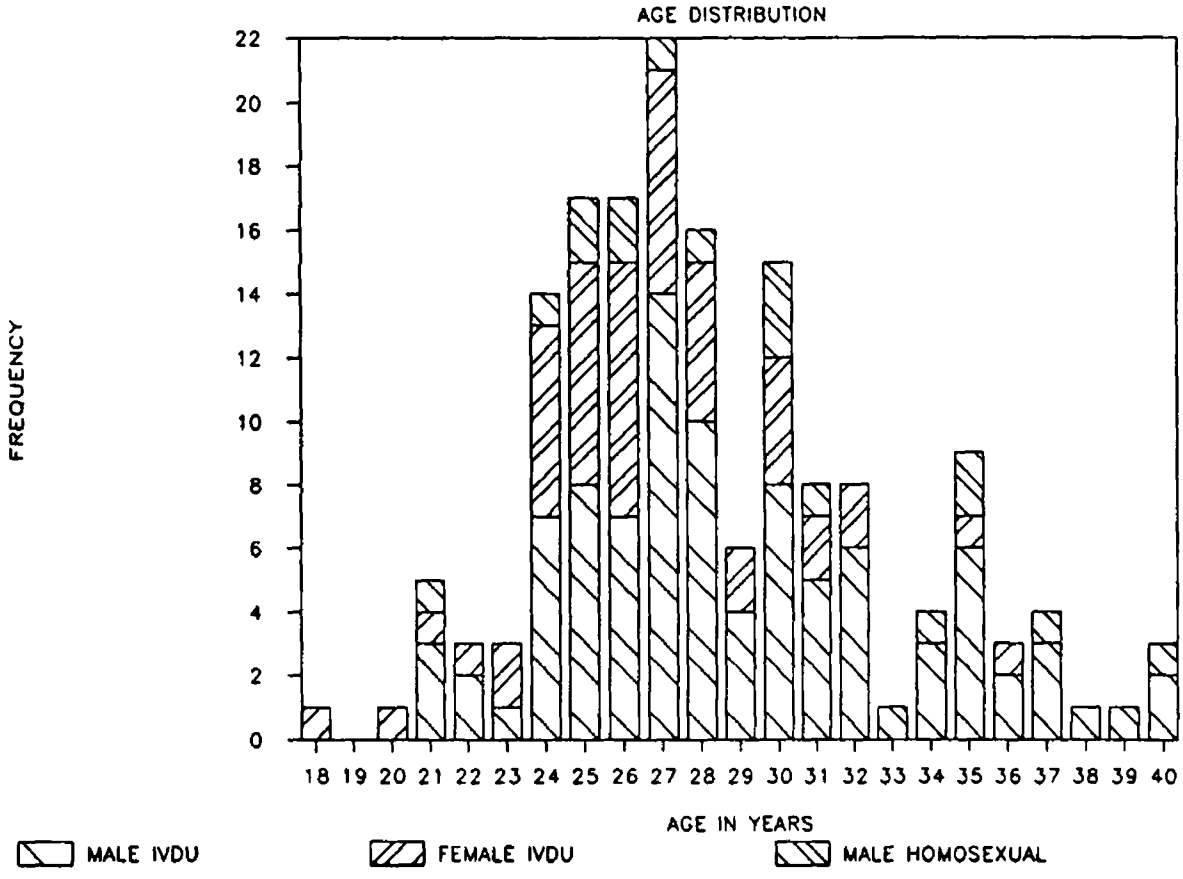


Table 6 1
Summary Statistics for Age distributions, in years

	Male IVDU	Female IVDU	Homosexual
Mean	28 85	26 63	30 32
Median	28 00	26 00	30 00
Std Dev	4 38	3 41	5 36
No of cases	92	51	19

As these three groups constitute the main risk groups, the reader interested in detailed age profiles for other risks is referred to Appendix D, file Survey1 out

When questioned on their living arrangements 96 or 53 3% said they were living alone or had living arrangements other than with a male or female partner When asked to specify most said they were living with their family, parents or brothers and sisters 41 or 22 8% said they were living with a male and 43 or 23 9% said they were living with a female There was one missing observation in this question

Most patients were in receipt of regular care elsewhere in addition to the care they received at St James' hospital Only 5 of the 181 surveyed said they received no other regular care The replies to this question would be very important if the survey had been carried out at several centres as originally planned

Section 2. HIV Details

In this section patients were asked how many times they had been tested for the HIV virus and on which dates They were also asked to give their CDC classification and if at CDC stage 4 they were asked when they had progressed to this stage They

were also asked about the HIV status of their regular partner It was hoped that some preliminary information on incubation periods and durations positive could be obtained from the patient replies to these questions

When asked how many times the patient had been tested for the HIV virus it was observed that replies ranged from 0 to 20 times The mean number of times tested over all risk groups was 2, however 57% or 103 patients, were tested only once Two patients said they were never tested Within the male IVDU, female IVDU and homosexual groups most patients were tested only once for the virus

The distribution of patients overall risk groups and within the male and female IVDU and homosexual groups over all CDC classifications is summarised in Table 6 2 below Patients may be classified at one or more stages of the disease, AIDS Once a patient is classified as CDC stage 4, they are at the AIDS stage

Table 6 2
Distribution of patients over CDC classifications

CDC Classification	Over all Risks	Male IVDU	Female IVDU	Homo-sexual
CDC1	1	1	0	0
CDC2	79	37	27	4
CDC3	54	24	18	8
CDC4a	1	0	1	0
CDC4b	0	0	0	0
CDC4c1	27	16	3	5
CDC4c2	10	7	1	2
CDC4d	1	1	0	0
CDC4e	3	3	0	0
Not Classified	1	0	1	0
Missing Observations	4	3	0	1
Total	191	92	51	20
% at Stage 4	27	29	9	35

The length of time for which the patient had been positive at the time of interview was computed from the date of first positive test and date of interview When we looked at all 181 patient replies we found that data was missing for 55 patients This was due mainly to the fact that many people interviewed could not remember the month of their first positive test Looking at the remaining 126 patient replies we found that the mean length of time patients had been positive was 2 08 years, with a median of 2 00 years, standard deviation of 1 83 years and a range of 0 to 6 years Most people, 35, had first tested HIV positive less than one year previous

There were 95 patients who had not yet reached CDC stage 4 and had dates of first positive HIV test The mean duration positive of these 95 patients was 1 99 years, with a median of 2 00 years, range of 0 to 6 years and a standard deviation of 1 83 years Again most of these 95 patients had first tested HIV positive less than one year previously There was a total of 29 patients at CDC stage 4 who had dates of first positive HIV test available The mean duration positive of these 29 patients was 2 48 years, with a median of 2 00 years, range of 0 to 6 years and a standard deviation of 1 83 years Most patients in this group had first tested HIV positive at least one year previous

A summary of incubation information for those who were at CDC stage 4 and for whom date of reaching this stage and date of first HIV positive test was available

and is given in Table 6 3 below More details are provided in Appendix D in files, Survey21 out to Survey26 out

Table 6 3
Summary of Incubation Period Data

Incubation Period (yrs)	Over all Risks	Male IVDU	Female IVDU	Homosexual
Mean	1 65	1 63	-	1 86
Median	1 00	1 00	-	0 00
Mode	0 00	0 00	-	0 00
Std Dev	1 88	1 71	-	2 34
Range	0 - 5	0 - 5	4	0 - 5
No of cases	26	16	1	7

Of those patients who had a regular HIV positive partner we asked when their partner had first tested HIV positive Of the 181 patients questioned, 48 or 26 5% said that they had a regular partner who was HIV positive Of these 48, 21 knew the date of their partners first HIV positive test From these replies we saw that the mean length positive of the regular partners was 2 38 years, with a median of 2 years, standard deviation of 2 11 years and a range of 0 to 6 years positive Given the high percentage of non response to this question, these figures can at best be regarded as guidelines

Section 3a Heterosexual Partner Details

Within this section patients were asked various questions on the nature and extent of their heterosexual partner contacts As male and female IVDU's make up 139 of the 155 patients to whom this section was relevant (the other 16 patients consisted of bisexuals, female IVDU's with homosexual activity only and those male and female heterosexuals with other risks) we shall look at their replies in detail Those interested in the details of the other groups are referred to Appendix D

Of the 92 male (51 female) IVDU's surveyed, 34 males and 21 females described their sexual activity as non existent, 16 males and 7 females as seldom or occasional, 37 males and 16 females as frequent (at least once a week) and 5 males and 3 females as very frequent, (at least once a day) There was no reply given to this question by 4 females surveyed

When asked if there had been any change in their sexual activity pattern since becoming HIV positive 39 males and 15 females said they had fewer partners, 48 males and 31 females said there was no change and 3 males and 1 female said they had more partners There were 2 missing observations to this question amongst the males and 4 amongst the females

When asked for their current average number of partners per month 36 male IVDU's and 22 females said they had no partners, 52 males and 25 females said one partner, 3 males and no females said 2 to 5 partners per month and 1 male and no females said they had six to ten partners per month No male or females said they had more than 10 partners per month There were no missing observations for the males and 4 missing for the females on this question

One of the key questions asked in this section was, the average number of partners per year The distribution of replies given by the male and female IVDU's to this question is provided in Figure 6 2 and summary statistics are in Table 6 4 Further details are provided in Appendix D, files Survy3a1 out to Survy3a7 out

FIGURE 6 2

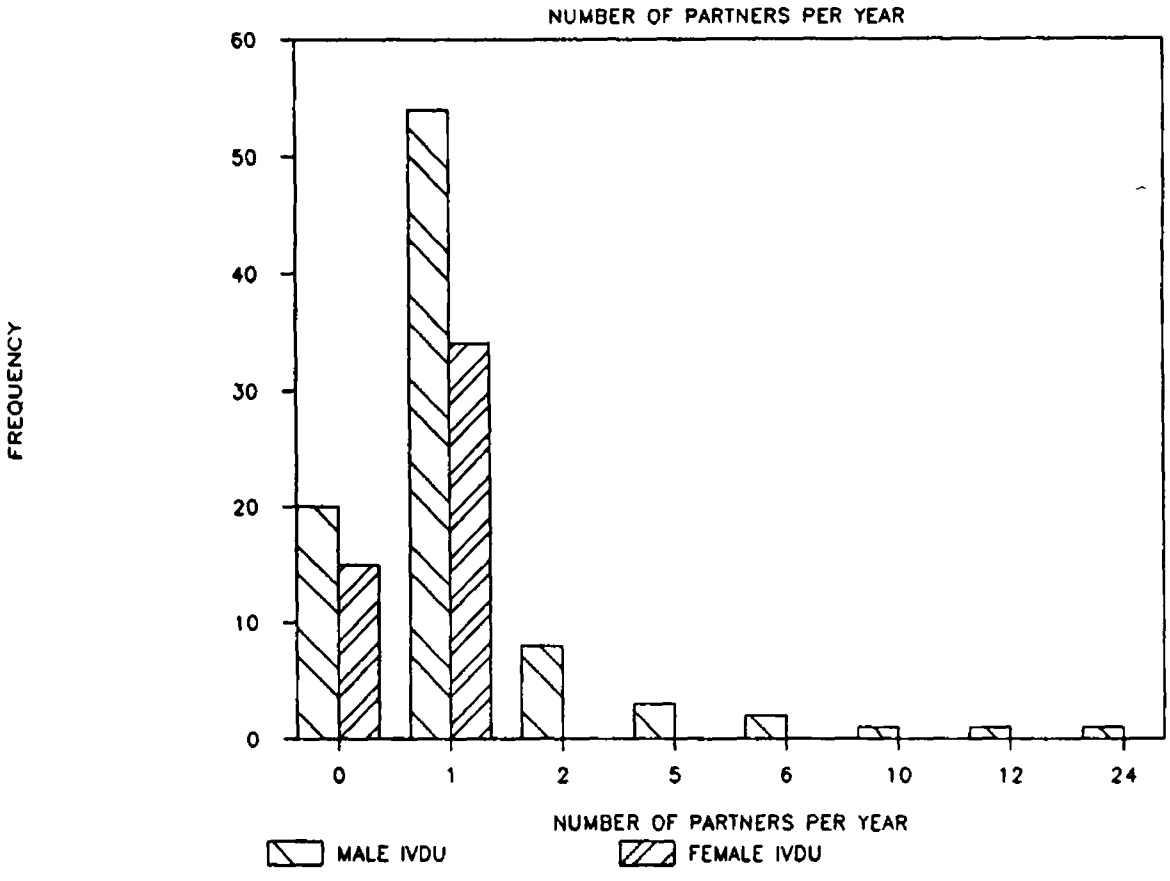


Table 6 4
Distribution of the number of partners per year

	Male IVDU	Female IVDU
Mean	3 86	0 69
Median	1 00	1 00
Std Dev	21 85	0 47
No of Cases	91	47

Within the male IVDU's, one patient said he had 208 partners per year This did not agree with this patients reply to the question on number of partners per month This patients reply has considerably distorted the summary statistics for this question and we shall take this into account in Chapter 7 when we are estimating the transmission model parameters If we ignore this obvious outher we see that the number of partners per year for the male IVDU's ranges from none to 24

The age at which patients first became heterosexually active is also important for the transmission model parameters A summary of replies to this question for the male and female IVDU's is given in Table 6 5 below

Table 6 5
Summary statistics for age of first heterosexual activity, in years

	Male IVDU	Female IVDU
Mean	15 07	16 04
Median	15 00	16 00
Mode	15 00	16 00
Std Dev	2 10	2 40
Range	10 - 24	7 - 21
No of Cases	91	47

The female IVDU whose first heterosexual activity was at 7 years was a case of child sexual abuse The range for females if we ignore this one case was 11 to 21 years

When asked if patients or their partner used contraceptives 15 males and 24 females said they never used any contraceptives 24 males and 4 females said sometimes and 49 males and 18 females said they always used some form of contraceptive When then questioned on the type of contraceptive used 69 males and 17 females said they used condoms or condoms plus another form of contraceptive 13 males and 22 females said they used no form of contraceptive Here we can see that there are small discrepancies in replies to this question

Section 3b Homosexual Partner Details

Similar questions were asked of those who engaged in homosexual activity A total of 25 male patients said they engaged male homosexual activity Of these 3 were bisexual and 2 were either homosexual or bisexual plus IVDU Summary descriptive statistics were prepared for each of these three groups individually In this chapter we provide the replies of the purely male homosexual group only

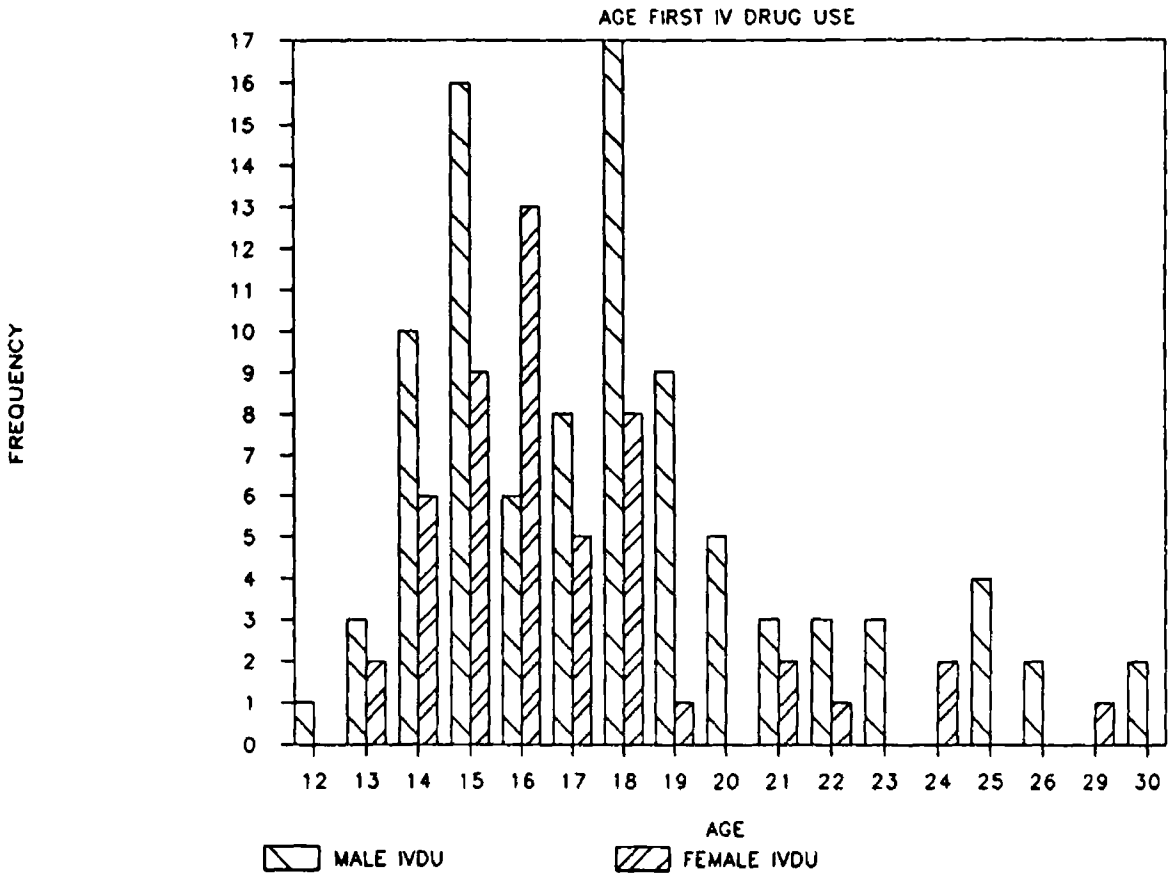
Of the 20 replies received 8 described their sexual pattern as non existent, 6 as seldom or occasional, 5 as frequent (at least once a week) and 1 as very frequent (at least once a day) When asked if this pattern had changed since becoming HIV positive 14 said they had fewer partners and 5 said there was no change There was one missing observation on this question When asked to give their average number of partners per month, most, 12, said they had one partner per month 6 said they had no partners and 1 said they had between 2 and 5 partners per month No patient had any more than 5 partners There was again 1 missing observation on this question

When asked to give the number of partners per year replies ranged from none to 20 partners The replies to this question will play an important part in parameters describing sexual activity in transmission models The mean number of partners per year was 4 05, the mode was 1, median 2 and standard deviation of 5 16 All 20 patients answered this question

When asked to list their types of sexual activity 9 said they engaged in active sex, 11 in passive, 10 in oral and 11 in other types of sexual activity Only 6 patients said that they or their partner always used condoms, 5 said sometimes and 6 said they or their partner never used condoms There were 3 missing observations on this question

Patients were then asked at what age they first became homosexually active Again this will be a key question in any transmission model One patient did not reply to this question Of the 19 replies received answers ranged from 12 to 24 years The mean age of first homosexual activity was 16 90 years, the median was 16 years,

FIGURE 6 3



replies were bimodal at 16 and 18 years and the standard deviation was 3 21 years

Section 4· Drug Use Details

In this section patients were asked about the nature and extent of their drug use We shall look at the male and female IVDU replies separately

When asked if they used IV drugs in the past 90 of the 92 male and 49 of the 51 female IVDU's said they had used IV drugs in the past When then asked if they were using IV drugs now 25 males and 10 females said they were, the others had stopped for various reasons

One of the key questions in this section was the age at which the patient first used IV drugs The information from this question will be used to estimate introduction rates to the male and female IVDU populations, for use in the transmission model Summary information for this question for males and females is provided in Figure 6 3 and Table 6 6

Table 6 6
Summary statistics for age of first IV drug use, in years

	Male IVDU	Female IVDU
Mean	17 94	16 84
Median	18 00	16 00
Std Dev	3 69	3 01
No of Cases	92	51

When asked how often one would inject each day and each week replies were similar for both males and females A summary of replies given for daily IV injections

is provided below in Table 6 7

Table 6 7
Summary statistics for number of IV drug injections per day

	Male IVDU	Female IVDU
Mean	2 80	2 28
Median	3 00	2 00
Mode	3 00	3 00
Std Dev	2 53	1 50
Range	0 - 20	0 - 5
No of Cases	92	51

Patients were next asked if they shared needles with other IV drug users and how many people they would share with in one week Replies varied considerably and are summarised in Table 6 8 below

Table 6 8
Summary statistics for number of people shared needles with in one week

	Male IVDU	Female IVDU
Mean	5 70	6 94
Median	2 00	3 00
Mode	1 00	0 00
Std Dev	11 93	9 44
Range	0 - 99	0 - 40
No of Cases	91	51

Although the mode in the female data was 0, (14 females said they shared with no one), 8 females said they shared with 10 people per week There was one missing observation in the male IVDU data for this question

When asked about the life of needles 37 of the 91 males and 17 of the 49 females who replied to this question said that a needle would last less than one week 19 males and 10 females said it would last 1 to 2 weeks, 17 males and 11 females said 2 to 4 weeks and 18 males and 11 females said a needle would last more than 4 weeks Finally patients were asked if their drug use pattern had changed since becoming HIV positive 33 of 90 males and 22 of 50 females who replied to this question said that they used IV drugs less now 18 males and 10 females said they used IV drugs more often since becoming HIV positive Finally the remaining 39 males and 18 females said that there was no change in their IV drug use since becoming HIV positive

Some preliminary information was collected in this section from those female patients who had given birth since becoming HIV positive Of the 62 females surveyed 21 or 35% of the 60 who replied to this question said they had given birth since becoming HIV positive Of the 50 female IVDU's who replied to this question 16 or 32% said they had given birth since becoming HIV positive When then asked the number of live deliveries these 16 women had produced, 12 said they had 1 live

delivery, 2 said they had 2 live deliveries (not twins) and 1 women said she had 3 live deliveries since becoming HIV positive One women did not reply to this question

A full discussion of the results and findings of this HIV survey are provided in Section 4 below, and the importance of certain key questions to parameter estimation is also discussed

6.4 Discussion

The primary aim of this HIV transmission survey was to provide an insight into the drug use and sexual behaviour of the patients surveyed Questions in the survey were specifically designed to give the necessary information on essential mathematical model parameters This information we shall use to estimate key model parameters in Chapter 7 This transmission model will then be used to provide long term estimates of the prevalence of the HIV virus and eventual AIDS cases in Ireland

The majority of questionnaires were administered by a research nurse in St James' Hospital Although it was originally planned to have 200 patients surveyed, due to time constraints only 187 were finally completed Obviously as time progressed those who attended the clinic more often were already surveyed and it was difficult to survey those who attended less regularly We can see from the CDC distribution profiles in Table 6 2 that this did not imply that only those who were very ill were surveyed

The male female ratio of clinic attenders is known to be approximately 2/1 Our survey although carried out on a first come first served basis, also provided us with a male/female ratio of approximately 2/1 We also saw that the majority of patients surveyed were in the male IVDU group as expected from the known distribution of HIV cases in Ireland given in Chapter 1 These results lead us to be believe that those surveyed were a representative sample of those HIV positive in Ireland

The age profiles for those surveyed was as expected with the mean age in the homosexual group higher than that of the IVDU group Also we can see from Table 6 1 that female drug users tend to be younger than male users The mean age of those using IV drugs was, however, higher than one might expect

As expected most patients received regular medical attention elsewhere in addition to St James' Hospital The information on where else patients received medical care would be of use if this HIV transmission survey were to be administered elsewhere in the future Having successfully completed a pilot and main survey, we would be in a position to use our survey as a prototype for further investigations of this type in Ireland

As the mean number of times patients had been tested for the HIV virus was twice, data from viral reference laboratories on proportions testing HIV positive would have to be looked at in detail to ascertain if this had been taken into account

It is interesting to note that the highest percentage of those at stage CDC4 were within the homosexual group This confirms the belief that the homosexual group were the first group in Ireland to acquire the HIV virus Similarly, within the IVDU group more males than females surveyed were at stage CDC4 Replies to the questions on how long since the patient first tested HIV positive and the known lengths of the incubation period for those at stage CDC4, provided in Table 6 3, showed that patients incubation periods were very short, with the mode for incubation period and for length of time positive over all risks at less than one year This has serious implications for the health authorities in relation to planning and spread of the disease Patients are obviously not presenting for HIV tests until some

time after they have actually become HIV positive This emphasises the importance of other methods such as the back projection method and the transmission model method, wherby we can derive accurate estimates of the numbers HIV positive at any one time

Replies to questions within the IVDU group, on heterosexual activity were modest, with the majority of both males and females describing their sexual activity as non existent Later questions however showed less modesty when the majority of males and females said they had on average one partner per month Earlier replies may have been the result of the nature and position of the question within the survey itself Replies to questions on average number of partners per year and frequency of sexual contact also seemed more realistic, with the exception of one male reply Replies to the age of first heterosexual activity showed that males became sexually active at an earlier age than women

From the point of view of transmission of the disease it was distressing to note that 13 males and 22 females said they used no form of contraceptive This may be due to lack of care with regard to the transmission of the virus or it is also possible that some of these replies came from those whose regular partner is also HIV positive

Questions on homosexual activity appear to be truthfully answered While this is generally uncommon in surveys of this nature [29], (in Ireland homosexuality is illegal), patients' past medical histories and risk group information is already known to the clinic's medical staff Also, as surveys were administered in a genito urinary clinic both staff and patients are familiar with asking and replying to questions of a sensitive nature

Replies to the questions on drug use were also comprehensive All patients surveyed answered the key questions on the age of first drug use and number of injections per day The majority of IVDU's injected 3 times a day and the mean number of people shared with in one week was approximately 6 These rephes have serious consequences for the transmission of the HIV virus between drug users Finally we see from the survey rephes that approximately one third of all women surveyed had given birth since becoming HIV positive This confirms Ireland as one of the countries where mother to infant transmission cannot be ignored

We believe that this survey, as a prototype, was very successful It has demonstrated that patients attending clinics are willing to answer questions of a personal and delicate nature We believe that the administration of the survey by trained medical staff contributed to this Some short-commings must however be mentioned All patients surveyed were HIV positive, we were unable to administer the survey amongst non HIV positive individuals at risk of infection Also, we were unable to contact the haemophiliac and heterosexual groups The survey has, however, highlighted those areas where urgent health education is required, the results themselves, in relation to presenting for HIV tests at an early stage, condom use, births to HIV positive mothers and needle sharing provide a case for this Finally it provides us with the necessary and detailed sensitive data required for parameter estimation for use in our transmission models

Chapter 7

Deterministic Models for HIV and its Progression to AIDS.

> ' All epidemiology, concerned as it is with the variation of disease from time to time or from place to place, must be considered mathematically, however many variables are implicated, if it is to be considered scientifically at all
> And the mathematical method of treatment is really nothing but the application of careful reasoning to the problem at issue ' *Sir Ronald Ross, 1911 [44]*

7.1 Introduction

Sir Ronald Ross was awarded the Nobel Prize for his contributions to the detection of the transmission modes of malaria He recognised and published the importance of the mathematical model in the study and control of infectious diseases It is with the sentiments expressed by Ross above that we boldly proceed in this chapter

Research on mathematical models of the HIV virus and its progression to AIDS has to date concentrated on the homosexual community In many parts of western Europe and America the majority of cases of the virus were identified within this group To-day, however, researchers are returning to their models and using the insights gained from them to model spread of the disease within the heterosexual population From the beginning of the AIDS epidemic in Ireland it was observed that we were unlike the rest of western Europe, and would have to proceed immediately to the difficult problem of modelling the spread of the HIV virus within the intravenous drug users, who comprised the main vector of spread in the Irish population The research presented in this chapter on parameter estimation and model building is the first and only work of it's kind in Ireland The aim of this research was to predict levels of HIV infection within both the Irish intravenous drug using and homosexual populations This chapter represents a significant first step towards these objectives We would envisage the extension of this work to encompass more accurate parameter and model predictions along with a qualitative study of the models employed This can only only be achieved by the continuation of the HIV survey discussed in Chapter 6

Encouraged by the advice of Ross, 'however many variables are implicated method of treatment is really nothing but the application of careful reasoning', we proceed

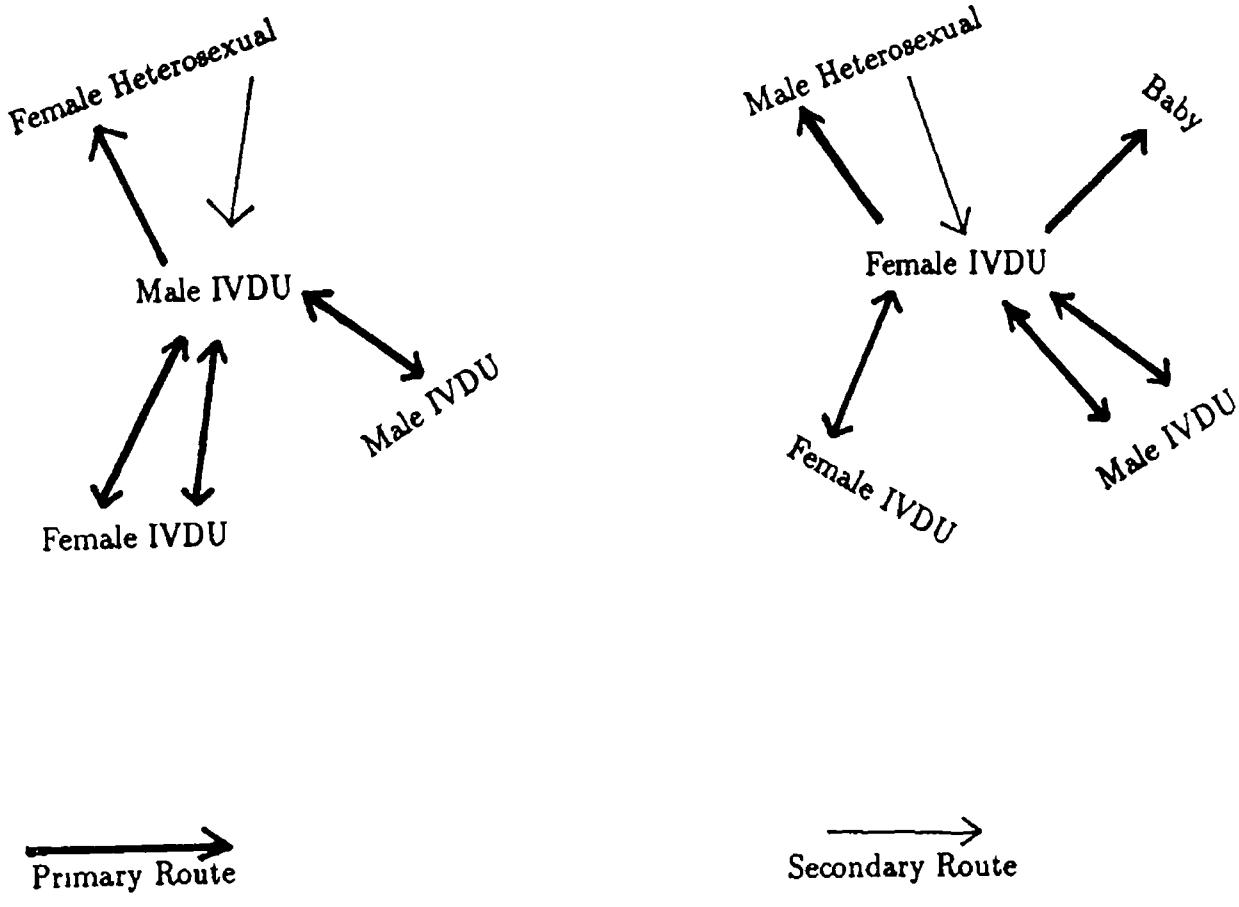


Figure 7 1 Transmission Routes of the HIV virus within the IVDU groups

in this chapter to describe and formulate simple mathematical models for the spread of the HIV virus in the Irish IVDU and homosexual populations, to estimate key model parameters from the HIV survey described in Chapter 6 and finally to provide predictions and recommendations based on the results of the models

7.2 IVDU Transmission Model with Recruitment.

The routes of transmission of the HIV virus from and to the male and female IVDU group can be seen in Figure 7 1 above We have both primary and secondary trans mission routes, with primary routes representing the main routes of transmission

For practical reasons of parameter estimation and simplicity we restrict our model to the primary routes of transmission and to within the male and female drug using populations We assume that the population mixes homogeneously, that all infectious individuals eventually develop AIDS and we make the further assump tion that those in the AIDS class do not contribute to the spread of the disease The assumption that all HIV positive individuals progress to the disease is reasonable Recent evidence suggests [16] that the proportion of people infected with HIV who

eventually develop AIDS is higher than originally thought and may be as high as 80% or even greater as the the duration of the incubation period is seen to increase

We split the total population of drug users at time t into three exclusive compartments of susceptibles, infectious and AIDS, denoted by $X(t)$, $Y(t)$ and $A(t)$ respectively We denote the different sexes within the population by the subscripts mu and fu, for male and females Hence the population of male drug users at time t is denoted by $P_{mu}(t)$ and the population of female drug users at time t is denoted, $P_{fu}(t)$

Suppose now we have a freely mixing community of P_{mu} male drug users and P_{fu} female drug users Let the rate of sexual contact of females with males be c_{fu} per unit time Then in unit time X_{fu} susceptible females contact $c_{fu}X_{fu}$ males, of whom $(c_{fu}X_{fu})(Y_{mu}/P_{mu})$ are infected Let the probability of infection passing from an infected male to a susceptible female be β_1 in a single contact, (i e β_1 is the male to female transmission probability) then the rate at which new female drug user infections occur as a result of sexual contact with a male drug user, is given by

$$c_{fu}\beta_1 X_{fu}\frac{Y_{mu}}{P_{mu}}$$

Similarly, the rate at which new male drug user infections occur as a result of sexual contact with a female drug user is given by

$$c_{mu}\beta_2 X_{mu}\frac{Y_{fu}}{P_{fu}},$$

where β_2 is the probability of female to male transmission and c_{mu} is the rate of sexual contact for males per unit time

The rate at which new male and female drug user infections occur will also depend upon the extent of needle sharing within the drug using population Let the rate of needle sharing per unit time for females with other males and females be n_{fu} per unit time Then in unit time X_{fu} susceptible females contact $n_{fu}X_{fu}$ males and females of whom $n_{fu}X_{fu}(Y_{mu}+Y_{fu})/(P_{mu}+P_{fu})$ are infected Let the probability of infection passing from an infected drug user to a susceptible drug user via needle sharing be β_3 in a single contact Then the rate at which new female drug user infections occur due to needle sharing is given by,

$$n_{fu}\beta_3 X_{fu}\left[\frac{Y_{mu}+Y_{fu}}{P_{mu}+P_{fu}}\right]$$

The rate at which new male infections occur due to needle sharing is given by,

$$n_{mu}\beta_3 X_{mu}\left[\frac{Y_{mu}+Y_{fu}}{P_{mu}+P_{fu}}\right]$$

Where n_{mu} is the rate of needle sharing per unit time for male drug users

The number of susceptible male and female drug users, X_{mu} and X_{fu} respectively, will increase due to recruitment to the drug using population and will decrease due to sexual contact and needle sharing with infectious female and male drug users The number of susceptibles will also decrease due to normal migration rates out of the drug using population The rate of change in the numbers infectious will depend on recruitment from the susceptible classes and loss to the AIDS class through incubation of the disease and normal migration Finally the rate of change in the AIDS classes will depend on those in the infectious class who have incubated the

disease and loss due to death from AIDS and normal migration out of the drug using population

We can now formulate a differential equation transmission model to describe the rate of change in the number of susceptible, infectious and AIDS patients in the male and female intravenous drug using populations We have,

$$\frac{dX_{mu}(t)}{dt} = \Lambda_{mu} - n_{mu}\beta_3 X_{mu}(t)\left[\frac{Y_{mu}(t)+Y_{fu}(t)}{P_{mu}(t)+P_{fu}(t)}\right] - c_{mu}\beta_2 X_{mu}(t)\frac{Y_{fu}(t)}{P_{fu}(t)} - \mu X_{mu}(t), \quad (7\,1)$$

$$\frac{dX_{fu}(t)}{dt} = \Lambda_{fu} - n_{fu}\beta_3 X_{fu}(t)\left[\frac{Y_{mu}(t)+Y_{fu}(t)}{P_{mu}(t)+P_{fu}(t)}\right] - c_{fu}\beta_1 X_{fu}(t)\frac{Y_{mu}(t)}{P_{mu}(t)} - \mu X_{fu}(t), \quad (7\,2)$$

$$\frac{dY_{mu}(t)}{dt} = n_{mu}\beta_3 X_{mu}(t)\left[\frac{Y_{mu}(t)+Y_{fu}(t)}{P_{mu}(t)+P_{fu}(t)}\right] + c_{mu}\beta_2 X_{mu}(t)\frac{Y_{fu}(t)}{P_{fu}(t)} - (\alpha+\mu)Y_{mu}(t), \quad (7\,3)$$

$$\frac{dY_{fu}(t)}{dt} = n_{fu}\beta_3 X_{fu}(t)\left[\frac{Y_{mu}(t)+Y_{fu}(t)}{P_{mu}(t)+P_{fu}(t)}\right] + c_{fu}\beta_1 X_{fu}(t)\frac{Y_{mu}(t)}{P_{mu}(t)} - (\alpha+\mu)Y_{fu}(t), \quad (7\,4)$$

$$\frac{dA_{mu}(t)}{dt} = \alpha Y_{mu}(t) - (\delta+\mu)A_{mu}(t), \quad (7\,5)$$

$$\frac{dA_{fu}(t)}{dt} = \alpha Y_{fu}(t) - (\delta+\mu)A_{fu}(t) \quad (7\,6)$$

Where

$$P_{mu}(t) = X_{mu}(t) + Y_{mu}(t) + A_{mu}(t), \quad (7\,7)$$

$$P_{fu}(t) = X_{fu}(t) + Y_{fu}(t) + A_{fu}(t), \quad (7\,8)$$

$X_{mu}(0), X_{fu}(0), Y_{mu}(0)$ and $Y_{fu}(0)$ are known constants and $A_{mu}(0) = A_{fu}(0) = 0$ Λ_{mu} and Λ_{fu} are the recruitment rates to the male and female IVDU populations respectively, $1/\alpha$ is the mean incubation period, $1/\delta$ is the AIDS related death rate and $1/\mu$ is the mean migration period This model is based on the one sex model of Anderson et al (1986) [5] Included within the (1986) model are two additional classes One the class of infectious individuals who do not go on to develop AIDS and two, a class of post infectious seropositives Anderson et al include recruitment, loss due to sexual activity with an infectious person and migration in their model Here we also incorporate loss due to needle sharing into the model In [5] the initial number of infectious people is assumed to be one We use the model in equations (7 1) to (7 8) to describe the spread of HIV in the drug using population given a stated, known number of HIV positive people at a certain point in time

7.3 Homosexual Model with Recruitment.

We now proceed with a simple compartment model which describes the transmission dynamics of the HIV virus within the male homosexual community We do not consider the contribution of bisexuals to the numbers of susceptible, infectious and AIDS This model is also given in terms of a set of differential equations which describe the rate of change in the susceptible, infectious and AIDS classes This model was first proposed by Anderson et al in 1986, [5] and was later developed by Blythe and Anderson in 1988 [9] We have,

$$\frac{dX_{hm}(t)}{dt} = \Lambda_{hm} - c_{hm}\beta_4 X_{hm}(t)\frac{Y_{hm}(t)}{P_{hm}(t)} - \mu_{hm}X_{hm}(t), \quad (7\ 9)$$

$$\frac{dY_{hm}(t)}{dt} = c_{hm}\beta_4 X_{hm}(t)\frac{Y_{hm}(t)}{P_{hm}(t)} - (\alpha + \mu_{hm})Y_{hm}(t), \quad (7\ 10)$$

$$\frac{dA_{hm}(t)}{dt} = \alpha Y_{hm}(t) - (\delta + \mu_{hm})A_{hm}(t) \quad (7\ 11)$$

with

$$P_{hm}(t) = X_{hm}(t) + Y_{hm}(t) + A_{hm}(t) \quad (7\ 12)$$

The initial values of $X_{hm}(t), Y_{hm}(t)$ are known constants and $A_{hm}(0) = 0$ In this model X, Y, A, P represent the numbers of susceptible, infectious, AIDS and the total population as previously and the subscripts hm denote the homosexual population The parameter β_4 represents the probability of transmission of the disease in a single homosexual contact and all other parameters are as previously defined We are also assuming homogeneous mixing

7.4 Transmission Models, Parameter Estimates.

All parameters were estimated from the HIV survey discussed in Chapter 6 and from data on HIV testing supplied by the National Virus Reference Laboratory at the Department of Medical Microbiology, University College Dublin This is the first attempt at parameter estimation in Ireland To our knowledge very little survey work has been published on the difficult and sensitive information regarding needle sharing, frequency of needle use and needle life

Introduction Rates

The objective of this section was to provide actual realistic figures on the numbers of males and females taking up intravenous drugs for the first time each year in Ireland This data would then be incorporated into the model to provide details of how the total size of the intravenous drug using population changes from year to year In order to estimate the introduction rates to the male and female sexually active IVDU populations we began by considering the year of first drug use and year of first sexual activity of the 92 males and 51 females surveyed Details of the survey replies to these questions are provided in Figure 7 2 and 7 3

FIGURE 7 2

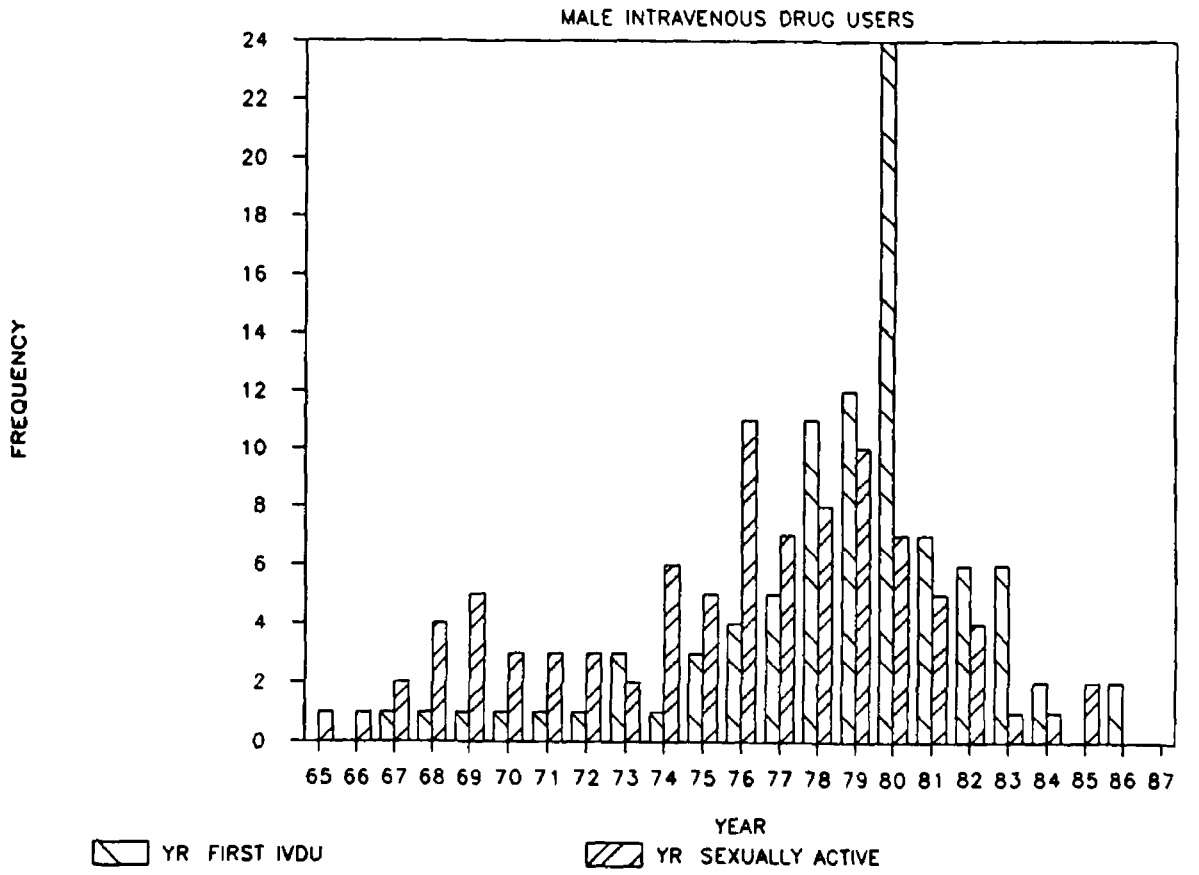
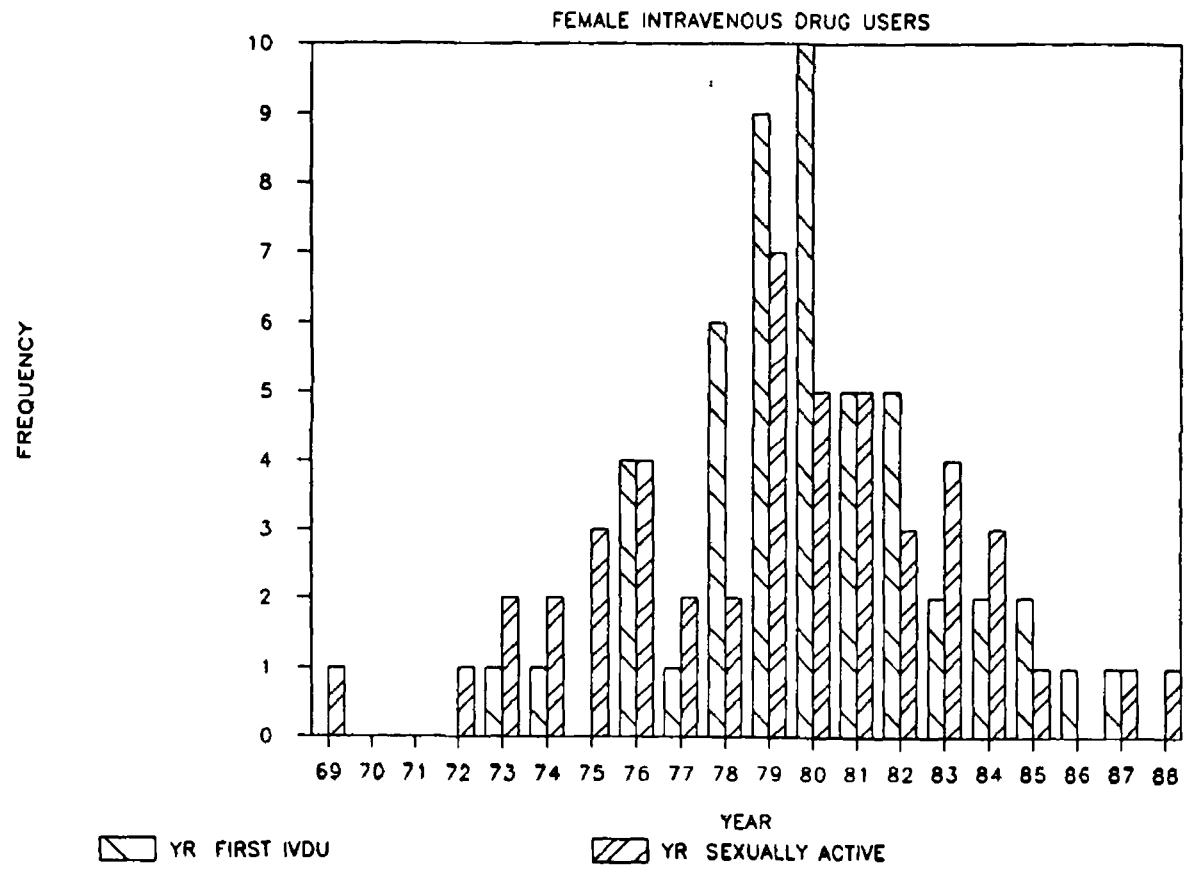


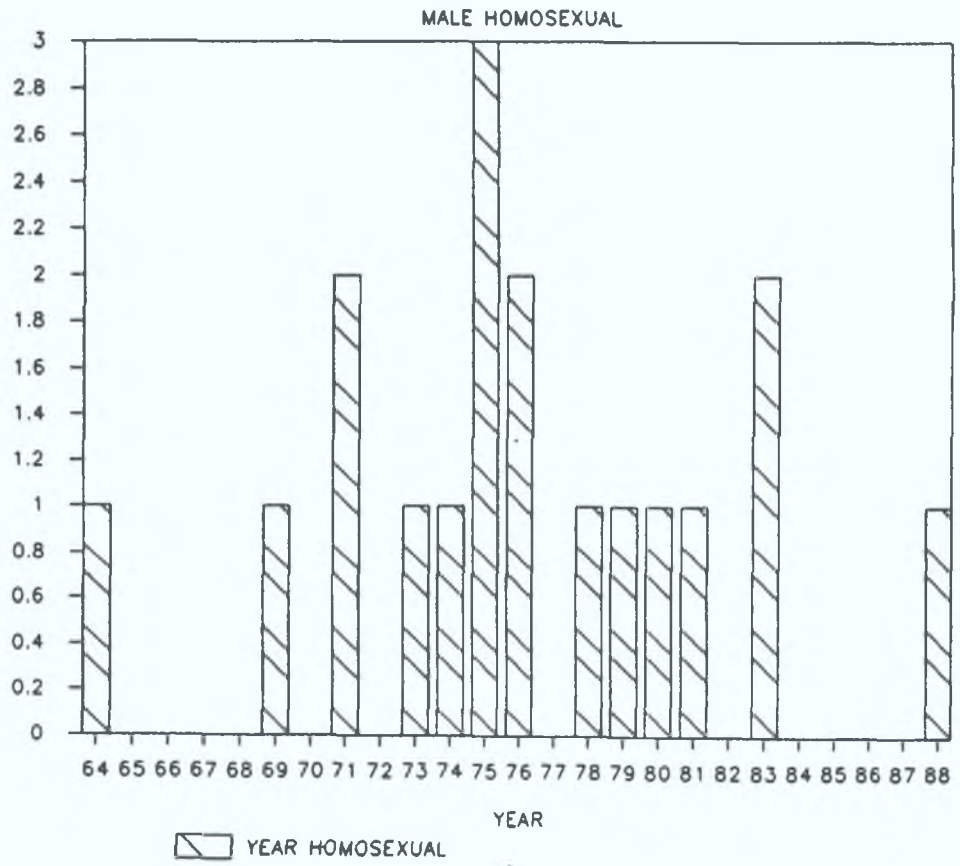
FIGURE 7 3



As the risk of infection from the use of IV drugs is known to be far greater than that from heterosexual sexual contact we decided to estimate the introduction rate from year of first IV drug use only. From this we saw that 75% of males and 64% of the females surveyed first took drugs before 1980. None of the males and only 2 of the females took their first IV drugs after 1986. We had hoped to combine the percentage taking their first IV drug each year with the known number of IV drug users, from the National Virus Reference Laboratory, to derive a minimum number of people taking IV drugs each year. This was not possible as none of those IV drug users surveyed took their first IV drug in recent years. We saw from the survey however, that the male drug users took their first IV drug over a period of 22 years and from this we could say that on average 4.55% took their first IV drug each year. Female drug users surveyed took their first IV drug over a period of 17 years and from this we could say that on average 5.88% took their first IV drug each year. We then combined this information with information on the minimum number of drug users users known from the virus laboratory to derive a minimum estimate of the numbers taking IV drugs for the first time each year. Results for this parameter are provided in Table 7.1 below.

A similar approach was used to estimate the introduction rate to the male homosexual population each year. We see from Figure 7.4 that the homosexuals questioned became homosexually active over a period of 24 years. From this we can say

FIGURE 7.4



that on average 4.17% become active each year. This figure can then be combined with data on the total numbers of homosexuals from the virus laboratory to give a minimum estimate of the numbers becoming homosexually active each year. Results for this parameter are provided in Table 7.1.

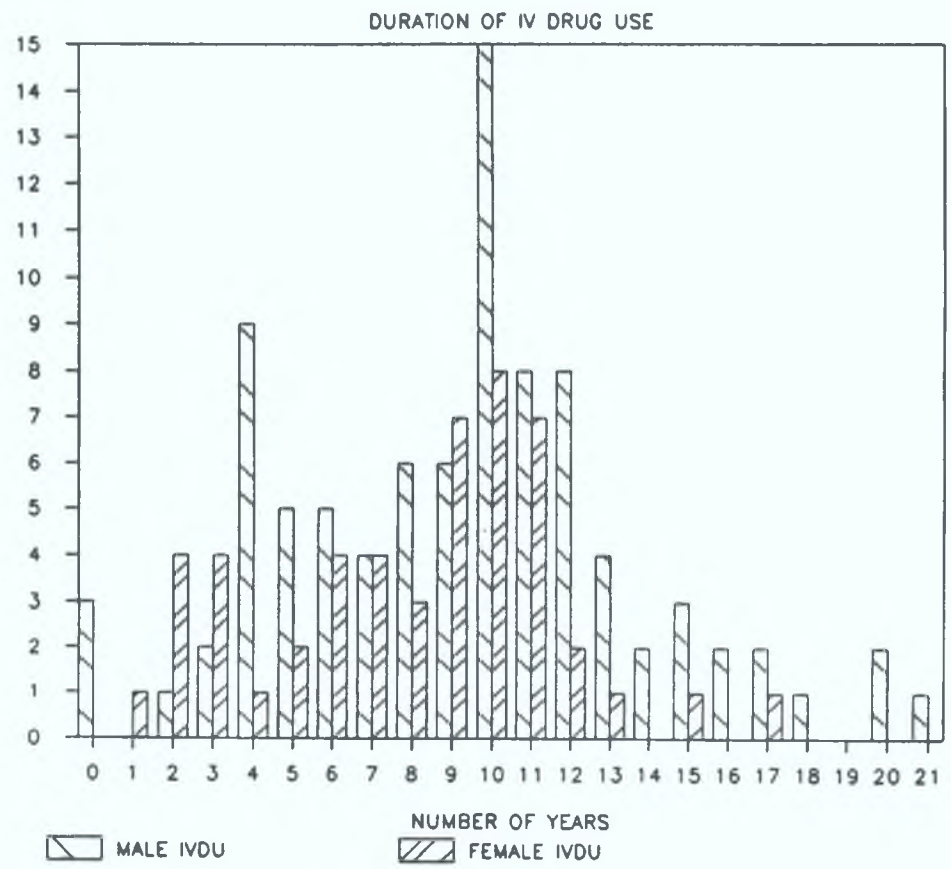
Table 7.1
Annual Introduction Rates.

Group	Parameter	Value
Male IVDU	Λ_{mu}	119
Female IVDU	Λ_{fu}	64
Homosexual	Λ_{hm}	66

Migration Rate.

The objective in this section was to estimate the actual numbers that stop taking intravenous drugs each year or that cease to be homosexually active. To estimate migration rates out of the male and female drug using populations we computed the length of time for which those surveyed had used IV drugs for. This was derived from questions in the HIV transmission survey on date of first IV drug use and date at which the patient stopped using IV drugs. Not all of those whom we surveyed had given up IV drugs at the time of interview. For these we computed a minimum period of IV drug use from date of first use to date of interview. Details are provided in Figure 7.5.

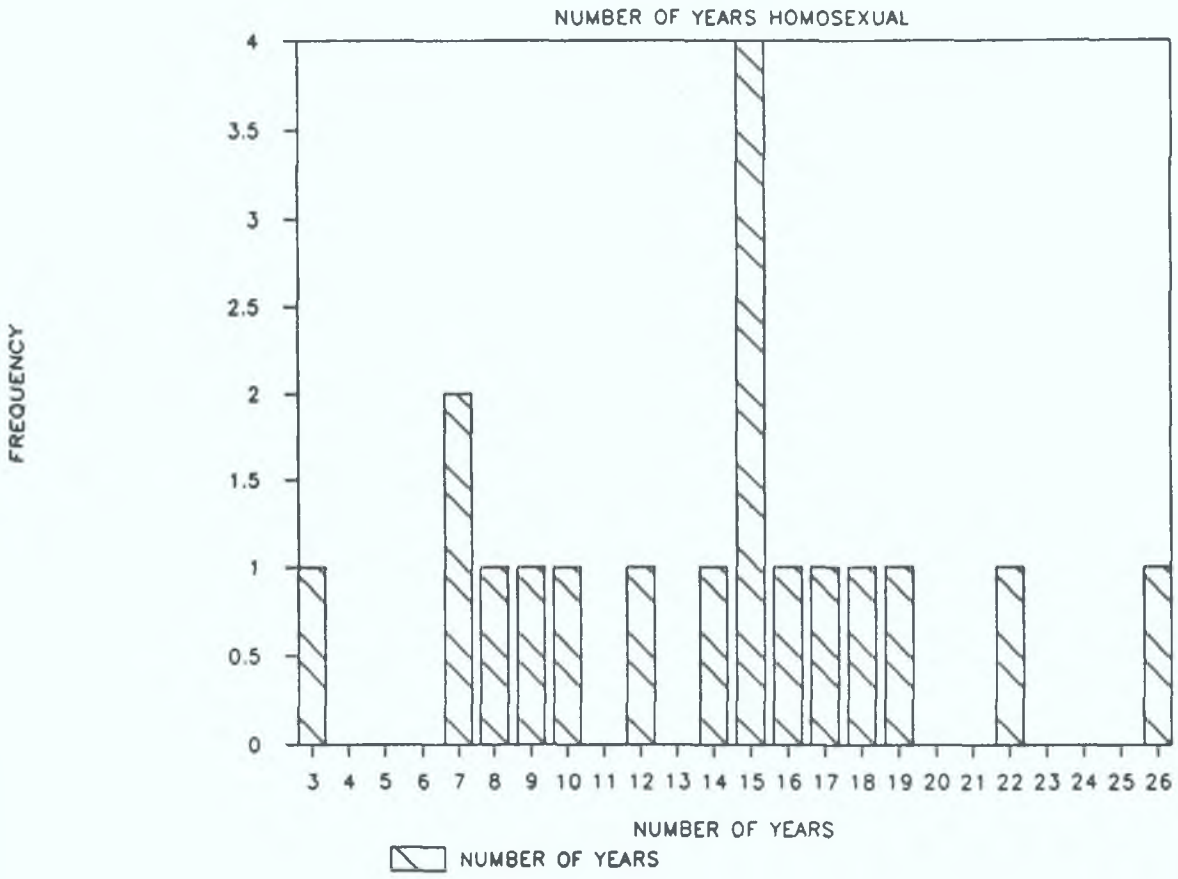
FIGURE 7.5



The mean duration of IV drug use was computed for males and females and the reciprocal of this was used as an estimate of the migration rate out of the male and female IVDU populations. Results are provided in Table 7.2.

To derive the migration rate out of the male homosexual population we again looked at the length of time for which those surveyed had been homosexual. The results are given in Figure 7.6.

FIGURE 7.6



We found that all surveyed were still homosexually active and had been so for a mean of 13.78 years. We decided to use the Blythe and Anderson (1988) [9] approach and estimate of 30 years for the mean duration of homosexual activity as the mean duration derived from our survey was an obvious under estimate.

Table 7.2
Annual Migration Rates.

Group	Parameter	Value
Male IVDU	μ_{mu}	0.107
Female IVDU	μ_{fu}	0.125
Homosexual	μ_{hm}	0.033

Sexual Activity.

In our transmission model we describe the parameters c_{mu}, c_{fu} and c_{hm} as the mean number of partners per unit time. It is suggested elsewhere [33] that a better estimate of this parameter is given by the mean number of partners per unit time plus the variance to mean ratio. From questions in our survey on the average number of partners per year we could easily compute this parameter for both the male and female IVDU and homosexual populations. Details of replies to this question were given in Chapter 6. Results for the parameter are provided in Table 7.3, where the 95% confidence interval on the mean is given by $\bar{X} \pm (t_{\nu,1-\alpha/2} \times \sigma/\sqrt{n})$ in each of the three cases.

Table 7.3
New Partners Per Year.

Group	Parameter	Value	95% C.I.
Male IVDU	c_{mu}	7.440	6.400 to 10.770
Female IVDU	c_{fu}	1.007	0.958 to 1.166
Homosexual	c_{hm}	10.610	10.570 to 17.840

Needle Sharing.

The nature and extent of needle sharing is a key factor of spread of HIV amongst the intravenous drug using group. Loss from the susceptible to the infectious population will depend primarily on the parameter. Very little is know about the needle sharing habits of drug users. In our survey we were very fortunate to obtain such detailed replies by so many drug users.

We saw in the model (7.1) to (7.8) that the rate at which new HIV infections occur amongst male and female IVDU's depends upon the the extent of needle sharing within the population. In our survey we asked how many people one would shared needles with in one week, we also asked how long a needle would last. It was thought unrealistic to ask how many people one would share with in one year as patients could not be expected to remember and give accurate replies. We decided to use results from the question on number of people shared with in one week as a minimum estimate for the needle sharing parameter, and details of the replies are given in Figure 7.7. We found that one male IV drug user said he shared with 99 people in one week. Replies this patient had given to other questions on needle use, such as frequency of IV injections per day , were not consistent with this answer and it was decided to treat this case as an obvious outlier. Results on the mean number of people shared needles with for females and males without this outlier, along with the corresponding 95% confidence intervals computed as previously are provided in Table 7.4.

FIGURE 7.7

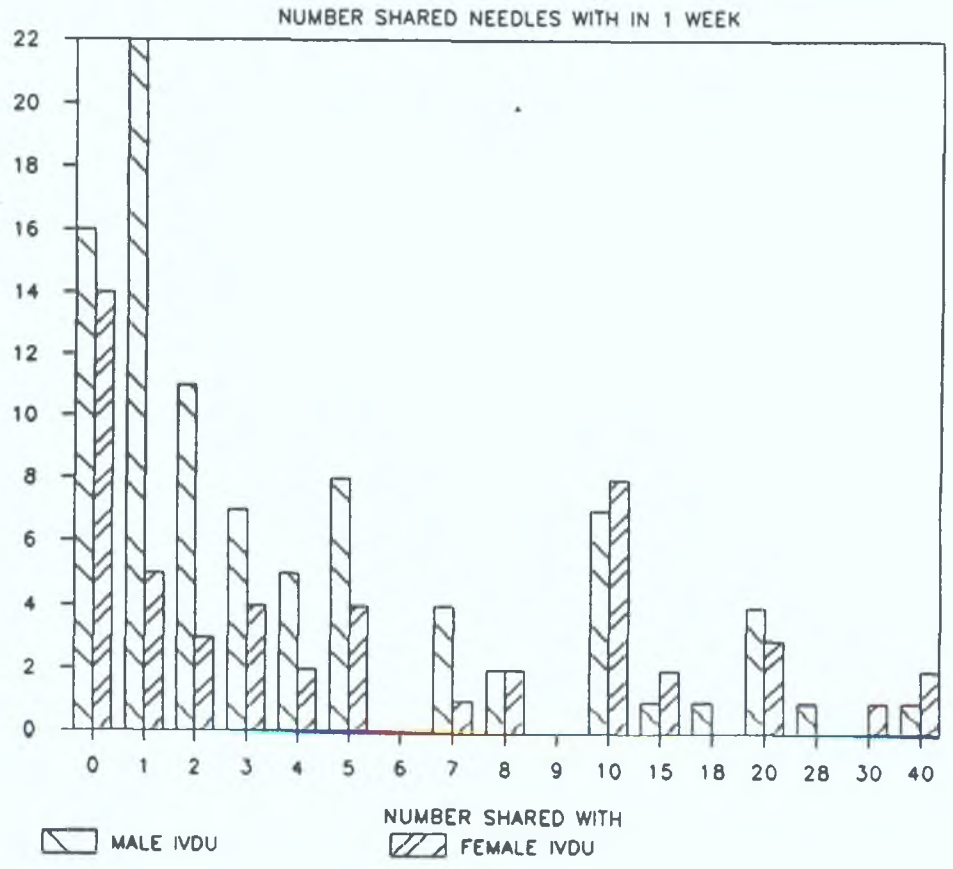


Table 7 4
Number Shared Needles with per Week

Group	Parameter	Value	95% C I
Male IVDU	n_{mu}	4 667	3 253 to 6 081
Female IVDU	n_{fu}	6 941	4 298 to 9 584

Other Parameters

The mean duration of survival time from the onset of AIDS to death, $1/\delta$, was assumed to be 1 year in accordance with known estimates [9] From our survey we examined all patients who were at CDC stage 4 (AIDS) and found the mean length of time from date of reaching stage 4 to date of interview to be 10 5 months This can be seen in Figure 7 8

The mean incubation period, $1/\alpha$, was taken as 8 years from published estimates [5] The probability of transmission in a single sexual contact, β_1, β_2 and β_4 from an infectious male to a susceptible female, from an infectious female to a susceptible male and from an infectious homosexual to a susceptible homosexual respectively were also taken from published estimates [18] As we know of no published estimates of the probability of transmission of the virus in a single needle sharing act we used the estimate of β_1 as a lower bound It is known that the probability of transmission during needle sharing is at least as great as that due to sexual contact Parameter values used are given in Table 7 5

FIGURE 7 8

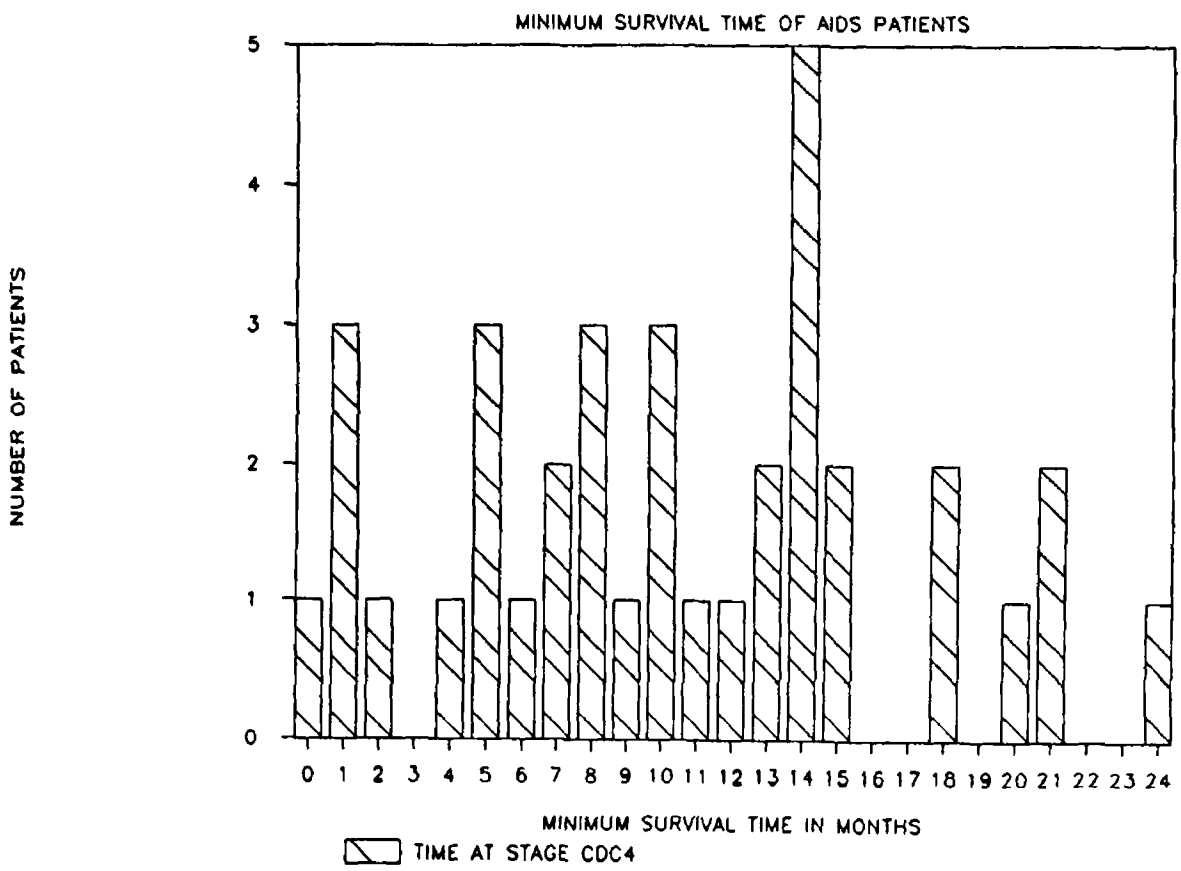


Table 7 5
Parameter Estimates

Parameter	Value
α	0 125
δ	1 000
β_1, β_3	0 020
β_2, β_4	0 010

7.5 Transmission Model Results, Minimum Values.

To provide estimates of the level of HIV infection in the Irish IVDU and homosexual populations we solved the models described in equations (7 1) to (7 8) and equations (7 9) to (7 12) using the NAG [38] library routine D02EBF This routine integrates a stiff system of first-order differential equations over a range with suitable initial conditions, using a variable-order, variable step Gear method, and returns the solution at points specified by the user The driver program for this routine is supplied in Appendix C HIV testing first started in Ireland in 1985 We choose then, to model the spread of the disease over a range of 15 years, from given initial values in 1985 to predicted values in the year 2000 We assume that there are no great changes in the habits of the population during that time and that no HIV vaccine will be introduced during that time Numbers of susceptible, infectious and total tested at the end of 1985 for the IVDU and homosexual groups were obtained from the virus laboratory and used as initial values This was the only accurate data available and used as initial values will provide us with a minimum estimate of the initial prevalence in each compartment of the transmission models Data from the virus laboratory combined figures for male homosexuals and bisexuals We used the ratio of male homosexuals to bisexuals found in our survey to split the combined number provided Parameters used are given in Tables 7 1 to 7 5 above and initial values are provided in Table 7 6

Table 7 6
Transmission Model Initial Values

Group	Susceptible	Infectious	AIDS	Population
Male IVDU	358	128	0	486
Female IVDU	97	48	0	145
Homosexual	246	23	0	269

Predictions for the numbers susceptible, $X(t)$, infectious, $Y(t)$, and with AIDS, $A(t)$, at time t, from the transmission models are given in Tables 7 7 and 7 8 These results are based, as we have stated earlier, on the assumption that there are no changes in behaviour or introduction of Government intervention policies during the 15 years

Table 7 7
IVDU Transmission Model Results

Year	$X_m(t)$	$X_f(t)$	$Y_m(t)$	$Y_f(t)$	$A_m(t)$	$A_f(t)$	$P_m(t)$	$P_f(t)$
1985	358	97	128	48	0	0	486	145
1986	244	89	281	91	17	5	542	185
1987	154	69	391	137	32	11	576	216
1988	110	56	442	167	43	15	595	239
1989	95	51	461	186	48	18	604	255
1990	89	49	467	198	51	20	608	267
1991	87	48	470	206	52	22	610	276
1992	87	48	471	212	53	23	611	282
1993	86	48	472	216	53	24	611	288
1994	86	48	472	220	53	24	612	292
1995	86	48	473	223	53	24	612	295
1996	86	48	473	225	53	25	612	297
1997	86	48	473	226	53	25	612	299
1998	86	48	473	228	53	25	612	300
1999	86	48	473	229	53	25	612	302
2000	86	48	473	230	53	25	612	302

We can see from Table 7 7 that the susceptible population diminishes very quickly and remains at a constant level after 1993 The total population of male and female drug users continues to rise slowly The values predicted in each of the compartments do not represent the true size of the IVDU population at that time but rather the size of the population based on the initial minimum numbers fed to the model Given this restriction the model predicts a rapid increase in the numbers of infectious IVDU males, $Y_{mu}(t)$, between 1985 and 1989 and in the numbers of infectious IVDU females, $Y_{fu}(t)$, between 1985 and 1990 With the total number of IVDU's HIV infectious rising from 176 in 1985 to 665 in 1990 After these increases the numbers infectious remain stable with a total of 703 IVDU males and females infected by the year 2000 The growth in AIDS cases is more rapid amongst male drug users with no cases in 1985 and 17 cases in 1986 There are only 5 cases of AIDS amongst female drug users in 1986 Figures continue to rise very slowly giving a total of 78 cases in the year 2000

It is interesting to compare the results of the IVDU transmission model above with the results of the improved back projection method discussed in Chapter 4 The model above predicts a minimum of 647 HIV positive male and female drug users in 1989 This does not include those with AIDS The virus reference laboratory knew of 520 HIV positive drug users in 1989 These 520 represented 57 15% of all known cases If we assume that the transmission model prediction of 647 cases in 1989 represents 57 15% of all cases at that time we arrive at an estimate of 1,132 infectious people in Ireland in 1989 This is a lower figure than that estimated in Chapter 4, where, by improving upon the back projection method we predicted between 1,978 to 10,610 infectious people, by summing the estimated annual incidences from 1985 to 1989, (see Tables 4 2, 4 5 and 4 9)

Results of the transmission model in equations (7 9) to (7 12) describing the spread of HIV infection in the male homosexual community are given in Table 7 8

Table 7 8
Homosexual Transmission Model Results

Year	$X_{hm}(t)$	$Y_{hm}(t)$	$A_{hm}(t)$	$P_{hm}(t)$
1985	246	23	0	269
1986	271	50	3	324
1987	269	98	7	373
1988	238	166	13	417
1989	191	239	21	451
1990	148	300	29	477
1991	117	341	36	494
1992	99	366	41	506
1993	89	380	44	513
1994	84	387	46	517
1995	81	392	47	520
1996	80	394	47	522
1997	79	396	48	523
1998	79	397	48	524
1999	79	398	48	525
2000	79	398	48	525

We see from Table 7 8 that the population of male homosexuals is increasing due to the fact that the recruitment rate is greater than the migration rate Again we do not presume that this represents the actual size of the homosexual population in Ireland but rather a minimum estimate based on the initial values The number of infectious homosexuals rises from 23 in 1985 to 50 in 1986, giving a doubling time of approximately one year This pattern continues until 1988 after which the rate of increase in the numbers infectious slows down Both the numbers infectious and the number of AIDS cases stabilise at approximately 390 and 47 respectively after 1995

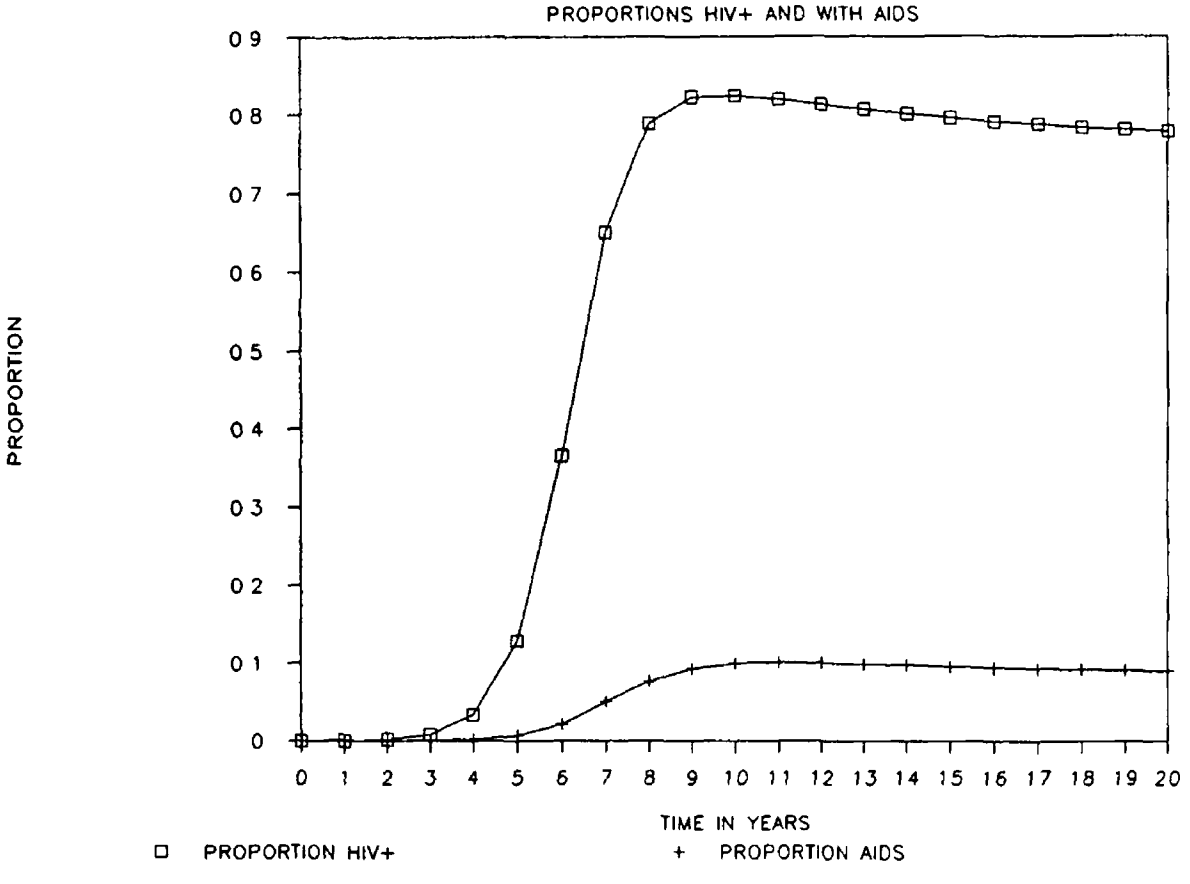
Results presented in this section represent predictions on the minimum numbers HIV positive and with AIDS from 1985 in the IVDU and homosexual populations It will be interesting to see how the predictions, based on calculated initial values and spread from 1980, of the next section compare with the 1981 to 1989 predictions of the improved back projection method

7.6 IVDU Transmission Model Results Using Calculated Initial Values.

In the previous section results presented were based on the minimum numbers of IV drug users known to the virus reference laboratory In this section we shall assume a population of 5000 male and 2500 female susceptible IV drug users These numbers are based on a crude estimation of the size of the IVDU population using the direct approach as discussed by Hillier (1988) [16] We introduce one male infectious into this population at time $t = 0$ equivalent to 1980, and model the transmission of the infection through the population given certain assumptions We continue to assume the same percentages take drugs for the first time each year as we found in our HIV transmission survey This gives an introduction rate of approximately 228 male IVDU's and 147 female IVDU's each year All other parameters are as given earlier and we assume that initially there are no AIDS cases in the population We then model the spread of the infection over a period of twenty years from 1980 to 2000

given no changes in behaviour or introduction of Government intervention policies The total number of HIV infectious drug users and AIDS cases expressed as a proportion of the total population size are plotted in Figure 7 9 We have proportion HIV infectious equals $y(t)$ where $y(t) = [Y_{mu}(t) + Y_{fu}(t)]/[P_{mu}(t) + P_{fu}(t)]$ and the proportion of AIDS cases equals $a(t)$ where $a(t) = [A_{mu}(t) + A_{fu}(t)]/[P_{mu}(t) + P_{fu}(t)]$ We can see from Figure 7 9 that initially there is a rapid increase in the proportion HIV infectious This proportion infectious peaks 9 years after the introduction of the infection and then decreases slightly over the next 11 years The first AIDS cases appear 4 years after the introduction of the infection and the proportion with AIDS peaks after 11 years If we assume that the infection was introduced by a single HIV positive male drug user in 1980 then the model predicts a total of 2663 infectious (but not AIDS) and 327 AIDS cases in 1991 These decrease to 1584 infectious and 183 AIDS cases by the year 2000

FIGURE 7 9



We arrive at some encouraging results if we now compare the IVDU transmission model with calculated initial values, predictions for infections amongst IV drug users in 1989 with those figures predicted by the improved back projection method of Chapter 4 The improved back projection method predicts a range of 2,358 to 10,826 infectious people in Ireland between 1981 and 1989 According to the transmission model, there were a total of 3,316 infectious IV drug users, $Y_{mu}(t) + Y_{fu}(t)$, in Ireland in 1989 We have seen that IV drug users account for 57 15% of all known HIV positive people. Given this percentage and the transmission model predictions, we estimate a total of 5,802 infectious people in Ireland in 1989 This number, derived from the transmission model predictions is in the middle of the 2,358 to

10,826 range predicted by the improved back projection method

Looking closer at the individual predictions of the improved back projection method we see that given exponential growth in AIDS cases this method predicts a total of 4,824 infectious people between 1981 and 1989, (Table 4 2) This prediction is very similar to the 5,875 cases predicted by the transmission model above As a result of the similarities in the results of the two methods we can approach the next section, assessing the effects of possible Government intervention policies, with increased confidence

7.7 IVDU Transmission Model Results given Intervention Policies.

We now model the spread of the infection given the calculated initial conditions for 1980 discussed above and we set the parameters c_{mu} and c_{fu} equal to zero from 1991 This is equivalent to assuming that all drug users do not have unprotected sexual contacts from this time, this may be the result of a Government safe sex campaign Given these conditions the model predicts a total of 1496 male and female IVDU's HIV infectious and 172 AIDS cases by the year 2000

If a large scale needle exchange program was introduced in 1991 instead , this would be equivalent to setting $n_{mu} = n_{fu} = 0$ from 1991 Under these circumstances the model predicts 1043 HIV infectious and 123 AIDS cases by the year 2000 This is a considerable decrease from the 1584 infectious and 183 AIDS cases predicted by the model given no intervention policies The proportions HIV infectious and with AIDS given these three situations are plotted in Figure 7 10 and Figure 7 11 respectively

FIGURE 7 10

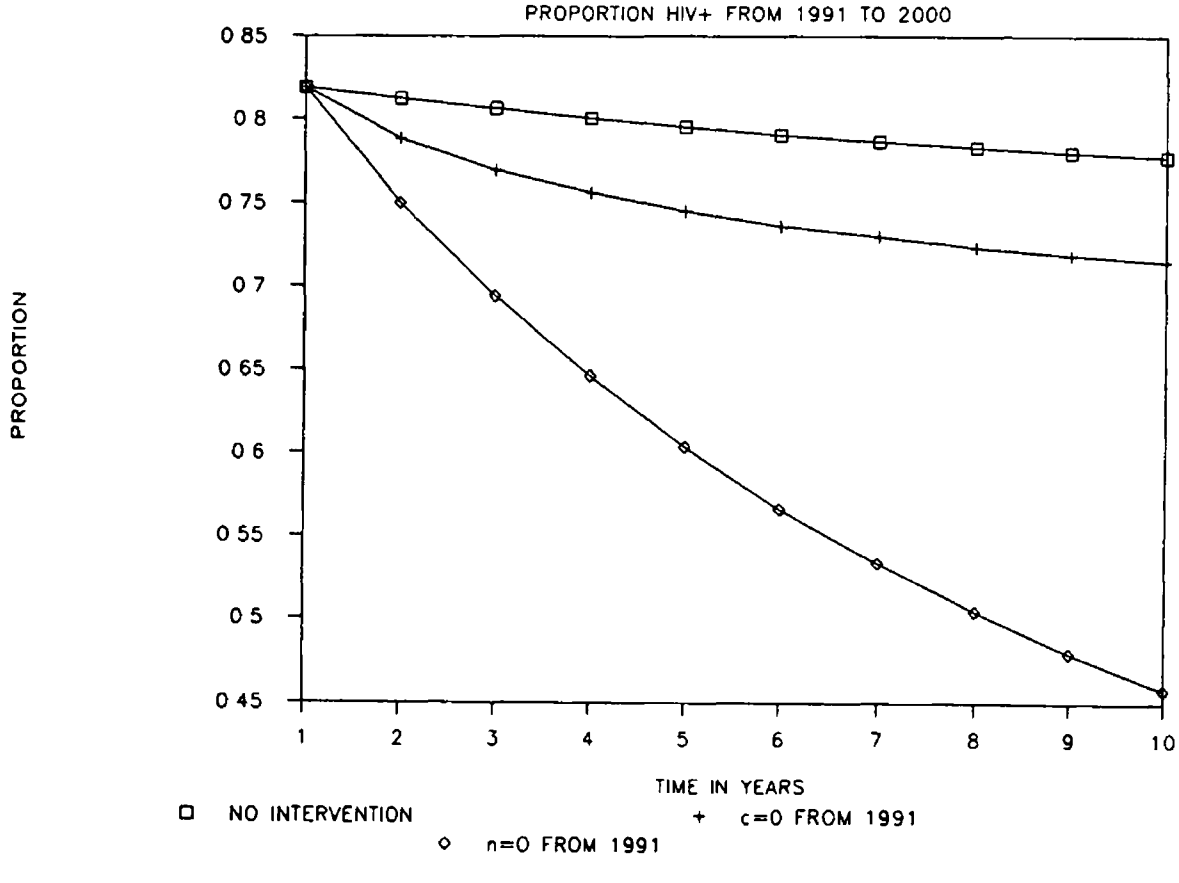
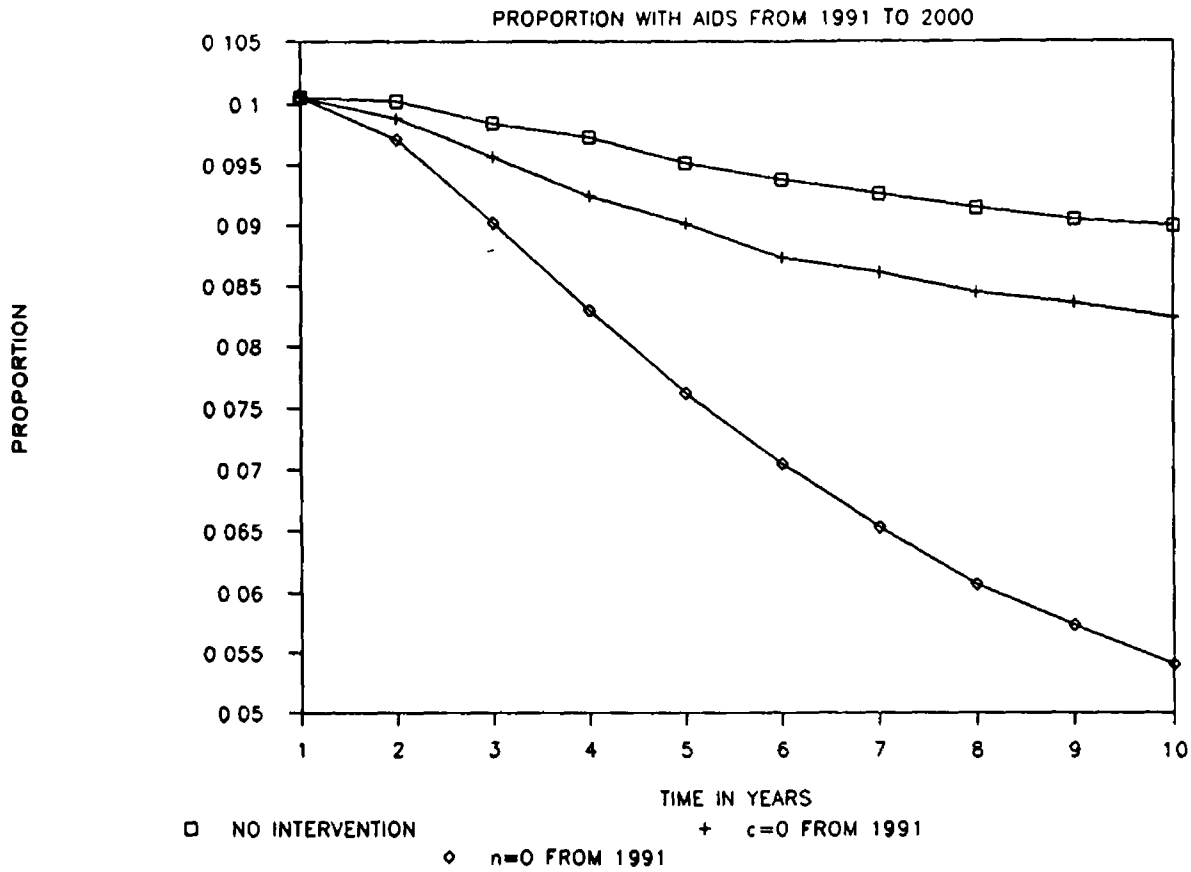


FIGURE 7 11



7.8 Discussion.

The objective of this chapter was to provide estimates of the size of the HIV positive population in Irish IV drug users and homosexuals Our aim was to achieve this by the implementation of transmission models describing the spread of the virus within these two groups Parameter estimates for these models were to come from a HIV survey that was conducted by us at the genito urinary clinic at St James Hospital Dublin We believe that these objectives were realised and the results of this chapter are evidence of this

Looking closer at our results, we can see where difficulties were encountered and overcome Parameter estimates proved more difficult than we originally thought We had hoped to estimate the introduction rates to the IVDU and homosexual populations by asking patients the year in which they first used IV drugs or first became homosexually active This information could then be combined with estimates of the size of these populations to provide estimates of the numbers entering the two groups each year We were unable to do this We found that the majority of those surveyed had entered the particular risk group some years previously, none had entered in the very recent past We are aware now of one Irish/European study that is in progress at the Irish Health Research Board This study will examine the incidence of IV drug use and the numbers attending the clinics for the first time each year We look forward to the results of this study, when completed it will be possible to utilise this data in order to provide a minimum estimate of the numbers taking IV drugs for the first time each year. From our own survey, we were able to provide a crude estimate of the mean number of people entering the IVDU and homosexual populations each year

We were very fortunate with our survey replies to questions on sexual contacts and IV drug use. The number of new partners per unit time is a sensitive and difficult question to administer in any survey. We believe that because our survey was conducted within a genito-urinary clinic, patient replies were more truthful. Staff are well trained and can gain the confidence of the patient. Also, because Dublin is a small city medical staff know their patients very well. In estimating the parameter on sexual contacts we did not take frequency of sexual contact within a partnership into account. This will effect the probability of contacting the virus and should be explored further given the availability of suitable data. Replies to questions on IV drug use were comprehensive, however little is known about the probability of transmission during needle sharing and more research is required into this area of the disease.

We chose out of necessity to model the spread of the disease from one drug user to another and from one homosexual to another. We have not taken spread from the drug user to the ordinary heterosexual or from the homosexual to the bisexual into account. Our survey was the first of its kind to be carried out in Ireland, it was directed towards the known, primary groups at risk. Now that we have seen that we can obtain answers to sensitive questions by careful survey design and administration by qualified medical personnel we look forward to the extension of this survey work to include questions on non IVDU partnerships and bisexual contacts.

Given the models' limitations we have succeeded in providing preliminary estimates of the level of HIV infection in the IVDU and homosexual populations. We know from the National Virus Reference Laboratory that approximately 515 drug users and 97 homosexuals tested HIV positive between 1985 and 31st. December 1989. Our models, given the minimum initial conditions in 1985 predict 647 and 239 infectious within the drug using and homosexual populations in 1989. If we calculate the size of the IVDU male and female populations in 1980 and introduce one infectious male at that time, the model predicts a total of 3,316 infectious drug users in 1989. When we estimate from this figure the size of the total number infectious, we arrive at an estimate of 5,802 infectious people. We have seen in this chapter how this result compares favourably with results from the improved back projection method. This encouraged us to look closer at the IVDU model and to give a preliminary assessment of the effects of possible Government intervention policies. In Figures 7.10 and 7.11 we saw the results of varying the parameters describing the number of new partners per unit time and number of people shared needles with per unit time. We saw that the introduction of a needle exchange program, even within the course of the epidemic, greatly effects the proportions infectious and with AIDS.

7.9 Conclusions and Recommendations.

We started this thesis with a number of quotes which portrayed the myths and uncertainties surrounding the transmission and spread of the HIV virus and AIDS, both within Ireland and world-wide. The objective of our work here was to explore these unknowns and provide the reader with a more comprehensive picture of HIV and AIDS in Ireland. To achieve this, in Chapters 1 and 2 we discussed the background to the disease in Ireland and the role of mathematical modelling in describing the spread of AIDS. From this we saw where key epidemiological data was lacking. We also saw how models to date have concentrated on the spread of the disease within the homosexual population. We believe that there is an urgent need for more comprehensive and detailed data collection on a national and regional scale. This will

allow the mathematical modeller to utilise and develop more realistic transmission models

In Chapters 3 we estimated the nature and effect of reporting delays on the data collection and found them to be minimal in Ireland This is the result of the prompt return of information on new HIV positives from the genito urinary clinics It is hoped that this will remain so We also provided estimates of the incidence of HIV infection in Ireland given the number of diagnosed AIDS cases We found that results relied heavily on both the distribution of the incubation period and the nature of the annual growth in AIDS cases Further research is required into both these areas of the disease In Chapter 4 we derived a new and unique solution to the integral equation model arising in back projection This allowed us to considerably improve upon the estimates of the level of HIV infection derived in Chapter 3 This new analytical solution can be applied to data from the U K and The United States The extension in the future, of the methods discussed in this chapter, to the individual risk groups in Ireland would be desirable, given sufficient data

In Chapter 5 we provided estimates of the minimum number of deaths from AIDS This was based on the number of AIDS cases known to the Department of Health and the distribution of the length of survival after the onset of AIDS Further work on estimates of survival times given the introduction of drugs that prolong the life of an AIDS patient or the introduction of HIV vaccines are required if estimates on the numbers of deaths are to remain accurate

The results of a HIV transmission survey were presented in Chapter 6 This provided detailed information on the habits and behaviour of those at risk of HIV infection and allowed us to derive in Chapter 7 the first and only estimates of transmission model parameters in Ireland The survey results presented in Chapter 6, particularly those on the habits and frequency of needle sharing and drug use have implications for the spread of the virus not only in Ireland but world-wide, in any country where HIV transmission by IVDU's is significant For these reasons we consider it highly desirable to review the survey questionnaire and to include more details on IVDU contacts with heterosexuals The extension of this revised survey to other centres would provide invaluable data and allow the mathematical modeller to explore further transmission possibilities

In Chapter 7 we introduced the first deterministic models of the transmission of HIV in the Irish IVDU and homosexual populations We provided predictions based on these models and the parameters derived from the survey Despite the models' assumptions, we saw that predictions on the numbers HIV positive corresponded with results from the improved back projection method It would now be desirable to develop these models further in line with the revised survey and to provide a more detailed analysis of the models employed

Finally we believe that the work of this thesis is just the first in a series of steps that must be taken if the mathematician, and those working with AIDS patients are to provide society with the means of understanding and preventing this epidemic

> 'There are of course, intellectual and aesthetic satisfactions in understanding the mechanisms and processes underlying the natural world, but, in the face of misery and suffering on a monumental scale, epidemic theory for its own sake is a luxury mankind can ill afford The world must not only be interpreted it must be changed ' *Norman T J Bailey 1957 [7]*

Appendix A

HIV Transmission Survey, Pilot Survey Report

A.1 General description of the survey

Purpose of the survey
The aim of this survey was to investigate the social, sexual and drug habits of those at risk from the Human Immunodeficiency Virus (HIV). It was our intention to look particularly at the rate of needle use in the drug abusing population and the rate of sexual partner change amongst all individuals at risk. In addition to this we aimed to estimate the rate of introduction to each of the at risk populations. This information is essential to the construction of any mathematical or statistical models for the transmission dynamics of the disease.
Material Covered
The participants in the survey were drawn from the Genito Urinary Clinic at St. James hospital Dublin. All patients attending the clinic have been tested HIV positive. There is a total of approximately 300 patients registered at the clinic, although not all of these are regular attenders. For the purposes of this pilot survey it was agreed with the clinic that twenty patients would be surveyed. It is hoped to survey approximately two hundred patients in the final survey. Due to clinic difficulties a total of nineteen patients were eventually questioned.
Information Collected
The information collected in the pilot survey can be broken down into four categories. These were,
1. Personal Details.
This section included the patients initials, data of birth, sex, marital status and information on where else the patient was under regular care.
2. History of HIV.
In this section the patient was asked to which risk groups they belonged, whether or not they had been tested for the HIV virus and if so when, how frequently and the results of these tests. They were also requested to state their CDC classifications and if they were classified as stage CDC 4 they were asked to state when they progressed to stage 4. In addition to this the patients were asked if they were in receipt of any AIDS related drugs and if so when they had first started to receive this drug. Within this section patients were asked if they had any sexual contacts other than with their regular partner and if so how frequently. They were then asked questions similar to earlier questions on the HIV status of their regular partner.
3. Risk Activity.

Within this section patients were asked to list their sexual orientations and the age at which they became heterosexually active They were then asked a series of questions relating to the rates of partner change and use of contraceptives Within this section patients were asked if they had ever abused intravenous drugs If so they were then requested to give estimates on the extent of their drug use, needle sharing and the lifetime of their needles Patients were also asked at what age they first abused intravenous drugs Female patients in this section were asked if they had given birth since becoming HIV positive and if so they were then asked to provide details on the HIV status of their children

4 Homosexual Activity

This section requested those who engaged in homosexual activity to answer questions on their sexual activity similar to those asked of heterosexuals Finally patients were asked to list any other relevant information

Method of data collection

The data described above was collected by the medical staff at the clinic This included the consultant, the senior registrar and a research nurse The survey was administered by the staff while patients were attending the clinic for reasons associated with their HIV status

Sampling Method

The nineteen patients involved in the pilot survey were questioned on a first come first served basis

Assessment

The primary aim of this pilot survey was to assess its feasibility, to access accuracy of replies and time involved in administering the survey We found that it took approximately one month to survey nineteen patients We also found that some of the survey questions were misunderstood This was apparent from certain inconsistencies in patient replies We shall examine this aspect in more detail in later sections Finally we feel that the pilot was very successful as it brought to light patients' misunderstandings and willingness to answer sensitive questions

A.2 Statistical Analysis

Introduction

Within this section we propose to give a brief description of the steps followed to ensure accuracy, the equipment utilised in the statistical analysis and finally a discussion of the results of the pilot survey

Accuracy and Equipment

All questionnaires were read and checked prior to data entry Each questionnaire was then assigned a case number for ease of reference Data was entered onto the VAX via kermit and the word processing package Wordstar Data was entered in fixed format with each variable being assigned a short variable name and fixed position Hardcopy records of the variable names and positions were kept Approximately one hundred variables were identified SPSSX the statistical package for the social sciences was used to analyse the data In order to shorten subsequent command files all data definitions and derived variables were stored in system files These could then be readily accessed The statistical analysis of the pilot survey was broken down into several sections which followed along the lines of the sections within the survey itself

Personal Details

The initials and date of birth of each patient were crossed checked From this we

saw that no patient was interviewed more than once The distribution of the sex of the patients was examined and can be seen in Table A 1 below While the ratio of males to females is almost one to one in the pilot we believe that this will not be the case in the final survey as there approximately 76 female HIV positives attending the genito-urinary clinic at St James and there are over 200 male HIV positives in attendance

Table A 1
PATIENTS SEX

	FREQUENCY	%
MALE	10	52 6
FEMALE	9	47 4
TOTAL	19	100 0

The majority of the patients in the pilot survey were single We believe that in the final survey we shall not require such detailed information on the marital status of the patients Our primary interest is in knowing whether or not the patient is in a stable relationship This question has been adjusted accordingly A table of the marital status of the patients surveyed is provided below

Table A 2
PATIENTS MARITAL STATUS

	FREQUENCY	%
SINGLE	12	63 2
COHABITING WITH A MALE	2	10 5
MARRIED	3	15 8
DIVORCED SEPARATED	1	5 3
TOTAL	18	100 0

The age of the patients was derived from their dates of birth The mean age of those questioned was 27 years and ages ranged from 18 years to 38 years The distribution of the patients ages is given below in Table A 3

Table A 3
AGE DISTRIBUTION

AGE	FREQUENCY	%
18	1	5 3
22	2	10 5
23	1	5 3
24	1	5 3
25	1	5 3
26	1	5 3
27	2	10 5
28	1	5 3
29	2	10 5
30	2	10 5
31	1	5 3
32	1	5 3
33	1	5 3
34	1	5 3
38	1	5 3
TOTAL	19	100 0

Cross tabulations of age with risk group were produced in order to examine the age distributions within each of the risk groups We found that the drug abusing group was the youngest while the homosexual group tended to be older Some patients were classified under more than one risk group A summary of the information in these crosstabulations are provided in Table A 4

Table A 4
AGE WITHIN RISK GROUP

Risk Group	Mean Age	Range	No of patients
Drug Abuser	25	18 to 34	7
Reformed drug abuser	27	22 to 33	9
Homosexual	33	29 to 38	2
Bisexual	26	none	1
Partner of HIV positive	30	26 to 33	3
Other risk	30	none	1

HIV Status

All patients questioned had been tested for the HIV virus All patients were HIV positive Many patients had been tested more than once When questioned on the dates of these tests and their results many patients could not remember All patients remembered when they first tested positive with the exception of three patients who tested positive some time in 1985 As the patients experienced difficulty in remembering all dates this question has been modified for the final survey We shall now question patients on the date of their last negative test (if applicable) and the date of their first positive test The distribution of the number of tests per patient are given in Table A 5 below We found that the mean number of tests per patient was two, with the number of tests ranging from one to seven

Table A 5
NUMBER OF TIMES TESTED

TIMES TESTED	FREQUENCY	%
1	12	63 2
2	3	15 8
4	1	5 3
7	2	10 5
MISSING	1	5 3
TOTAL	18	100 0

How long patients have been positive for was derived from the date of the survey (July 1989) and the dates the patients tested positive This of course will not provide a completely accurate picture of the duration of the patients incubation periods due to the fact that patients may have been HIV positive long before they were tested for the virus For these reasons we feel that the question on the date of the patients last negative result (if patients can recall this) is of the utmost importance The length of time the patients have been positive was computed in months We found that this time ranged from as little as one month to as long as fifty nine months with the mean length positive at twenty nine months The distributions of the durations positive are provided in Table A 6 below

Table A 6
DISTRIBUTIONS OF DURATIONS POSITIVE (In months)

MONTHS	FREQUENCY	%
1	1	5 3
2	1	5 3
5	1	5 3
6	1	5 3
8	2	10 5
18	1	5 3
20	1	5 3
25	1	5 3
30	1	5 3
38	1	5 3
42	1	5 3
44	1	5 3
46	1	5 3
49	3	15 8
56	1	5 3
59	1	5 3
TOTAL	19	100 0

The mean duration HIV positive was seen to be 29 21 months and the standard deviation was 20 15 months

Patients were next asked to state their CDC classification When the pilot survey was designed we were unaware that a patient could be classified under more than one stage The main survey has been modified accordingly If patients were classified as CDC stage 4 they were then asked to state when they had progressed to this stage We also asked in the pilot if patients were in receipt of any AIDS related drugs and if so what drug and when did they first start to receive this drug We have found in the pilot that all patients who progress to stage 4 receive Retrovere immediately, this question has therefore been modified accordingly It is also interesting to note that those patients who are in the AIDS classes (CDC4C1, CDC4C2, CDC4D and CDC4E) have been HIV positive for longer than those who are not classified as having AIDS, see Table A 7

Table A 7
MEAN LEHGTH POSITIVE WITHIN CDC CLASSIFICATION

CDC Stage	Length Pos	Range	No in Class
CDC1			0
CDC2	14 8	1 to 42	6
CDC3	30 7	5 to 49	6
CDC4C1	33 7	5 to 59	6
CDC4C2	33 5	18 to 49	2
CDC4D			0
CDC4E		46	1

Partners HIV Status

Patient replies to the questions on sexual contacts with regular and alternative partners proved to be very inconsistent This may have been due to the sensitive nature of the questions and/or the design of these questions Also patients could not state

with any certainty if their regular partner had been tested for the HIV virus and if so the results of the test Only 11 of the 19 patients say that their partner has been tested yet 12 patients gave the results of their partners test For these reasons part of this section in the final survey has been omitted and questions have been rewritten in a less sensitive way

Heterosexual Risk Activity

Within this section we first asked patients to state their sexual preference We then questioned on the nature and extent of their sexual contacts In addition we also questioned patients on their use of contraceptives Of the 19 patients surveyed 15 were heterosexual, 2 homosexual and 2 were bisexual Looking first at the replies relating to heterosexual activity we found that 6 patients missed the question on age at first heterosexual contact and 2 patients said that it was non applicable As this is one of the central questions to the survey (as the data is needed to estimate the introduction rates to the sexually active populations) we have moved it to a more prominent position in the final survey The mean age of first heterosexual contact of the eleven replies to this question was 16 64 years with a standard deviation of 2 46 years and a range of 13 to 22 years The mode was also 16 years Sexual permissiveness was not evident from the replies Twelve of seventeen patients are reported as having a single sexual partner in the past year The number of partners in the past five years per patient ranged from none to fifty Eleven of the seventeen patients said that they had no partners within the previous month As our sample size was very small and the questions very sensitive the main survey was considerably modified Patients will not now be asked directly to quantify their number of partners When asked about contraception 9 of the 17 heterosexually active (15 heterosexuals and 2 bisexuals) patients said that they never used any form of contraceptive 5 patients said that they sometimes did and only 2 patients said that they always used some form of contraception Of the 7 patients who used contraceptives 6 said that they used condoms Homosexual activity was analysed separately

Homosexual Risk Activity

Of the 19 patients who answered the pilot survey 2 males said that they were homosexual and one male said that he was bisexual Because of such a small sample size replies to the questions on homosexual practices shall be summarised briefly The average age at first homosexual activity was seen to be 15 3 years with a range of 12 to 21 years When questioned on the number of homosexual partners in the last 5 years replies ranged from none to 365 2 patients said that they had no partners in the last year while one patient said he had one None of the patients had had any partners within the previous month Patients engaged in a range of homosexual activity but when questioned on the use of condoms 2 patients said that they never used them It is difficult to deduce any relevant information from this sample due to its size and the range of replies given by the three patients

I V Drug Use

Sixteen of the nineteen patients said that they do or did use needles Each of the 16 said that they also shared needles Fourteen of these said that they had not shared within the last week The range of injections per person per day was between 1 and 10 with the range per week of 3 to 42 Tables of these frequency distributions are given below

Table A 8
DISTRIBUTION OF NUMBER OF IV INJECTIONS PER DAY

NUMBER	FREQUENCY	%
1	2	10 5
3	6	31 6
4	3	15 8
5	2	10 5
6	2	10 5
10	1	5 3
MISSING	3	15 8
TOTAL	19	100 0

The mean number of IV injections per day was 4 and the standard deviation was 2 16 The mean number per week was just under 26 and the standard deviation was 11 32 The age of first needle use varied from 13 to 26 years with the mode at 15 years and the mean age at 17 1 years This distribution is given in Table A 9

Table A 9
DISTRIBUTION OF AGE OF FIRST IV DRUG USE

AGE	FREQUENCY	%
13	1	5 3
14	1	5 3
15	5	26 3
16	1	5 3
17	3	15 8
18	2	10 5
20	1	5 3
23	1	5 3
26	1	5 3
MISSING	3	15 8
TOTAL	16	100 0

The mean age of first IV drug use was 17 13 years and the standard deviation was 3 40 years Ω We saw from the survey that all of the heterosexuals and bisexuals with the exception of one patient used needles This one heterosexual patient contracted the virus in an African country Neither of the two homosexuals used needles We also found that of the 16 patients using needles 8 were male and 8 female This is maybe due to the fact that we had 9 females and 10 males participating in the pilot We do not expect to get even numbers of males and females in the final survey due to the fact that there are more HIV positive drug using males than females

A.3 Conclusion

The primary aim of this pilot survey was to test the feasibility of a major survey with sensitive questions on the sexual habits and drug use of HIV positive patients Questions in the survey were designed to give us the necessary information on essential mathematical model parameters This information is needed in order to provide long term estimates of the prevalence of the HIV virus and eventual AIDS cases in Ireland

The pilot was very successful as it highlighted patients' misunderstandings about certain questions It also demonstrated to us that we could not expect to get accurate

quantitive details in certain questions In addition to this we found that one of the central questions that of the age of first heterosexual contact was missed by the interviewers This question has now been moved to a more prominent position Data from the replies was sketchy due to the small sample sizes, particularly in the homosexual group For this reason preliminary estimates of the model parameters are unlikely to reflect the true situation

Finally one must stress to other researchers the importance of a preliminary pilot survey this we feel is reflected in our results

Appendix B

HIV Transmission Survey Questionnaire

HIV TRANSMISSION MODEL SURVEY

Prof A D Wood, Ms H Ruskin, Ms C Comiskey, Dublin City University, Dublin

Interview Details

Hospital/Clinic name

1) St James 2) Pearse St 3) Other (please specify) ☐

Date of interview ☐☐☐☐☐☐

Interviewers initals ☐☐

SECTION 1 PERSONAL DETAILS

1 Initals of the patient ☐☐

2 Patients date of birth ☐☐☐☐☐☐

3 Patients sex 1) Male 2) Female ☐

4 Please list the patients risk category ☐
1) Male I V D U only
2) Female I V D U
3) Male homosexual only
4) Male bisexual
5) Male homosexual or bisexual and I V D U
6) Other, please specify

5 Is the patient ☐
1) Cohabitating with a male
2) Cohabitating with a female
3) Living single
4) Other, please specify

6 Where else is the patient under regular care? Please list all those that apply
1) St James ☐ 1
2) Mater Hospital ☐ 2
3) Pearse St ☐ 3
4) Mountjoy ☐ 4
5) Own Doctor ☐ 5
6) Not under regular care elsewhere ☐ 6
7) Others, please specify ☐ 7

SECTION 2 HIV DETAILS

1 How many times has the patient benn tested for HIV?

2 Please give the approximate dates of the patients
a) first positive test, (state month and year)
b) last negative test, (state month and year)

3 If you have a regular partner are they HIV positive

1 No
2 Yes
3 Do not know
4 No regular partner

If yes when did they test positive, state month and year

4 Please tick the patients C D C classifications

1 CDC 1
2 CDC 2
3 CDC 3
4 CDC 4a
5 CDC 4b
6 CDC 4c1
7 CDC 4c2
8 CDC 4d
9 CDC 4e
10 Patient not classified

5 If CDC 4, please give the date when the patient progressed to stage 4 (state month and year)

SECTION 3a HETEROSEXUAL PARTNER DETAILS

1 Would you describe your sexual activity pattern as

1 Non-existent
2 Seldom or occassional - at least once a month
3 Frequent - at least once a week
4 Very frequent - at least once a day

2 Has this pattern changed since you became HIV positive

1 Fewer partners
2 No change
3 More partners

3 At present would you say that your average number of partners per month was

- 1 No partners
- 2 One partner
- 3 Two to five partners
- 4 Six to ten partners
- 5 More than ten partners

4 At present what is your average number of partners per year?

5 At what age did you become hetrosexually active?

6 Do you or your partner use contraceptives?

- 1 Never
- 2 Sometimes
- 3 Always

7 What sort of contraceptive do you or your partner use?

- 1 Condoms
- 2 Oral contraceptives
- 3 Condom plus another form of contraceptive
- 4 Coil
- 5 Sterilization
- 6 Other, please specify
- 7 None

SECTION 3b HOMOSEXUAL PARTNER DETAILS

1 Would you describe your sexual pattern as

- 1 Non-existent
- 2 Seldom or occasional - at least once a month
- 3 Frequent - at least once a week
- 4 Very frequent - at least once a day

2 Has this pattern changed since you became HIV postive

- 1 Fewer partners
- 2 No change
- 3 More partners

3 At present would you say that your average number of partners per month was

- 1 No partners
- 2 One partner
- 3 Two to five partners
- 4 Six to ten partners
- 5 More than ten partners

4 At present what is your average number of partners per year?

5 Please list your types of sexual activity

- 1 Active
- 2 Passive
- 3 Oral
- 4 Other

6 Do you or your partner use condoms?

- 1 Never
- 2 Sometimes
- 3 Always

7 At what age did you become homosexually active?

SECTION 4 DRUG USE DETAILS

1 Have you used intravenous drugs in the past?
1) No 2) Yes

2 Are you using intravenous drugs at present?

- 1 No, stopped when became HIV positive
- 2 No, stopped when became pregnant
- 3 No, stopped for other reasons, please state
- 4 Yes, am using I V drugs at present

If no, please state month and year when stopped

3 Please answer the following

- 1 Age of first needle use
- 2 How often would you inject each week?
- 3 How often would you inject each day?
- 4 How many people would you share a needle with in one week?
- 5 How long would a needle last?
  - (a) Less than one week
  - (b) One to two weeks
  - (c) Two to four weeks
  - (d) More than four weeks

4 Has this pattern changed since you became HIV positive? ☐

1 Less frequent use
2 No change
3 More frequent use

5 If you are female and HIV positive ☐
Have you given birth since becoming HIV positive?
1) No 2) Yes

If yes,

(a) How many live deliveries have you had? ☐
1) 1 2) 2 3) 3
4) More than 3, please specify number

(b) Were any of these twins? ☐
1) No 2) Yes
If yes, please give number of set of twins ☐

(c) Please answer the following

	1st Child	2nd Child	3rd Child
Age (in months)			
Number of tests			
Any positive results 1) No 2) Yes			
Date of positive result			
Result of last test 1) Neg 2) Pos			
Date of last test			

Any other relevant information

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Appendix C

Numerical Analysis

C.1 Introduction

The transmission of HIV infection within the Irish IVDU and homosexual populations was described in Chapter 7 The NAG library routine D02EBF [38] was used to solve these systems of non linear differential equations The reader is provided below with a simple driver program, in double precision, for use with this routine We show here the program for the IVDU model, given certain known inital conditions This program can easily be modified for use with the system of equations describing the homosexual model

C.2 Program Listing

```
C      HIV TRANSMISSION MODEL SOLVER  D02EBF
C      MINIMUM ESTIMATES, IVDU POPULATION MODEL
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(8,26), Y(8)
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=8
       IW=26
       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)=358 0D0
      Y(2)=97 0D0
      Y(3)=128 0D0
      Y(4)=48 0D0
      Y(5)=0 0D0
      Y(6)=0 0D0
      Y(7)=486 0D0
      Y(8)=145 0D0
      H=1 0D0
      I=24
      IFAIL=1
      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(8), Y(8)
C
      REAL*8 BETA1,BETA2,BETA3,NMU,NFU,CMU,CFU,LAMDAMU,LAMDAFU,MUMU,MUFU,
     +  ALPHA,D
C
      BETA1=0 20D0
      BETA2=0 10D0
      BETA3=0 20D0
      NMU=4 6670D0
      NFU=6 9410D0
      CMU=7 440D0
      CFU=1 007D0
      LAMDAMU=119 0D0
      LAMDAFU=64 0D0
      MUMU=0 107D0
      MUFU=0 125D0
      ALPHA=0 1250D0
      D=1 0D0
      F(1)=LAMDAMU-NMU*BETA3*Y(1)*(Y(3)/Y(7)+Y(4)/Y(8))
     +  -CMU*BETA2*Y(1)*Y(4)/Y(8)-MUMU*Y(1)
      F(2)=LAMDAFU-NFU*BETA3*Y(2)*(Y(3)/Y(7)+Y(4)/Y(8))
     +  -CFU*BETA1*Y(2)*Y(3)/Y(7)-MUFU*Y(2)
      F(3)=NMU*BETA3*Y(1)*(Y(3)/Y(7)+Y(4)/Y(8))
     +  +CMU*BETA2*Y(1)*Y(4)/Y(8)-(ALPHA+MUMU)*Y(3)
      F(4)=NFU*BETA3*Y(2)*(Y(3)/Y(7)+Y(4)/Y(8))
```

```
     +  +CFU*BETA1*Y(2)*Y(3)/Y(7)-(ALPHA+MUFU)*Y(4)
        F(5)=ALPHA*Y(3)-(D+MUMU)*Y(5)
        F(6)=ALPHA*Y(4)-(D+MUFU)*Y(6)
        F(7)=F(1)+F(3)+F(5)
        F(8)=F(2)+F(4)+F(6)
        RETURN
        END
C
        SUBROUTINE PEDERV(X, Y, PW)
C       WE OMIT THIS ROUTINE, TO ALLOW NAG TO COMPUTE JACOBIAN INTERNALLY
        RETURN
        END
C
        SUBROUTINE OUT(X, Y)
        IMPLICIT NONE
C       SCALAR ARGUMENTS
        REAL*8 X
C       ARRAY ARGUMENTS
        REAL*8 Y(8)
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=1,8)
        X=XEND - FLOAT(I)*H
        I=I-1
        RETURN
99999 FORMAT (1X,1PD11 4,8(2X,1PE12 5))
        END
```

Appendix D

Diskette Files

FILE NAME	CONTENTS
Survey sps	SPSSX command file showing all data definitions, records, variable names and labels used in the analysis of HIV Survey
Survey1 out	Analysis of Section 1 personal details, of HIV Survey, includes information for all risk groups
Survey21 out	Analysis of Section 2, HIV incubation details, for risk group 1 (male IVDU)
Survey22 out	As above, but for risk group 2, (female IVDU)
Survey23 out	As above, for risk group 3, (male homosexual)
Survey24 out	As above, for risk group 4, (male bisexual)
Survey25 out	As above, for risk group 5, (male homosexual/bisexual and IVDU)
Survey26 out	As above, for risk group 6, (male and females with other risks)
Survy3A1 out	Analysis of Section 3A of HIV Survey, heterosexual partner deatails, for risk group 1
Survy3A2 out	As above, for risk group 2
Survy3A4 out	As above, for risk group 4

Survy3A5 out	As above, for risk group 5
Survy3A6 out	As above, for risk group 6, males only
Survy3A7 out	As above, for risk group 6, females only

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