MODELLING THE PROGRESSION OF TREATMENT SCENARIOS IN THE HIV/AIDS EPIDEMIC

By

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ABSTRACT

Advances in recent treatments for HIV/AIDS patients have shown dramatic outcomes in extending the incubation period and AIDS survival time, whilst also providing significant improvements in the quality of patients' lives.

This thesis establishes a model of the HIV/AIDS epidemic that incorporates the effects of treatments, in particular, the introduction of highly active antiretroviral therapy (HAART), which became widely available during 1996.

The technique of compartmental modelling is employed in an attempt to reproduce observed AIDS incidence/prevalence, HIV incidence/prevalence, and deaths from AIDS data. There are movements between compartments (sub-populations affected by the HIV/AIDS epidemic) each with an associated parameter. Each sub-population has a differential-difference equation associated with it. Once these equations have been solved numerically they give a set of steady-state solutions, from which it is possible to estimate HIV/AIDS incidence and prevalence.

Some parameter values within the model are obtained from surveys, census results, etc., but others are derived using a maximum likelihood estimation (MLE) procedure. The use of realistic values gives impressive results, creating a remarkable fit with routinely collected data relating to levels of HIV/AIDS incidence and prevalence in the UK homosexual population.

Finally, the model is used to project levels of incidence and prevalence over the next few years, and to investigate several possible 'what-if' scenarios, with a brief investigation into the consequent cost implications.

GLOSSARY

AIDS – Acquired Immune Deficiency Syndrome

ARC – AIDS Related Complex

ART – Antiretroviral Therapy

AZT – anti-HIV drug, Zidovudine

BHIVA – British HIV Association

CASCADE – Concerted Action on SeroConversion to AIDS and Death in Europe

CD4 - large glycoprotein molecule found on surface of T lymphocytes

CDC – Centers for Disease Control

CDR – Communicable Disease Report

CDSC – Communicable Disease Surveillance Centre

CHAVI – Centre for HIV/AIDS Vaccine Immunology

CI – Confidence Interval

CTL – Cytotoxic T Lymphocyte

DH or **DoH**– Department of Health

DNA – Deoxyribonucleic Acid

EIP – Evolutionary Infectivity Profile

ENAADS – European Non-Aggregate Data Set

ECEMA – European Centre for the Epidemiological Monitoring of AIDS

GLC – Green Light Committee

GRIDS – Gay-Related Immune Deficiency Syndrome

GSK – GlaxoSmithKline Plc.

GUM – Genitourinary Medicine

HAART – Highly Active Antiretroviral Therapy

HBM – Homo/Bisexual Men

HC – Heterosexual Contact

HIV – Human Immunodeficiency Virus

HLA – Human Leukocyte Antigens

HPA – Health Protection Agency

HTLV – Human T-Lymphotropic Virus

HVDDT – HIV Vaccine Design and Development Teams

IP – Incubation Period

IPD – Incubation Period Distribution

IVDU or **IDU** – Intravenous Drug User

KS – Kaposi's Sarcoma

MEDFASH – Medical Foundation for AIDS and Sexual Health

MLE – Maximum Likelihood Estimation

MLR – Mixed Leucocyte Reaction

MMWR – Morbidity and Mortality Weekly Report

MSM – Men who have Sex with Men

NATSAL – National Survey of Sexual Attitudes and Lifestyles

NHS – National Health Service

NIAID – National Institute of Allergy and Infectious Diseases

NIH – National Institutes of Health

NRTI – Nucleoside-analogue Reverse Transcriptase Inhibitor

NS – Negotiated Safety

PACT – National Association of NHS Providers of AIDS Care and Treatment

PBMC – Peripheral Blood Mononuclear Cells

PCP – Pneumocystis Carinii Pneumonia

PCT – Primary Care Trust

PDF – Probability Distribution Function

PEP – Post Exposure Prevention

PGL – Persistent Generalised Lymphadenopathy

PHLS – Public Health Laboratory Service

PI – Protease Inhibitor

PLATO – Pursuing Later Treatment Options

RNA – Ribonucleic Acid

RT – Reverse Transcriptase

SCIEH – Scottish Centre for Infection and Environmental Health

SE – Standard Error

SI – Susceptible, Infected

SIV – Simian Immunodeficiency Virus

SIR or **SIS** – Susceptible, Infected, Recovered or Susceptible again

SOPHID – Survey of Prevalent HIV Infections Diagnosed

STARHS – Serological Testing Algorithm for Recent HIV Seroconversion

STD or **STI** – Sexually Transmitted Disease or Infection

TAC – Treatment Action Campaign

TB – Tuberculosis

TSP – Tropical Spastic Paraparesis

UAI – Unprotected Anal Intercourse

UAPMP - Unlinked Anonymous Prevalence Monitoring Programme

UN – United Nations

UNAIDS – Joint United Nations Programme on HIV/AIDS

UPS – Unprotected Penetrative Sex

VB – Visual Basic

VCT – Volountary Counselling and Testing or Volountary Confidential HIV test

WHO – World Health Organisation

CONTENTS

CHAPTER 1

INTRODUCTION

The aim of this thesis is to produce an excellent fitting mathematical model of the HIV/AIDS epidemic, over the years 1979-2002, in order to create confidence in predicting future counts of HIV and AIDS incidence, HIV/AIDS prevalence and deaths from AIDS, and to investigate the effect of certain 'what-if' scenarios.

In order to achieve this goal, an appreciation of the history of HIV/AIDS needs to be obtained, including a biological comprehension of how HIV attacks the immune system and spreads between individuals. In particular, knowledge of the progression of treatment scenarios is crucial in understanding the shape of the epidemic and how it has changed over time. This first chapter of the thesis consists of a literature review which provides a background of the HIV/AIDS epidemic significant when building the mathematical model. Chapter 2 focuses on the creation of the model, comparing compartmental transmission modelling to other mathematical and statistical techniques, illustrating the Cardiff model for the first time within the thesis, defining all the parameters involved, and discussing the assumptions employed. Chapter 3 utilises the Cardiff model, estimating 5 parameters, using the maximum likelihood estimator (MLE) technique, to produce as good a fit as possible between observed and expected AIDS incidence. Within Chapter 3, the Entry Rate is investigated in order to decide which form it should take in order to allow the best fit possible, and the inclusion of HIV incidence data and/or deaths from AIDS data into the fitting process (via the minimisation of the chi-square) is explored to see if the overall fit of the model can be improved. It is not until Chapter 4 that the model in its final format is seen, introducing and estimating the parameter r (treatment effect), splitting time up into periods subject to the introduction of treatments and including HIV and deaths from AIDS data in the minimisation of the chi-square. The fit created by the model employed in Chapter 4 is outstanding and allows confidence in projecting the short-term future of the HIV/AIDS epidemic, hence extrapolations up until the year 2008 and drawn at this point. Chapter 5 uses the model produced in Chapter 4 to investigate possible future 'what-if' scenarios, including: a change in the number of male homosexuals living in the UK; a change in the number of

These numbers are now significantly shy of the true amounts, due to the continuous and ongoing damage that the HIV/AIDS epidemic still inflicts on the world today.
Globally, HIV is continuing to spread, especially in areas with large population densities, such as India and China. WHO and UNAIDS reported in June 2002, that 40 million people worldwide were estimated to be living with HIV, of whom 28.5 million live in sub-Saharan Africa (CDSC 2002).
Table 1.1, on the previous page, provides a summary of the impact the HIV/AIDS epidemic has had on the world by December 2002 (UNAIDS and WHO 2002).

1.1.1 The Discovery of HIV/AIDS

An article in the Morbidity and Mortality Weekly Report (MMWR), on the 5th June 1981, states that a rare pneumonia, Pneumocystis Carinii Pneumonia (PCP), caused by a micro-organism called Pneumocystis Carinii infecting the lungs, was reported in 5, previously healthy, homosexual men from Los Angeles (CDC 1981[a]). On the 4th July, of the same year, the MMWR reported that 26 cases of a rare type of skin cancer, Kaposi's Sarcoma (KS), had been diagnosed (CDC 1981[b]). All 26 individuals (6 of whom lived in California and the remainder in New York) were young homosexual males suffering from a weakened immune system (Tavanyar 1992). The occurrence of these rare diseases, in such succession, among a well-defined group of people was considered very unusual. This, together with the fact that before 1980 there were only a few requests for the unlicensed drug pentamidine (used for treatment of PCP and available only through CDC in Atlanta) compared with increased demand from 1980 onwards, created support for the idea that these reported cases were indeed a new distinct clinical syndrome.
It was soon recognised that the reported patients had profound defects in their cell-mediated immune response, thus the new syndrome was named the Gay-Related Immune Deficiency Syndrome (GRIDS), until 1982, when it was re-named Acquired Immune Deficiency Syndrome, most commonly abbreviated to AIDS. The change of name took place when the same condition was found, not only in homosexual men, but also in haemophiliacs, intravenous drug users (IVDU's) and heterosexuals (Brookmeyer & Gail 1994). In retrospect, it appears that sporadic cases of AIDS in the US had already occurred since 1968 and probably earlier (Grmek 1990).

The similarity with the epidemiology of Hepatitus B with AIDS incurred the hypothesis that a transmissible agent was the most likely cause of AIDS. A new class of virus, called a retrovirus, was isolated from a homosexual man with generalised lymphadenopathy (which can precede AIDS) in 1983, by a group of French investigators, lead by Montagnier, from the Institut Pasteur. The retrovirus was thought to be the cause of this weakened immune system, thus the causative agent of AIDS (Gallo & Montagnier 1988), and was named the lymphadenopathy associated virus. In 1984, a similar virus was isolated by Gallo and co-workers from the National Institute of Health in the US. This virus was named human T-lymphotropic virus type III (HTLV-III). Finally, in 1986, the virus was officially named as Human Immunodeficiency Virus, or HIV (Tavanyar 1992). Also in 1986, HIV-2 was found in two people with AIDS in West Africa. HIV-2 is much less common than HIV-1 (usually just referred to as HIV), and is closely linked to Simian Immunodeficiency Virus (SIV) which infects monkeys. Both HIV-1 and HIV-2 are transmitted in the same way and both lead to AIDS.

When AIDS was first recognised, in 1981, it was not unusual for patients with the disease to live no longer than 1 or 2 years. The epidemic spread quickly and by the end of 2000 there were more than 36.1 million people living with HIV worldwide (UNAIDS 2002). The infection introduces more than 15,000 new patients every day, of which the vast majority, over 95%, are in resource poor countries. KS is now one of the most common tumours in Africa and the most frequent tumour found in patients with HIV-1 infection (Smith *et al.* 2004). Today, AIDS is the leading cause of death in Africa and the 4th most common cause worldwide (UNAIDS 2002).

Dr. Angus Nicoll, Director of PHLS Communicable Disease Surveillance Centre, states: "HIV and AIDS are a huge global health problem and the challenge is at its most acute in developing countries, particularly in sub-Saharan Africa. There are also growing epidemics in China, Russia, Indonesia and West Africa... At the same time.. we cannot afford to be complacent about HIV in Western Europe, including in the UK.. worryingly, there is no sign that the problem is diminishing – in fact, the truth is completely the opposite" (PHLS 2002[a]).

1.1.2 The immune system and HIV/AIDS

Tavanyar (1992) provides a descriptive, easy to understand, explanation of how HIV reproduces within the body. Other publications of note are: Brookmeyer & Gail (1994); Kirschner (1996); and AIDS Knowledge Base (1999).

The immune system's objective is to detect foreign agents, such as viruses and bacteria, recognise them, and attempt to eliminate them from the body. These foreign substances, known as antigens, do not only include viruses and bacteria, but also cancer cells or transplanted organs. The immune system, having recognised the antigen, destroys it fairly quickly; however, if the antigen is unfamiliar to the immune system the elimination process may take longer. If the process takes too long, infection occurs and the immune system produces antibodies, which attach themselves to the particular antigens and removes them, to get rid of the infection.

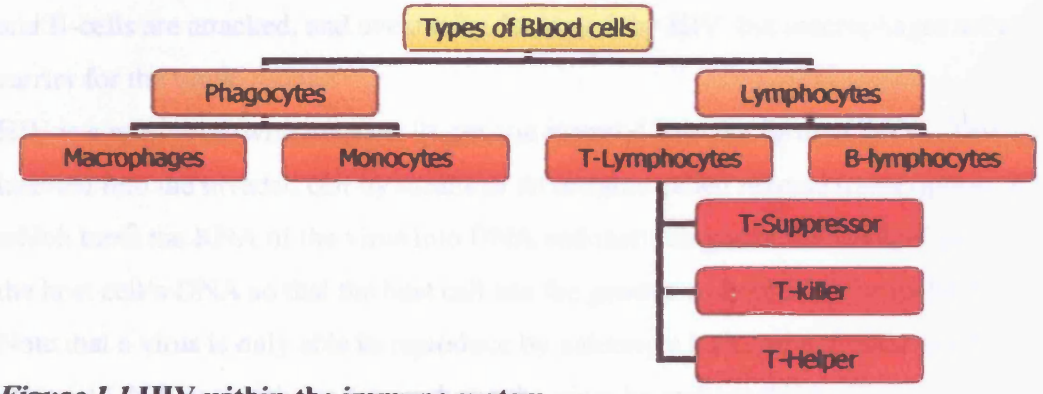

Figure 1.1 **HIV within the immune system**

To understand how HIV attacks the immune system it is important to know the types of blood cells within the immune system, and how they try to eliminate antigens (as illustrated in Figure 1.1). Firstly, there are two types of phagocytes (white blood cells): macrophages, consisting of large cells, and monocytes, smaller immature forms of macrophages which have the ability to transform into macrophages if necessary. Secondly, lymphocytes are white blood cells that control the way the body deals with infection. B-lymphocytes (B-cells) produce the antibodies which try to dispose of the antigens, either by directly killing the antigen or by making it easier for other cells in the blood to do so. T-lymphocytes (T-cells) can act as either: T-suppressor cells, which

suppress the response of the immune system to the invasion of antigens, i.e. halt the production of antibodies from the B-cells once the infection has been eradicated; T-cytotoxic (T 'killer') cells, which stop the organisms within the infected cells from reproducing and, hence, spreading the infection; or T-helper cells, which have a supervisory role over all T-lymphocytes, B-lymphocytes and macrophages. It is these T-helper cells, which detect the presence of an antigen and send monocytes/macrophages to eliminate it, that are targeted by HIV for depletion, hence weakening the immune system. The T-helper cells, B-cells and macrophages all carry a molecule called CD4. Once HIV has entered into the bloodstream, irrespective of mode of transmission, the virus most commonly attaches itself to the CD4 molecule. Note that other receptors do exist, as it has been possible to infect CD4-negative cells also (Lewin & Crowe 1994). Potential accessory receptors are galactosyl ceramide on brain and bowel cells and Fc and complement receptors in cells of the monocyte/macrophage lineage. Both T-helper cells and B-cells are attacked, and eventually destroyed, by HIV, but macrophages act as a carrier for the virus.

HIV is a retrovirus, which means its genetic material is in the form of RNA. This RNA is inserted into the invaded cell by means of an enzyme called reverse transcriptase (RT), which turns the RNA of the virus into DNA and then integrates the DNA of the virus into the host cell's DNA so that the host cell has the genetic code of HIV for its lifetime. Note that a virus is only able to reproduce by entering a host cell and injecting the genetic material DNA so that the cell reproduces the virus by making RNA. Houweling & Coutinho (1997) give a very detailed and informative explanation of different sub-families of retroviruses, how they are made up of a variety of proteins and how, HIV in particular, uses those proteins to infect an individual. Prior to the discovery of HIV, only two retroviruses had ever been found in humans: human T-lymphotropic virus type I (HTLV-I), the cause of adult T-cell leukaemia and tropical spastic paraparesis (TSP), and human T-lymphotropic virus type II (HTLV-II), associated with a T-cell variant of hairy cell leukaemia.

After acquiring the HIV virus, the body starts to manufacture antibodies, which become detectable at about six weeks; at this stage a person is said to be HIV-positive. The viral DNA may stay within the host cell for a long time without reproducing; this period of

time is known as the latent period. During the latent period the immune system responds to HIV as it would any other infection, by releasing antibodies, which generally takes 3-6 months. This process of producing antibodies is known as seroconversion, and may be accompanied by mild symptoms such as fever, lethargy, and a sore throat (Tindall *et al.* 1988). Quite early on in AIDS research, virologists were able to confirm that, around the time of seroconversion in the host, there was a substantial peak in viraemia (measure of viral load). This fell to almost negligible amounts as the immune system responded and the patient would then exhibit an asymptomatic period of, maybe, eight years or longer duration.

After the latent period, HIV begins full-scale reproduction. The cell DNA, containing the genetic material of HIV, is stimulated and HIV particles move to the surface of the invaded cell. The particles explode, taking sections of the cell's membrane with them and using it to form the wrapping for new viruses. The infection process then restarts. As the virus reproduces within an HIV positive individual, more and more CD4 cells are eradicated and so the CD4 cell count decreases over time. Eventually, the immune system is progressively overcome and the patient becomes quite ill, with levels of viraemia increasing towards another peak. More serious symptoms may develop including permanently swollen glands (Persistent Generalised Lymphadenopathy, or PGL) and more unpleasant symptoms such as oral thrush, chronic diarrhoea, fevers, night sweats, and severe weight loss. Also, the mental illness associated with HIV, HIV encephalopathy (AIDS dementia complex), and other psychiatric symptoms are facilitated by the ability of macrophages carrying the HIV virus to enter the brain, breaking the blood-brain barrier (Gallo & Montagnier 1988). Collectively, these symptoms are known as AIDS Related Complex or ARC and permit a diagnosis of AIDS itself. Two of the most common conditions associated with AIDS are pneumocystis carinii pneumonia (PCP), symptoms of which may be present but unalarming over a period of weeks to months (for instance, a dry cough, dyspnoea at exertion and fever), and Kaposi's sarcoma (KS), a form of skin cancer where a malignant tumour of the blood vessels results in lesions which are usually multiple, purple to red, painless, firm nodules and plaques that may affect any part of the skin.

In summary, the virus works by destroying the immune system, which is the body system concerned with fighting infections and cancers. HIV strikes the CD4 cells, which play an important role in immune function; as the CD4 cell count decreases, the body becomes increasingly susceptible to opportunistic infections and cancers which take advantage of the weakened immune system.

1.1.3 Definition of AIDS and the importance of markers

AIDS is officially diagnosed by the presence of one or more defining conditions. The system of case definitions for AIDS which is currently used worldwide, is the 1987 classification system laid down by the Centres for Disease Control (CDC) in Atlanta, Georgia, CDC (1987). However, the CDC revised this classification scheme (CDC 1992[a]) to integrate the CD4 cell count (CDR 1993). The European Non-Aggregate Data Set (ENAADS) is used throughout this thesis as the main source of data, and this employs the 1993 European AIDS surveillance case definition to classify AIDS cases (EuroHIV 2003). The definition includes 26 AIDS defining conditions, the latest of which was added in 1993 (Ancelle-Park 1993). The US definition for AIDS is identical to the European AIDS surveillance case definition with the exception of one criteria; within the US an HIV positive individual with a CD4 count <200 cells/μl is classified as an AIDS case (CDC 1992[a]). Ancelle-Park (1992) gives five reasons why this criterion was not adopted into the European Centre for the Epidemiological Monitoring of AIDS:

"1) The extensive but varied coverage for medical care and other social benefits in Europe makes the US and European issues of access to care very different.
2) Since all diseases included in the 1987 definition severely affect patients' wellbeing, the vast majority of these patients will seek health care and will probably be diagnosed as AIDS cases, so completeness of reporting can be assessed quite easily... The completeness of reporting of the number in the total population of HIV-infected persons who have a CD4 count below 200/μl would be difficult to estimate.

3) Those with ready access to lymphocyte phenotying would be over-represented if the CDC definition were applied ... interpretation of trends would be subject to bias, and linkage with data would be impossible.
4) ... symptom-free HIV-infected people would be labelled as "AIDS", which would carry psychological and social consequences for them.
5) CD4 cell counting is not yet well standardised."

Within the UK, the most common indicators of AIDS are PCP, candidiasis, KS, mycobacterium tuberculosis, wasting, encephalopathy, lymphoma, cytomegalovirus, toxoplasma and other forms of mycobacterium (CDR 1999[b]). Of these diseases, some occur more frequently in particular risk groups than others; for instance, in the homosexual category the risk of KS is five times greater than for any other risk sub-population (McKie 1986).

In the pre-HAART (Highly Active Antiretroviral Therapy) era most deaths were associated with recent AIDS-defining events. Since then, the situation has become more complex; the current definition of AIDS is no longer a near complete marker for overall progression (The Antiretroviral Therapy (ART) Cohort Collaboration 2003). After the introduction of treatments such as HAART, the hazard ratio for death fell from an already reduced value of 0.47 in 1997 to 0.16 in 2001 (CASCADE Collaboration 2003). Clinical event rates are now so low that most studies concentrate on virological and immunological end-points (Mocroft *et al.* 2003).

Markers are a consequence of disease and are used to monitor the progress of disease within the body; the incubation period can be described as a progression through a marker path. In 1990, Goedert defined three classifications of markers: Immunological markers, viral markers and clinical markers. Brookmeyer & Gail (1994) provide three reasons for the importance of markers:

1) Markers characterise the natural history of HIV infection,
2) Markers are useful for surrogate endpoints in clinical trials (alternatives to traditional endpoints of AIDS diagnosis and death),
3) Markers make useful prognostic factors for predicting progression to AIDS and thus useful in the clinical management of patients.

The most commonly used markers are CD4 count and viral load (HIV-RNA). In general, the lower the CD4 cell count, the worse the condition of the immune system and hence the severity of the illness. Viral load is the measurement of HIV-RNA blood levels and denotes the level of viral activity within the blood stream. Hence, increases in viral load correspond to a worsening of health, which is the opposite trend to the CD4 cell count. The monitoring of these two markers, with respect to (3) above, can provide information about whether an individual is a slow, medium or fast progressor to AIDS (CDC 1997[a]). Both markers have independent predictive value, yet CD4 seems to be the stronger individual predictor (HIV Paediatric Prognostic Markers Collaborative Study Group 2003). In 2004, The PLATO Collaboration published results, based on 2488 people with three-class virological failure, which strongly indicate that the current CD4 cell count, but not the current viral load, determines the short term risk of death in this setting. However, the viral load retains some independent prognostic significance in prediction of risk of new AIDS or death. Viral load appeared to be a major determinant of the CD4 cell count slope. Van Sighem *et al.* (2003) discovered that a high baseline CD4+ T cell count; absence of CDC category-C event before the start of HAART; and no or limited prior treatment with antiretroviral drugs, were all clinical markers associated with higher survival probability and a slower progression to AIDS. In accordance with this, Deeks (2003) found that low pre-treatment counts of CD4-positive T cells and high pre-treatment viral loads are associated with a greater risk of virological failure. The Antiretroviral Therapy (ART) Cohort Collaboration (2003) examined 9323 patients, who started HAART, survived and were followed up for longer than 6 months. Initial immunological and virological response, as reflected by CD4 cell count and viral load, were, again, found to be the two most important factors for prediction of progression to AIDS or death. They discovered that patients whose 6 month CD4 cell count was less than 25 cells/μL had the worst prognosis. Age 50+; transmission through IDU; and an AIDS diagnosis before or within 6 months of starting HAART were also found to be predictive.

Other studies on markers and their ability to predict the progression to AIDS or death show that sex or ethnicity do not have an affect on disease progression, despite reports that average viral load levels may be lower in girls than in boys (The HIV Paediatric

Prognostic Markers Collaborative Study Group 2003); age and IVDU are significant predictors for progression to death but not for development of AIDS (Van Sighem *et al.* 2003); and maternal HIV disease and death are very strong predictors of child mortality (Dabis 2003).

More recently, markers have proved to be of great importance in monitoring the effect of therapy. Within both clinical trials and the general population, frequent measurements of CD4+ cells and viral load are in use so that the effect of treatment on HIV/AIDS can be supervised. This is of particular significance if HIV should become resistant to the current treatments available as measurements in CD4 count and viral load would indicate this.

1.1.4 Surveillance of HIV in the UK

In 1950, the use of the term surveillance, which was previously limited to following persons who had been in contact with patients in order to isolate them as soon as early symptoms were recognised, changed from a person-oriented to a population-oriented instrument and, consequently, achieved a more quantitative basis (Houweling 1997). In 1963, disease surveillance was defined as 'the continued watchfulness over the distribution and trends of incidence through the systematic collection, consolidation and evaluation of morbidity and mortality reports and other relevant data' and the regular dissemination to 'all who need to know' (Langmuir 1963). Surveillance provides a stimulus to keep prevention and control activities moving rapidly and in the right direction, guiding the response to individual cases as well as public policy (Berkelman *et al.* 1997), however, in Langmuir's definition programmes for prevention and control were not yet considered a fundamental part of the surveillance system. It has only been over the last 50 years that the concept, methods and applications of disease surveillance have developed in this way (Thacker & Berkelman 1988). Recent practiced definitions include WHO's description of surveillance at the 21st World Health Assembly (1968), Last (1983) and Klaucke *et al.* (1988), the latter of which defined epidemiological surveillance as 'the ongoing and systematic collection, analysis and interpretation of health data in the process of describing and monitoring a health event. This information is used for planning, implementing and evaluating public health interventions and

programmes. Surveillance data are used both to determine the need for public health action and to assess the effectiveness of programs'. A thorough summary of the modern concept of public health surveillance is given by Berkelman *et al.* (1997). Despite the vast improvements in surveillance, over the past few years especially, there is still plenty of room for further development and advancement in the rate of diagnoses of HIV infection (DH 2002).

1.2 Transmission of HIV

In 1981, it was presumed that homosexuals were the only risk group for AIDS, due to the fact that the first AIDS cases reported were in gay men (CDC 1981[a], 1981[b]). However, soon after, in 1982/1983, other risk groups were acknowledged, including heterosexuals, haemophiliacs and mother-to-child transmission exposure categories (Brookmeyer & Gail 1994). Tavanyar (1992) states that HIV is detectable in the blood, breast milk, urine, faeces, semen, saliva, vaginal secretions, rectal secretions and the fluid that surrounds the brain. However, when determining the risk of transmission, the amount of virus that an HIV negative person is exposed to is a crucial factor. Therefore, HIV transmission via blood, semen, vaginal secretions and breast milk are the only realistic possibilities. Today, the European Non-Aggregate AIDS Data Set (ENAADS), which is the principle dataset used throughout this thesis, classifies reported AIDS cases into a number of different exposure categories, the main four of which are detailed in the following sections of this chapter (they are, homosexual, heterosexual, IVDU's and vertical transmission). The 8 distinct classifications defined by ENAADS are as follows:

- Homo/bisexual male
- Injecting drug user (IVDU)
- Homosexual/bisexual male & IVDU
- Haemophiliac/coagulation disorder
- Transfusion recipient
- Heterosexual contact
- Mother-to-child

- Nosocomial infection[1]
- Other/undetermined[2]

[[1] including patients infected in health care setting]

[[2] including cases of occupational exposure such as health care workers]

1.2.1 Homosexual Transmission (MSM)

In the UK, United States and Western Europe, male homosexuals have contributed the largest proportion of the cumulative reported cases of AIDS, although this is now falling as the epidemic in other groups begins to accelerate. Homosexual transmission has always been the main mode of spread of HIV/AIDS in the UK due to the increased risk of contraction during gay sexual activities and the average sizeable number of sexual partners. One particular study showed that HIV negative gay men had an average of 25 partners per year whereas HIV positive homosexuals had an average of 60; some homosexual men were reported to have had several hundred partners in their lifetime (McKie 1986). Today, there is a continuing high rate of transmission among homosexual and bisexual men (DH 2002). Approximately 15,100 men who have sex with men (MSM) were living with diagnosed HIV at the end of 2001 in the UK and an estimated 4200 remain undiagnosed, CDSC (2002). According to this same report (CDSC 2002: "HIV and AIDS in the UK in 2001"), 57% of MSM live in London. They remain the group at greatest risk in the UK with 1415 new diagnoses reported for 2001 by the end of June 2002. However, while prevalence of the virus is increasing, the proportion of MSM infected has fallen from 52% in 2000 to 50% in 2001. This does not mean that fewer homo/bisexual men are becoming infected year on year. In fact, in 2004, Murphy *et al.* collected specimens from 8,908 homo/bisexual men attending GUM clinics in England, Wales and Northern Ireland. 1,816 were HIV-1 positive, of which 332 were from individuals whose HIV infection had not previously been identified. The serological testing algorithm for recent HIV seroconversion (STARHS) was performed on 331 of the 332 specimens. STARHS is a dual testing algorithm in which specimens that are confirmed HIV-positive following detection by a sensitive screening assay are tested on

an assay which has been changed to make it less sensitive. Specimens that are unreactive on this less sensitive assay are deemed to be new infections while specimens that are reactive in both assays are deemed to be infections that have been established for some time. Subsequently, STARHS recognises primary infection if it arises within the region of 6 months before an HIV positive specimen is collected (Janssen *et al.* 1998). Of the 331 specimens whom STARHS was performed on, 82 were identified as recent infections, giving a predicted annual incidence of 3.5% (earlier findings, commencing in 1995, indicated a HIV incidence of approximately 2.5% per year). The data suggest an upward trend in the rate of HIV transmission and provide an early warning of a potentially significant rise in HIV incidence. This increasing incidence implies a failure in current prevention methods. Goldberg (2002) estimated HIV prevalence and found that a mean annual growth of 1020 cases in men who have sex with men (MSM) are anticipated over the years 2002-2005 (63% expected to be living in London).

1.2.2 Heterosexual Transmission

Since heterosexuals have fewer sexual partners than homosexual men (Johnson *et al.* 1992 and Williams & Anderson 1994), the AIDS epidemic within the heterosexual risk group has proven not to be as severe. Although the heterosexual community in Europe, for the most part, has not seen a serious epidemic develop, a subset of that population – migrants – is facing its own more circumscribed threat. Two-thirds of all heterosexually acquired HIV infections during 1997-2000 in the UK were in migrants from high-prevalence countries and in 2002 three-quarters of heterosexually acquired HIV infections diagnosed in the UK are thought to have been acquired in Africa (EDITORIAL 2004). There is an increasing impact of the global situation on heterosexuals in the UK (DH 2002). Most of the heterosexually infected probably acquired their infection from outside the UK (the majority of which from sub-Saharan Africa).

The increasing number of reported heterosexual infections in the UK provides cause for concern with an over three-fold increase in the number of heterosexual cases diagnosed each year since 1999 (Carter 2003). In contrast to the proportion of individuals infected through homosexual sex decreasing, the proportion that contracts the virus through heterosexual sex has risen from 31% in 2000 to 36 % in 2001. In fact, annual numbers of

new diagnoses of heterosexually acquired infection have outnumbered those in MSM each year since 1999 (CDSC 2002). In 2002, 3305 new cases of heterosexual transmission of HIV were recorded. That is almost twice the1691 new diagnoses involving gay men made in the same year. Also in 2002, HIV prevalence was estimated by Goldberg who found that a mean annual 1150 cases in non-injecting heterosexuals are anticipated over the years 2002-2005 (63% expected to be living in London). It may also be worth noting that 66% of all instances of heterosexual transmission in 2002 were women (Carter 2003). This could be due to the fact that the risk of transmitting HIV during heterosexual exposure is higher for male-to-female than for female-to-male. In fact, studies by Padian *et al.* (1991); European Study Group (1992) and Haverkos & Battjes (1992) estimate the male-to-female infection risk to be at least twice as high as in the female-to-male case. Additionally of interest in the transmission of HIV heterosexually are the findings by Peters *et al.* (2004) that suggest that HLA antigens in seminal fluid and vaginal secretions might induce mucosal alloimmunisation (an immune system response) in women, and to a lesser extent in men, during unprotected sex. In HIV-1 infection, the viral coat contains HLA class I and II proteins. Ejaculates contain epithelial cells, which express HLA antigens, and cell-free HLA antigens. Stimulation of T cell proliferation (MLR – mixed leucocyte reaction) was greatly increased in peripheral blood mononuclear cells (PBMC) for women practising unprotected intercourse in response to their partners' PBMC compared to unrelated control cells. The MLR of male cells stimulated with cells from the female partners also showed a similar increase compared with controls but only with the highest percentage of stimulating cells. The evidence that mucosal alloimmunisation occurs naturally during sexual intercourse indicates a physiological function of enhancing genital immunity to sexually transmitted pathogens and supports the concept of alloimmunisation as a strategy for vaccination against HIV-1 infection.

1.2.3 IVDU's

Intravenous drug users (IVDU's) are the third largest risk group in the United Kingdom, after MSM and heterosexuals. When an HIV-positive individual injects drugs the virus enters the needle and syringe. After injecting, IVDU's may draw blood back into the

needle and syringe from the vein. This mixes with any of the remaining drug and then the IVDU injects again. This technique increases the risk of infection. If an HIV positive IVDU then shares a needle and syringe with an HIV negative IVDU, the virus is directly entered into the blood stream. Friedland (1989) identifies the following significant risk factors for IVDU's:

1. Frequency of which IVDU's inject drugs,
2. Frequency of needle sharing,
3. Proportion sharing needles (works) with more than two other IVDU's.

Experimentally, a single flush of a syringe or needle with water leads to an approximate 70% decrease in the proportion that contain sufficient HIV-1 to replicate in culture, while two flushes decrease that proportion by 95%. Furthermore, heating in water at 60-65°C will inactivate HIV-1 within seconds (Schmid *et al.* 2004). Despite the high risks involved, the numbers of new HIV diagnoses in IDU's remain low (CDSC 2002). However, an increase in hepatitis C transmission in IDU's (DH 2002) could suggest that the epidemic amongst this population group is set to expand.

It has been argued that unsafe injections are a major if not the main mode of HIV-1 transmission in sub-Saharan Africa. However, a report by Schmid *et al.* (2004) indicates that there is no compelling evidence as such. In the 1980's, WHO estimated that unsafe injections and the use of other inadequately sterilised skin-piercing instruments caused 1.6% of HIV-1 infections in Africa. More recent estimates have put the proportion at 2.5% of all infections in sub-Saharan Africa. Even with these modest estimates, there are worrying facts about this mode of transmission that can not be ignored. For instance, the numbers of injections administered for health reasons has been estimated at an average of 3.4 per person per year in low-income and middle-income countries. Of these, about 39% are given with unsafe injection equipment. Injections given with re-used equipment are more common in the Middle East and South Asia than in sub-Saharan Africa where 2.1 injections are estimated per person per year, of which 18% are given with reused equipment resulting in a mean of 0.4 potentially unsafe injections per person per year (Schmid *et al.* 2004).

1.2.4 Vertical Transmission

In the majority of vertical transmission cases, it is impossible to determine the route of infection from mother-to-baby. Perhaps the most common route of HIV infection takes place between mother and baby during pregnancy, when HIV can cross through the placenta and into the foetus. Another route is during birth, when the baby is exposed to the mother's infected blood and vaginal secretions. Krivine *et al.* (1992) argue that transmission of HIV is most likely to occur this way, during delivery. Even if a child survives pregnancy and birth without infection, s/he can still contract HIV via the mother's breast milk. A study by Dunn *et al.* (1992) estimated that breastfeeding increases the rate of vertical transmission by 14%. As a consequence of this high probability, European and American HIV-positive mothers are advised not to breast-feed (CDC 1998). However, where infectious diseases and malnutrition are the main cause of infant deaths, World Health Organisation (WHO) advise breast-feeding to be the best option, even for those women who are HIV-positive (Panos Institute 1992). The European Collaborative Study, in 1991, produced estimates of overall probability of transmission of HIV from mother-to-child by all routes discussed above. They ranged from 11.4% to 16% dependant on the adjustments for babies lost to follow up. Up to the age of 18 months a baby's blood contains identical antibodies to the mother; consequently, all babies born to HIV-positive mothers are seropositive initially. If a child is still seropositive at 18 months, if the virus was cultured, or if the HIV antigen was detected in two different samples, then that child is classified HIV-positive (European Collaborative Study 1991). By this time the child may already have been diagnosed with AIDS or died from HIV-related conditions. The natural history of HIV disease in children is described as bimodal; many children progress rapidly to AIDS or death during the first year of life, while others have a better prognosis, some now surviving into young adulthood (Abrams & Kuhn 2003). 20-25% of children infected with HIV-1 progress rapidly to AIDS or die during infancy, with slower disease progression in older children (HIV Paediatric Prognostic Markers Collaborative Study Group 2003).

Improvements of antenatal diagnoses of HIV have continued (CDSC 2002). Maybe as a consequence to this, the prevalence of HIV in pregnant women is increasing. More than 3 million children are estimated to be living with HIV infection, and hundreds of

thousands continue to become infected annually. In 2002, there were 800,000 newly infected children worldwide, most of them in sub-Saharan Africa. Fortunately, due to antiretroviral therapy during pregnancy, few babies are now born with HIV infection in areas where access to these therapies is widespread (Abrams & Kuhn 2003). Even in resource poor settings, such as Africa, where mortality of those infected generally exceeds 40-50% in the first two years of life, prevention of mother-to-child transmission of HIV by antiretroviral is, vitally, now a feasible public health approach (Dabis 2003).

1.3 HIV as a global epidemic

Though we tend to call it 'the global AIDS epidemic', what we are facing is not one epidemic, but many. The introductory Editorial to the Lancet, volume 364, states that 'Each of these epidemics has a different dynamic and course, each varying from city to city, village to village, community to community' (EDITORIAL 2004). How each of these epidemics, around the world, will develop and evolve depends on many variables, some known and some not yet discovered. Biology may play a part, with certain strains and sub-types spreading more easily than others; host genetics may make some populations more or less susceptible; and culture, economics and politics certainly shape each epidemic's course, but perhaps the most important factor is the willingness of political leaders to acknowledge the crisis and implement needed interventions swiftly even in the face of political opposition.

1.3.1 Africa

The overwhelming burden of HIV/AIDS is still concentrated in this region, which accounts for only 3% of the global population yet some 50% of global HIV cases (Halperin & Epstein 2004); Africa is the hardest hit of the continents with some countries in the region witnessing the epidemic continuing to spread and others facing an increasing danger of, even greater, explosive growth. The virus now runs unbridled through the heterosexual populations of many sub-Saharan nations, while leaving more North African countries relatively untouched (UNAIDS 2002).

Throughout the entire world, the HIV/AIDS epidemic is most relentless in Southern Africa; with HIV prevalence growing higher than deemed possible, exceeding 30% in some South African countries (UNAIDS 2002). In 2002, in sub-Saharan Africa, there were another 3.5 million new HIV infections diagnosed and an estimated 2.4 million Africans lost their lives to AIDS (UNAIDS 2002). In contrast, Uganda, in the east of the continent, has managed to maintain diminishing trends in prevalence rates. It is the first African country to have restrained a major HIV/AIDS epidemic, demonstrating that it is possible to reduce the epidemic using human intervention.

Epidemiological data suggests that sexual contact continues to be by far the main mode of transmission in sub-Saharan Africa and inadequate care and attention addresses specific needs of African HIV infected women of childbearing age who are informed of their serostatus (Schmid *et al.* 2004). Of growing interest to epidemiologists is the contemplation that, in Africa, men and women often have more than one – classically two or three – concurrent relationships that can coincide for months or years. This trend differs from that of the serial monogamy more frequent in the west, or the one-off casual and commercial sexual encounters that occur everywhere (Halperin & Epstein 2004). Morris and Kretzschmar (1997) used mathematical modelling to compare the growth of HIV in two populations, one in which serial monogamy was the standard and one in which long-term concurrency was customary. Although the total number of sexual interactions was alike in both populations, HIV transmission was much quicker with long-term concurrency and the resulting epidemic was 10 times larger.

Now that treatments are becoming available in low-income and middle-income countries, Africa will undoubtedly be hugely relieved. At the end of 2001, fewer than 30,000 people were predicted to have been benefiting from antiretroviral drugs, a minute fraction of the millions of Africans who are in desperate need of them. The Barcelona Report (2002), produced by UNAIDS, gives a very informative look at the state of the HIV/AIDS epidemic in Africa and the political commitment present there to turn the tide against AIDS.

1.3.2 Asia

In contrast to Africa, HIV has been present in Asia for nearly two decades, yet widespread coverage has yet to occur (Halperin & Epstein 2004). Today, 20% of new annual infections occur in this region. The Barcelona Report on the Global HIV/AIDS Epidemic states that, in 2002, nearly 1 million people became infected with HIV and 490,000 people are predicted to have died from AIDS. 7.2 million individuals are presently living with HIV and only 30,000 of those people are on antiretroviral treatment. China is home to a fifth of the world's population; the growth of the epidemic is largely attributable to the developing epidemic in China alone. 1 million people are now living with HIV in China and official estimates propose a multiple upsurge in this figure in the near future.

1.3.3 High-income countries

Countries such as Australia, Canada and the USA have witnessed HIV/AIDS-related deaths significantly drop since 1995/1996, when antiretroviral therapy was first introduced. However, the last couple of years have seen this trend level off, with an estimated 15,000 people dying from AIDS in America last year. The response, in terms of prevention, to treatments becoming widely available has resulted in an increase in high-risk behaviour and, accordingly, some countries saw a rise in the rate of new infections. There is evidence that the epidemic is spreading into more deprived and poorer communities within some of these high-income countries. Consequently, there is a strong need to fight complacency and to reinvent prevention programmes. The main mode of transmission in the USA is that of sex between males; it accounted for the largest proportion (42%) of new infections in 2000. AIDS incidence rose during the 1980's, declined from the mid 1990's through 2001 and increased 2% in 2002 compared with 2001. The number of deaths among persons with AIDS continued to drop (14% from 1998-2002) and AIDS prevalence sustained its growth (CDC 2002).

1.3.4 Europe

Although more than 500,000 people are infected in Europe, with 30-40,000 new cases each year, the explosive growth of the epidemic, that was once feared, has not occurred. Instead, the disease has become established in high-risk populations. Even within these groups there are variations from country to country and even city to city (EDITORIAL 2004). EuroHIV's 2003 report on HIV/AIDS Surveillance in Europe is extremely valuable when summarising the progression of the epidemic in Europe to date and has been used as the main source of reference for the following synopsis of the epidemic within Europe, along with Hamers & Downs review published in the Lancet in 2004.

Central Europe

A cumulative total of 20,300 HIV infections were reported by the end of June 2003. Of these, 8,191 (40%) were in Poland and 5,580 (27%) were in Romania. Newly diagnosed HIV infection and AIDS remain low and moderately unchanged in recent years. In 2002, HIV reporting rates were highest in: Poland (15.0 per million population); Romania (15.0); and Slovenia (11.1). All other countries reported no more than 10 new HIV diagnoses per million population. HIV prevalence levels are minimal (<0.1% in most years) and show no distinct pattern over time. However, there were prevalence levels of over 2 per 100 000 blood donations reported in all or most of the last 5 years from: Albania (between 5 and 7 per 100 000); Bulgaria (2-5); Poland (2-3 overall, but <1 among repeat donors); Romania (5-10); Serbia and Montenegro (2-9); and Turkey (3-5). Elsewhere, levels remain small, generally <1 per 100 000.

Eastern Europe

A cumulative total of 324,913 HIV infections had been reported by mid 2003 by the 15 countries of the former Soviet Union. After increasing sharply for some years, the number of new HIV diagnoses fell for the first time in 2002 – from 100,580 (346.7 per million) in 2001 to 64,352 (222.5 per million) in 2002 (-36%). This decline appears to be continuing in 2003 due to a steep drop in cases reported among IDU (-53%). However, heterosexual contact (HC) cases continued to increase steadily (+31%).

Data for the East follow similar patterns in several countries (with some differences in timing). However, the data are disproportionately influenced by the Russian Federation (which accounts for 76% of all HIV infections ever reported in the East) where the

epidemic is extremely heterogeneous (60% of cumulative HIV infections reported by only 10 of its 87 regions).

Western Europe

At the start of the 21st century, HIV/AIDS maintains its status as a major public health problem in Western Europe. More than half a million people are living with an HIV infection that remains incurable and necessitates costly permanent treatment. UNAIDS and WHO published country-specific estimates for 2001, and estimated that 520,000 - 680,000 individuals were living with HIV in Western Europe by the end of 2003.

The HIV/AIDS epidemic in the UK is akin to that of the rest of N. Europe, while SW. Europe has experienced a much larger epidemic, especially amongst IDU's (CDSC 2002). In 2001, there was an additional increase in the total number of HIV infections in adults in the UK (DH 2002). The best estimate, at November 2002, of the total number of adults living with HIV in the UK at the end of 2001, undiagnosed or diagnosed, is 41,200 (CDSC 2002). By 2003, almost 50,000 people had been diagnosed with HIV in the UK (Carter 2003); an increase of 20% on the previous year. McHenry *et al.* (2002), Communicable Disease and Public Health, used data from 1996-2000 to extrapolate trends in prevalent numbers of diagnosed HIV infections for the years 2001-2005 using the method of back-calculation; the prevalence in 1996 was 14,205, this increased by 62% by the end of 2000 and 139% by the end of 2005. Possible drivers for this increase are a sustained rise in diagnosis and a continuing number of new diagnoses. Sexually Transmitted Infections (STI) are, in general, at their highest levels since records began. The country has the worst sexual health record in Western Europe.

It has been approximated that HIV incidence within Western Europe reached its peak in 1983, or thereabouts, among homosexual men, and peaked in 1987-88 among IDU's, with 120,000 homo/bisexual men and 144,000 IDU's having contracted HIV by 1985 and 1989, respectively. Heterosexually transmitted infections rose gradually during the late 1980's and early 1990's. The scale of newly diagnosed HIV infections (among countries with data available for a minimum of the last 6 yrs) has increased by 46%, from 8,021 in 1997 to 11,683 in 2002. The number of new HIV diagnoses among IDU's fell steadily (-9% between 1997 and 2002); that among persons infected through heterosexual contact (HC) grew noticeably (+116% over the same period); and that among homo/bisexual men

(HBM) rose in 2002 (+22% compared with 2001) after gradually decreasing between 1997 and 2001. The increase in HC cases is mostly a consequence of a rise in cases diagnosed originating from a country with a generalised HIV epidemic.

Recent movements within the epidemic of newly diagnosed HIV infections in Western Europe are propelled by the UK, which accounted for 30% of the population and about 40% of HIV diagnoses reported during 1997-2002, in a study by Hamers & Downs in 2004. Between 1999 and 2002, HIV incidence rose by about 20% each year with about a third of HIV-positive people being unaware of their serostatus (Carter 2003). Within the UK, there has been a steady increase in diagnoses of persons infected with HIV (from 147 in 1998 to 275 in 2002), the majority of these individuals most likely contracting HIV infection through partners infected from outside Europe. Note that 70% of HIV-positive immigrants were unaware of their serostatus on arrival into the UK, dispelling the myth that so-called treatment tourism is a problem (Power 2004).

Throughout Western Europe, following the introduction and widespread use of HAART, AIDS incidence and AIDS deaths declined sharply in the mid 1990's; thus, the number of people living with AIDS increased. AIDS incidence in Western Europe increased again in 2002 by 3% (compared with 2001). The number of deaths among persons with AIDS has continued to decline (-8% between 2001 and 2002), a cumulative total of 147,065 by mid 2003 had been reported (152,000, according to Hamers & Downs 2004). This implies that the number of persons living with AIDS has continued to increase and was estimated at approximately 108,000 by mid 2003 (107,000, according to Hamers & Downs 2004). Also, a proportion of people with HIV today are unaware of their infection, hence have no opportunity to benefit from antiretroviral treatment. For those who are aware of their serostatus, since access to health care is almost universal in Western Europe they are eligible for free treatment. In the UK and in Spain more than three-quarters of the patients seen for care in 2002, and eligible for antiretroviral treatment, were receiving therapy.

1.4 Treatments for HIV and AIDS

1.4.1 Mono-therapy

In section 1.1.2, details of how the HIV virus attacks and weakens the immune system were provided. That is, the insertion of HIV-RNA into the host cell, using an enzyme known as reverse transcriptase, converting the RNA into DNA and integrating the viral DNA with the host cells' DNA, ensuring that the host has the genetic material of HIV for their lifetime. There are currently more than 20 antiretroviral drugs (so called because HIV is a retrovirus) that have been approved for treating HIV infection (AVERT 2005[c]). These antiretroviral drugs work by interfering with the virus' ability to use enzymes in order to survive. They fall into two main types:

- Reverse transcriptase inhibitors (RT inhibitors) which interfere with an enzyme called reverse transcriptase (RT) that HIV relies on in order to reproduce.
- Protease inhibitors which interfere with the protease enzyme that HIV uses to produce infectious viral particles.

Treating an individual with just one of these drugs is called mono-therapy. This form of treatment was first introduced following the development of the premier anti-HIV drug zidovudine (AZT) in 1987. The early zidovudine therapy, despite initial optimism, was eventually shown not to be effective in delaying progression to AIDS. Primary prophylaxis for PCP, however, met with substantial achievement in reducing the extent of this particular condition as an AIDS-defining illness. Mono-therapy regimens result in significantly greater CD4 cell recovery compared with no therapy and suggest that continuous triple or quadruple therapy in acute HIV infection gives a high probability of short- to medium- term viral suppression, although the comparative potency of various therapies has not yet been clearly defined (Smith *et al.* 2004). In support of this, the Delta trial, Delta Co-ordinating Committee (1996), discovered that the two drugs zidovudine (AZT) and didanosine (ddI), in combination, are more effective than treating an individual with only the one drug zidovudine. Also, HIV can become resistant to any

one drug, thus, treatment regimens now involve a combination of 2 or 3 different drugs, with an increasing number of individuals receiving quadruple therapy (Beck *et al.* 1999).

1.4.2 The introduction of dual-therapy and HAART

HAART is a combination (cocktail) of potent and effective antiretroviral drugs such as protease inhibitors and nucleoside-analogue reverse transcriptase inhibitors (NRTI's). Since mid-1996, with the introduction of triple-combination antiretroviral therapy, a trio of retrovirals which the patient is required to take on a regular basis and indefinitely, there has been a well-documented reduction in mortality and risk of AIDS-defining illnesses (Van Sighem *et al.* 2003). Prior to the introduction of these new combination therapies, nearly 50% of young men who acquired HIV died from their infection within 12 years (NIH 2002[a]). Provided the HAART regime is faithfully adhered to, it seems to virtually clear virions (infectious virus particles) from plasma; indeed, the reduction occurs within the two weeks following the initiation of therapy. The short-term benefits of HAART are that both life expectancy and quality of life for HIV-infected patients improve. Smith *et al.* (2004) demonstrate that, if not an absolute explanation for the speedy resolution of KS, immune responses to the initiation of HAART could contribute to its reduced incidence. In fact, progression to an AIDS-defining illness, in those who can tolerate treatment and do not develop drug resistance, has now been effectively stopped as long as HIV is diagnosed and treated properly early enough in the course of clinical progression (McHenry *et al.* 2002). Another benefit of HAART is brought to our attention by Dabis (2003), who showed that a single dose nevirapine regimen can reduce by 40% the natural transmission rate from mother-to-child. In addition, the most potent short-course combined regimens can achieve residual peripartum transmission rates (rates of transmission from mother-to-child) of around 5% in breastfeeding populations (Dabis 2003).

The death rate across Europe dropped rapidly after the introduction of HAART; within 2 years of the widespread availability of HAART the numbers of deaths were less than a fifth of those before HAART (Mocroft *et al.* 2003). The HIV Paediatric Prognostic Markers Collaborative Study Group (2003) confirm that the rates of both morbidity and mortality have declined over calendar time – especially since 1996, coincident with the

widespread use of dual, then triple, antiretroviral therapy. Part of the decline might be attributable to changes in the infected and treated population during the years 1996-2000 and not just the initial impact of cocktail therapies. Over these years the population shifted towards one in a less advanced stage of HIV-1 infection at the start of HAART with a growing fraction of therapy-naïve patients (Van Sighem *et al.* 2003).

The optimum time to initiate HAART in asymptomatic patients is an issue that is hard to resolve; universal treatment seems compelling but would expose many to a premature risk of toxic effects and resistance development. For children, early treatment may delay, rather than overcome, the factors that influence rapid progression of disease. Although higher CD4 percentage and lower viral load in older children helps to predict when to safely defer therapy, markers cannot be used to identify younger children at low risk for progression (Abrams & Kuhn 2003). A study by Chang-Heok Soh *et al.* (2003) showed that CD4 improved substantially in children and adolescents who started protease inhibitor-based (PI-based) combination therapy for HIV-1 infection. There was an overall improvement in median CD4% between 1996 (first prescribed) and 2000 of 22% to 28%, with younger children showing a greater improvement than older children. However, for the majority of children, who were substantially immunosuppressed before they started PI-based therapy, it was not adequate to recover normal CD4%. In this article by Chang-Heok Soh *et al.* it is suggested that if normal immune function is the goal of therapy then current guidelines, which advocate delaying the start of therapy until lower CD4% values are reached, may not achieve this ultimate aim. However, when considering toxic events and treatment failure due to viral resistance, time for which effective treatments are available for any individual patient is limited. Current guidelines are now suggesting initiating HAART at later stages of infection, which should allow physicians more time to assess the potential barriers to adherence before prescribing HAART (Kleeberger *et al.* 2004).

1.4.3 Adherence and Resistance Problems

Drug toxicity, medication adherence and resistance emergence are the main obstacles to long-term therapy for HIV infection (Moyle & Boffito 2004). High levels of treatment failure have been reported, which have been associated with serious adverse events,

emergence of drug resistance, difficulties in maintenance of long-term adherence and the few types of drugs available (Mocroft *et al.* 2003).

Treatment Uptake and Adherence

The lack of availability of antiretroviral drugs is obviously damaging the potential for therapy in resource poor countries and, consequently, treatment uptake is poor. As an example of this, Dabis (2003) reports that only about 5% of all African HIV-infected pregnant women are receiving the treatment they need. There is an urgent requirement to develop simple and sustainable strategies for initiation and delivery of HIV care and therapy to large numbers of patients. In high-income countries, where the availability of anti-HIV drugs is widespread, those persons who are in touch with the resources and opportunities they need to initiate treatment might choose not to participate in therapy for a number of reasons, including not wanting to suffer the adverse effects of antiretroviral drugs and not being able to adhere to the burden of strict drug regimens. Adherence to drug regimes is not only difficult in terms of complicated rules and procedures, it is also incredibly time consuming. The proportion of person-time on HAART increased from 22% in 1997 to 57% in 2001 and is even greater than that today (CASCADE Collaboration 2003). Also, a large fraction of HIV-positive people are not on therapy when they should be due to lack of awareness of their serostatus. Even for those individuals who are on anti-HIV therapy, there are many factors associated with antiretroviral drugs, including complicated therapeutic regimens; depression; alcohol and drug use; and changes in daily routines, that may cause low adherence to treatment which then compromises the effectiveness of HAART (Kleeberger *et al.* 2004).

A significant problem associated with HAART, and the adherence to HAART, is the adverse effects of drugs which may result in increasing morbidity and a reduced quality of life. Virtually all of the current anti-HIV (antiretroviral) drugs available in the United Kingdom can produce side effects, some of which are severe. Adverse effects of antiretroviral agents may be considered early (occurring within 3-6 months of therapy) or late (occurring in individuals who are established on and tolerating a drug for some time). Most early toxicities, such as nausea and diarrhoea, rash and sleep disturbances, are predictable, transient and of mild to moderate intensity. These adverse events are generally manageable with advice and palliative drugs, only occasionally do they require

treatment modification. Late potential side-effects of HAART, such as hepatotoxicity, impaired glucose metabolism and diabetes mellitus, hyperlactatemia, hyperlipidemia and fat redistribution (Palacio *et al.* 2004), anaemia, peripheral neuropathy, pancreatitis, lipoatrophy, and lactic acidosis, whilst occurring in only a few individuals, are less amenable to management with palliative drugs and generally lead to therapy modifications or treatment interruption. Additionally, some of these late side-effects are potentially life-threatening and can lead to permanent disability or stigmatising morphological changes (Moyle & Boffito 2004). Adverse effects such as these may lead to suboptimal adherence to antiretroviral treatment, where adherence to these antiretroviral drugs is crucial to suppress virus levels (Kumarasamy 2004). Virological failure is generally defined as concentrations of HIV-1 RNA in plasma continuously above the level of detection (50-200 copies per mL) after at least 16-24 weeks of HAART. Failure in this way is common in clinical practice, with rates of 30-70% reported in many clinic-based cohorts, due to viral replication dynamics in the presence of incompletely suppressive antiretroviral therapy, that is: high viral replication rates; high mutability; and high plasticity (Deeks 2003). The sequential use of effective monotherapy is perhaps the most common cause of virological failure during the early HAART era. One study concluded that virological failure was common in patients with less than 80% adherence and rare in those with greater than 95% adherence. These findings are perturbing as the mean proportion is about 70% adherence. Virological failure rates have lowered recently possibly due to: the availability of more effective regimens; greater clinical expertise; and a better grasp among patients and clinicians on the value of adherence (Deeks 2003).

Adherence to antiretroviral drugs is also vitally important with respect to preventing drug resistance (Kumarasamy 2004); less than optimum drug exposure allows the virus to replicate in the presence of a selective pressure, thus leading to the emergence of drug-resistant variants (Deeks 2003). No recent outpatient visit; younger age; depression; and lower educational levels are all independent determinants of decreasing adherence. Furthermore, previous non-adherence predicts non-adherence at the next visit. Besides education, providers should assess and treat depression to enhance continued adherence to optimise the effectiveness of HAART (Kleeberger *et al.* 2004). Abdool Karim *et al.*

(2004) discuss the integration of HIV and TB care as a proposed strategy to improve the adherence to anti-HIV drugs. The simplest and most successful way, however, to ensure complete adherence and, consequently, minimise drug resistance and maximise therapy outcomes is through directly-observed HIV therapy (Kumarasamy 2004).

Drug Resistance

HAART is now widely used to treat HIV-1 infection. However, resistance to one or more of the drugs being used commonly arises during the course of treatment due to the selection of viral variants carrying mutations in key codons (where a codon is a sequence of nucleotides constituting genetic code) associated with reduced drug susceptibility (Cane *et al.* 2004). For an overview of some of the definitions and principles behind the biology of drug resistance see Deeks (2003) who discusses viral replication dynamics, viral fitness and viral latency. Barouch & Letvin (2004) report that viruses that carry mutations have increased replicative capacity and might, therefore, replace the original virus in the circulation. Two recent studies (Leslie *et al.* 2004 and Freidrich *et al.* 2004) address the issue of whether HIV with mutations in dominant cytotoxic T lymphocyte (CTL) epitopes (where an epitope is a site on the surface of an antigen molecule to which a single antibody molecule binds) is transmissible from one individual to another. Together, the data suggest that there is a fitness cost associated with maintaining the mutations, thus, the mutant virus reverts to wild-type sequences in recipients where there is an absence of immune selection pressure. By contrast, the mutant virus is maintained in donors as a result of ongoing selection pressure exerted by CTL specific for the wildtype epitopes. The lower fitness and infectivity of the drug-resistant variant compared with the wild-type variant, as well as lower viral loads in partially treated patients compared with untreated patients, may contribute to a lower than expected rate of transmission of drug-resistant HIV-1 (Deeks 2003).

HIV drug resistance is, however, increasing. The percentage of treatment-naïve patients infected with drug-resistant HIV rose from 10% in 1996 to 14% in 2001 (AIDS Weekly 2003). Among patients for whom drug therapy is not working, the percentage with resistance to any one drug has remained stable (at 70-80%) since 1996. The greatest concern is the number resistant to all three classes of drugs – increasing from 1% in 1996 to 14% in 2001 (AIDS Weekly 2003). Resistance testing of HIV-1 is now recommended

following treatment failure and also in some circumstances at primary infection. For more information on resistance testing see Cane *et al.* (2004). In patients for whom HIV replication is not suppressed after exposure to several drug classes, background treatment strategies remain unclear. Deeks (2003) suggests the following treatment strategies:

- First HAART failure – All patients probably have at least two opportunities to achieve complete or near-complete viral suppression.
- Multiple HAART failure – More and more drugs are needed to suppress HIV-1 in such patients, leading to more complex regimens, inconvenient dosing schedules, greater toxicity, and higher costs. Broadly speaking, there are 3 ways to treat a motivated patient with multi-drug resistant HIV-1:
    1) Multi-drug salvage regimens with the aim of complete suppression.
    2) Partial viral suppression and 'when to switch'.
    3) Structured treatment interruptions.

Salvage therapy, or rescue therapy, (that is, any regimen designed to suppress drug-resistant HIV-1 in a patient who has previously been treated with at least one HAART regimen) commonly fails to suppress HIV-1 since patients who could not adhere to a simple initial regimen are unlikely to manage more complicated salvage regimens. Plus, given the added complexity of newly resistant HIV-1, the barriers to a successful virological response worsen with each new regimen.

Treatment interruption is a topic that is constantly debated and seems to hold no strict format. Abrams & Kuhn (2003) have shown that in adults the interruption of treatment started during primary infection gives promising results. However, in children this has not yet been proven to be the case. Continuous HAART is associated with slower progression to death and AIDS in comparison with interrupted HAART, however, occasional treatment interruptions shorter than 3 months do not increase the risk of death, in fact short-term disease progression does not change and may even improve slightly (Van Sighem *et al.* 2003). Viral latency argues against long-term treatment interruption as a means of restoring drug-sensitive virus (Deeks 2003).

In patients for whom viral-load suppression to below the level of detection is not possible, achievement and upkeep of a CD4 count above 200 per μL becomes the primary aim. Long-term virological suppression is unlikely to be viable for many patients with three-class drug failure (as supported by recent findings from the T-20 vs Optimized Regimen Only Trials by Lalezari *et al.* (2003) & Lazzerin *et al.* (2003)), therefore, in such patients, the goal of therapy needs to be adapted to preservation and, if possible, increasing the CD4-cell count with the long-term objective of maintaining low mortality. The problems of serious adverse events, adherence to complicated regimens and absence of virological effect have not yet influenced mortality and morbidity in the population. The long-term effects of HAART are still unknown – predictions cannot be validated with currently available data and might be too optimistic considering the risk of toxicities and resistance (Van Sighem *et al.* 2003).

1.4.4 Up and Coming Treatment Therapies

There are approximately two dozen new anti-HIV drugs presently in development, as listed by the pharmaceutical research and manufacturer's association. They include:

- new protease inhibitors
- more potent and less toxic RT inhibitors
- new categories of drugs:
    - fusion inhibitors – interfere with HIV's ability to enter a cell
    - integrase inhibitors – impede HIV's ability to insert its genes into a cells DNA

Also, scientists are learning more about immune modulators and therapeutic vaccines. On May 17th 2002, the National Institute of Allergy and Infectious Diseases (NIAID) announced the new contract award in its HIV Vaccine Design and Development Teams (HVDDT). Over the next five years $22.8 Million will be provided for Wyeth Vaccines to expand research on a vaccine candidate that has been proven to prevent an AIDS like

disease in monkeys. Researchers are hopeful that this vaccine will stimulate both parts of the immune system, that is, stimulate both:

1) antibodies to neutralize any free-floating HIV
2) specialized immune cells to eliminate any cells that HIV still manages to infect

This particular vaccine candidate originated from the Yale University laboratory of NIAID grantee John K. Rose, PhD. Between 1997 and 2002, 6 potential vaccines have been tested around the world, and it is expected that, from 2002-2005, more than a dozen further potential vaccines will be ready for testing. NIAID Director, Anthony S. Fauci, M.D., believes that "HIV vaccine research is our best hope, along with other prevention efforts, to slow the spread of HIV... These trials will lead to a vaccine, perhaps not in a year or two, or even three years, but we will get there".

1.5 Strategies and Interventions to combat the HIV/AIDS epidemic

2001 was the 20 year anniversary of AIDS, and yet the epidemic is still in its early stages. There is proof that effective responses are possible, but only when full-scale action is taken. Unless this action is taken, the epidemic will continue to grow. Margaret I. Johnston, PhD, associate director for HIV/AIDS vaccines, NIAID, states that "HIV continues to spread unabated in many parts of the world... The public needs to understand that AIDS is not under control".

Viral load and CD4 monitoring combined with prompt ART when required should have been minimising the infectious hazard of diagnosed cases. However, the expected benefits from high coverage of combination ART in the diagnosed HIV infected population seem to have been negated by increasing high-risk sexual behaviour among some homo/bisexual men (Murphy *et al.* 2004). Effective interventions are needed to prevent acquisition of HIV infection in men who have sex with men. To date, no behavioural interventions specifically for this risk group have been implemented. The EXPLORE Study Team, in 2004, performed a randomised controlled study to investigate the effects of a behavioural intervention to reduce acquisition of HIV infection among

MSM. The overall estimate of a difference of 18.2% was uncovered, with more favourable estimates of effect in the first 12-18 months. This suggests that prevention of HIV infection among MSM, by a behavioural intervention, is a feasible option.

1.5.1 Prevention and Awareness

Among the young people of Britain, rising rates of STI's and increases in risk-taking behaviour continue to demonstrate the potential for HIV transmission and indicate that sexual health promotion for young people is, at present, not achieving desired results (Dougan *et al.* 2004). HIV prevention is built on behaviour changes, a response at the population level to the epidemic and to avoid risk; it can be supported and catalyzed but is not delivered as a traditional intervention. Other interventions, including voluntary counselling and testing services (VCT), care support networks, and even treatment, are greatly enhanced if HIV prevention creates the basic population response to be mobilized (Low-Beer 2004). HIV prevention can be highly successful; changing the course of an epidemic over a matter of years even in resource-poor settings. It has been shown that wide social communication leads to declines in casual sex of up to 65%. Uganda remains the best example of changes in population behaviours and communication, reducing HIV prevalence on a national level from 21.1% to 9.7% from 1991-98 and down further to 6.4% in 2001 (Low-Beer 2004). There have also been documented reductions in Thailand (by 55%, in casual and commercial sex, 1990-1993), Zambia (by 27% among male youth, 1996-99) and amongst the homosexual population in the USA. It is hoped that current initiatives to reduce STI's and promote safer sex may reverse HIV incidence. Unlinked Anonymous Prevalence Monitoring Programme (UAPMP) data indicate that 59% of previously undiagnosed HIV infections remain undiagnosed after the clinic visit, representing many missed opportunities to intervene and reduce HIV transmission (Murphy *et al.* 2004). Expanded access to treatment has the potential to attract millions of people into health-care settings and so offers critical new opportunities to simultaneously strengthen HIV-prevention efforts by delivering and reinforcing HIV-prevention messages. The widespread availability to HIV treatment will provide new incentives for HIV testing, which in turn will increase opportunities for counselling on HIV prevention. Increased knowledge of serostatus will subsequently enable prevention

programmes to develop interventions that are specifically tailored to the different needs of HIV-positive, HIV-negative and untested individuals (Gayle & Lange 2004). Sustainable treatment over the medium term depends on successful prevention. Gayle & Lange argue that to achieve a maintainable response to HIV/AIDS, prevention and treatment services must be brought to scale simultaneously. Unless annual HIV incidence falls sharply, treatment programs will be unable to keep pace with the number of people in need, and will become financially unsustainable. As antiretroviral therapy reduces AIDS deaths in areas where treatment is available, the disease may seem less threatening, thus leading to potential increases in sexually risky behavior resulting in the number of people living with HIV growing. Furthermore, as HIV-infected people on antiretroviral therapy become healthier, they are likely to become more sexually active, potentially creating additional opportunities for HIV transmission to occur. Studies attribute the increase in unprotected sex, at least in part, to the perception among many that HIV/AIDS is no longer as serious as it once was (Gayle & Lange 2004).
To stem further increases in HIV incidence, the UK Government needs to concentrate on the modernisation of sexual health services; the UK Department of Health's Sexual Health Strategy is aiming for a 25% fall in newly acquired HIV infections in England by 2007. Unlike with other infectious diseases, an infected person with HIV must act in certain ways to pass the virus on; it is here that the Government can act with education and services to prevent this onwards transmission (Power 2004).

1.5.2 Reducing costs of treatments and surveillance

Most of the public health challenges of HIV/AIDS can be, at least partially, dealt with using prevention and awareness campaigns, as discussed previously. Some of the main public health challenges in the UK as detailed by the CDSC (2002) are listed below:

1) Increasing numbers of diagnosed HIV infected people
2) Large and increasing impact of migration from high prevalence areas
3) Rising costs of care
4) Continuing transmission through MSM and increasing sexual risk taking
5) Numbers of newly diagnosed HIV infected individuals with advanced disease.

With reference to 3) on the previous page, a large proportion of costs of HAART arise in the postponement of AIDS resulting in a steep increase in the number of people requiring long-term treatment (CDSC 2002). The success of HAART and the growing number of new cases of HIV transmission has meant that there has been a 101% increase in demand for HIV care since 1997 (Carter 2003).

GlaxoSmithKline Plc (GSK) and the German drug manufacturer Boehringer Ingelheim have agreed to grant licences for production, import, sale and distribution of generic AIDS drugs in South Africa, after being charged with anti-competitive sales practices and excessive pricing by AIDS activists, including the Treatment Action Campaign, in 2002. This will undoubtedly help bring inexpensive medicines to millions of people living with HIV/AIDS in sub-Saharan Africa (Nelson 2003). Companies (including Cipla, who launched the first generic antiretroviral drug, zidovudine, in 1994, and has since then launched 10 different antiretroviral and fixed-dose combinations of antiretroviral drugs as single pills) have reduced the cost of combination HIV-antiretroviral treatment by such an extent, in the last year or two, that HAART can now be bought for less than US$250 a year. Falling prices of therapy are enabling physicians in the developing world to offer triple antiretroviral regimens to greater number of patients, who desperately need the life-saving drugs (Kumarasamy 2004). However, despite the cost of first-line combination generic antiretrovirals being less than $250 a year, the cost of the second-line combinations with protease inhibitors is ten times that amount. This large disparity in price will present a great challenge for resource–constrained settings in the scaling up of antiretroviral delivery. Immunological and virological monitoring of HIV-infected patients on HAART is critical. The cost of a CD4 cell-count is around $25 a test, and measuring viral load costs $100 a test. The cost of monitoring is higher than the cost of generic antiretrovirals in some resource poor countries (Kumarasamy 2004), hence, there is significant importance of identifying alternative assays that could guide treatment decisions (Mofenson *et al.* 2003).

1.5.3 Three-by-Five Initiative

In September, 2003, at the second UN General Assembly Special Session on HIV/AIDS, WHO and UNAIDS declared the lack of treatment in low and middle income countries to be a global health emergency and launched the "3 by 5" initiative, which aimed to enrole 3 million people on ART by the end of 2005 (Gutierrez *et al.* 2004). That means that the UN's new AIDS strategy aims to increase the number of people receiving antiretroviral treatment from only 7%, of nearly 6 million people, to 50%. Although AIDS is treatable, less than 5% of the 40 million people living with AIDS have access to antiretrovirals. The 34 countries targeted by the initiative are home to 94% of people needing treatment in the developing world (Mukherjee 2004). Baragona (2003), in an article for VOANews, explains that, under this plan, WHO's objectives are to: provide simple, standardised procedures that will make it easier to get more people treated and tested; provide technical help to countries on setting goals, finding money, hiring and training local workers and improving facilities; and help control costs by establishing global and regional networks of buyers. The report by Gutierrez *et al.* (2004) estimates that between US$5.1 billion and US$5.9 billion will be needed by the end of 2005 to provide the required antiretroviral therapy and support programmes, in addition to covering country-level administrative and logistic costs in order for 3 by 5 to work. Yet, to date, less than $2.3 billion has been paid to the Global Fund (Mukherjee 2004).

1.5.4 Similarities with other STI's

Between 1996 and 2002, the incidence of sexually transmitted infections (STI's), excluding HIV, rose by 43%. These data tell us that more and more people are having unsafe sex, hence serving as an early warning of the future path of HIV/AIDS. Furthermore, as well as causing disease and infertility, infection with other STI's may facilitate the transmission of HIV (Dougan *et al.* 2004), thus, the spread of HIV may be amplified by the increased prevalence of sexually transmitted diseases in the community. It is possible that the presence of both ulcerating and non-ulcerating sexually transmitted diseases (STD's) increase the risk of HIV infection three- to five-fold (Wasserheit 1992 and Laga *et al.* 1994). Effective STD control plans and the monitoring of HIV prevalence in STI patients is essential to HIV prevention (EuroHIV 2003).

In 2004, Pugh *et al.* produced a paper describing eight cases of infectious syphilis which were identified as two unrelated clusters in Walsall, West Midlands (population 250,000), over the four months from December 2002 to March 2003, illustrating the epidemiological diversity of the ongoing syphilis epidemic and emphasizing the need for continued vigilance to the potential of infection in high risk groups. In England, diagnosis of infectious syphilis began to rise in the late 1990's – congenital syphilis is rare in the UK, and few cases have been reported - cases of primary, secondary, and latent syphilis increased by 431% between 1998 and 2001. This increase was disrupted by a number of individual outbreaks, with clusters of infections also being reported. English outbreaks were associated with high rates of partner change within risk groups and simultaneous HIV infection that may well occur since it is possible that syphilis enhances HIV transmission.

Gupta *et al.* (2004) discuss the lessons one can learn from multi-drug resistant tuberculosis, which has many similarities with HIV/AIDS, including: serious adverse events from multidrug treatment; comprehensive management strategy for prevention and treatment; and the threat of drug resistance at individual and population levels. Furthermore, the diseases share management requirements that are particularly difficult to meet in resource-constrained regions, such as: long-term follow-up and assessment of patients; adequate supply, availability and affordability of drugs and diagnostic tools; intensive patient support to endure adherence to treatment; the need for laboratory monitoring; and the absence of evaluated, evidence-based policy for management.

The Green Light Committee (GLC) is a partnership formulated by the international community, designed to foster access to treatment for multidrug-resistant tuberculosis via an integration of the negotiated concessional prices and a system for ensuring proper use of second-line drugs. The GLC operates as a sole coordinating entity for the global multidrug resistant tuberculosis issue. As the international community moves rapidly to bridge the HIV/AIDS treatment gap by strengthening health systems, strategies developed for TB could help ensure that affordable, high-quality antiretroviral reach programmes are used appropriately.

Murphy *et al.* state in their report in 2004 that the substantial increase in homosexually-acquired gonorrhoea in 2000/2001, compared to earlier years, was sustained in 2002, and

their data suggest that this sensitive indicator of increased behavioural risk among homo/bisexual men was accompanied by an increase in HIV incidence. This underlines the importance of strengthening HIV prevention messages in response to adverse changes in the incidence of acute STI's. With dramatic increases in chlamydia rates among young women over the past decade, and the highest rates of gonorrhoea and concurrent partnerships among young people, concern about the potential for HIV transmission remains (Dougan *et al.* 2004).

CHAPTER 2

HIV/AIDS EPIDEMIC MODELS AND DATA

2.1 Mathematical and Statistical techniques to model epidemics

Once the AIDS data has been adjusted for both under-reporting and reporting delay, one can perform mathematical and statistical techniques, or projection methods, in order to reproduce that data and, thus, make predictions about certain 'what-if' scenarios. Numerous statistical methodologies have been produced for investigation into the HIV/AIDS epidemic, of which the three most common methods are back-calculation, using both data from the past and knowledge about disease development (i.e. the incubation period); extrapolation (or curve-fitting), using only data from the past and not knowledge about the present disease; and compartmental (or transmission) modelling, which uses knowledge necessary for back-calculation techniques and information concerning modes of transmission and their probabilities. All methodologies, according to Jager *et al.* (1993), involve trend analysis of observed AIDS incidence; re-enactment of HIV movements; models for transmission and spread of the disease; and estimation of key parameters for models reciting the development of disease stages. Bibliographies by Whithers (1989) and Fusaro *et al.* (1989) provide in depth explanations of these approaches, enclosing original ideas useful in quantitative methodology for infectious disease in general. Anderson (1989) and Gail & Brookmeyer (1988) also give annotations of some mathematical and statistical research as well as Castillo-Chavez (1989) who edited a thorough assessment of statistical and mathematical methodologies in HIV/AIDS modelling (Jager *et al.* 1993). It is the technique of compartmental modelling that will be applied throughout this thesis in order to model and predict the path of the HIV/AIDS epidemic. The other two methods are described briefly in the following sub-sections of this chapter. Also discussed is a fairly new approach to modelling infectious diseases using phylodynamics.

2.1.1 Extrapolation

Some authors use what is viewed as the simplest technique for predicting AIDS (Solomon 1996), that is, extrapolation of empirical curves fitted to observed AIDS incidence data (or some other well-defined data points). Curves that are most often used are the exponential (for the early years of the epidemic), exponential with a quadratic component, the logistic and the linear logistic (Department of Health and The Welsh Office 1988, cited in Heisterkamp *et al.* 1992). At the beginning of the epidemic, when exponential curves are usually fitted, the growth rate can be denoted by $a(t) = e^{\alpha+\beta t}$, where $a(t)$ is the number of new diagnoses at time t, with constant doubling time $\log 2/\beta$. Solomon (1996) states that this curve can be advantageous due to its mathematical simplicity and approximate relation to the solution of a number of simple theoretical models which encompass features of the 'at risk' population. Agreeing with epidemic theory, the growth rate decelerates and so further mathematical formulae contain sub-exponential growth. Solomon (1996) then goes on to detail that, in the mid to late 1980's, observed AIDS diagnoses rates were fitted using a variety of curves based on the exponential, for instance, the quadratic exponential model $a(t) = e^{\alpha+\beta t-\gamma t^2}$. In this curve, the rate of new diagnoses of cases rises to a peak before dropping symmetrically to zero. For recipients of blood or blood products, amongst whom nearly all new infections ceased in Australia (and elsewhere) when widespread screening of donated blood was introduced in 1985, the model is a satisfactory approximation to the trend of new diagnoses of AIDS (Solomon and Wilson 1993). In Australia, and in England and Wales, the linear logistic model has provided the best fits to observed AIDS incidence; the rate of new cases of AIDS is assumed to pass from exponential to linear growth relevant in the second phase of the epidemic, according to the expression $a(t) = (\alpha + \beta t)/(1 + e^{\gamma-\delta t})$. Distinctions between geographical regions, transmission groups and other categorical effects can be simply calculated by comparing the appropriate parameter estimates. Solomon (1996) informs us that alterations in the definition of AIDS, the introduction and availability of treatments, and other temporal changes, may be included by using change-point models (Solomon *et al.* 1990). The Report of a Working Group (1988); Solomon *et al.* (1990); and Taylor (1989) all provide further information on this area. Where the observed amounts are significantly large, one can fit nonparametric curves.

Examples of this are the application of Lowess (locally weighted scatterplot smoother) to smooth observed AIDS data with the intent to describe patterns in AIDS incidence (Cleveland 1979). See, for example, Rosenberg *et al.* (1992) and work by Zeger *et al.* (1989) who used splines to model the US AIDS data. Other researchers suggest semiparametric curves, combining parametric and nonparametric components (De Angelis *et al.* 1993), or propose fitting piecewise constant, linear or nonlinear models. Despite being, arguably, the most straightforward approach to forecasting AIDS data (Hethcote & Van Ark 1980 and Brookmeyer & Gail 1994), there are limitations to the method that Brookmeyer and Gail (1994) discuss fully. In extrapolation, a model is fitted to the AIDS data, from this model we can expand and forecast future AIDS cases. Numerous models will fit the current available AIDS data perfectly, as described above, however, when predicting the long-term numbers we may find the results differ greatly. Also, it can not be assumed that the model will fit future AIDS data. In spite of which curve is applied for the fit of the growth rate, knowledge of important characteristics of the epidemic cannot be directly included in this technique, unlike for epidemic models, which endeavour to replicate the true pattern of HIV infection, and the back-calculation method, which can involve 'external' information observed from surveys, cohorts and other studies (Solomon 1996). Despite this, extrapolation can be used to foresee short-term outcomes, although even these results need to be drawn with care and interpreted cautiously. The smoothness of the AIDS data, due to the infection rate being convoluted with the Incubation Period Distribution, or IPD, (Brookmeyer & Gail 1994) lends itself to the method of extrapolation. However, abrupt changes in AIDS incidence can occur, as seen in the US in 1993 due to the alteration in the surveillance definition of AIDS and the introduction of effective anti-HIV therapy in 1996. Thus, even a short-term extrapolation would be inadequate at predicting such changes.

2.1.2 Back-calculation

Mathematically speaking, back-calculation lies between extrapolation and compartmental modelling in terms of its complexity. It is one of the most used techniques when modelling observed AIDS incidence with the aim of predicting future values, as demonstrated by Brookmeyer & Gail (1988); Brookmeyer & Damiano (1989); and Isham

(1989). Taylor (1989), Solomon & Wilson (1990) and others also used back-calculation early on to reconstruct the size and shape of the past HIV infection curve from AIDS incidence data and from this predict future AIDS incidence. Becker *et al.* (1991) discuss the advantages and disadvantages of the various prediction procedures and give results from a non-parametric back-projection method where only the incubation time distribution is known. They determine that using the non-parametric method one can only predict the minimum size of the epidemic, as no information is applied for future HIV-incidence. Like the actuarial method, the method of back-calculation uses knowledge of the route of infection. In addition to this, it uses information about the incubation time distribution, and it is normal to identify an empirical curve for either the AIDS incidence or HIV incidence in order to retrieve future projections (Heisterkamp *et al.* 1992). Proposals from both Brookmeyer & Liao (1990[b]) and Solomon & Wilson (1990), suggest including other information in the process also, such as early treatment. The principle of back-calculation is that an estimate of the HIV incidence can be obtained by incorporating the observed AIDS incidence data and an estimate of the IPD with the use of back-calculation. Knowledge of any two of the distributions can determine the third and once the past infection curve has been recreated, using back-calculation, the equation, as shown below in equation (2.1), is used again in order to forecast future AIDS incidence, usually for periods of up to 5 years (Solomon 1996). The convolution equation used for back-calculation is as follows:

$$A(t) = \int_0^t g(s) \times F(t-s) ds \qquad \ldots\ldots (2.1)$$

where

A(t) = expected cumulative number of AIDS cases diagnosed by time t;

g(s) = infection rate at time s and;

F(t) = cumulative distribution of the incubation period.

Note that the incubation period must be less than t-s, since for every individual diagnosed with AIDS by time t, infection must have occurred prior to this, at time s (Brookmeyer & Gail 1994). This equation, in words by Solomon (1996), gives the basis of back-

calculation: "that a process of infection has occurred, and is possibly still occurring, in the population under study, and that infection with the virus is followed by the lengthy and variable incubation period until (at least in a majority of cases) an AIDS-defining illness is diagnosed". Solomon (1996) then goes on to say that it is still too early to decide whether some people will remain infected forever, without ever developing an AIDS-defining illness.

Brookmeyer & Gail (1994) state five limitations of the back-calculation method:

1) No predictions can be made for the future HIV infection rate,
2) Little information about recent infection rate,
3) The IPD is assumed known,
4) The IPD is assumed stationary,
5) Requires accurate AIDS incidence data.

Deterministic deconvolution ('deterministic' since the approach assumes no random variability in the cumulative AIDS data and 'deconvolution' referring to using known A(t) and F(t) to solve for g(s)) is the most simple form of back-calculation. However, it is not without its problems, consequently statistical deconvolution is the preferred method in both the discrete and continous cases. The general mathematical case for discrete deterministic deconvolution is shown in equation (2.2), this equation is solved to find estimates of the number of HIV infections in year i as a linear system of n equations in n unknowns.

$$\alpha_j = g_1 f_j + g_2 f_{j-1} + \cdots + g_j f_1 \qquad \ldots\ldots (2.2)$$

where

α_j = number of new AIDS cases diagnosed in the j^{th} year,

g_i = unknown number of individuals infected at the beginning of the i^{th} year,

f_i = F(i)-F(i-1) = probability that an individual develops AIDS during the i^{th} year of HIV infection.

From equation (2.2) above, it can be seen that the number of new AIDS cases diagnosed in year 1 of the epidemic can be written as $\alpha_1 = g_1 f_1$. Solving this for the number of

individuals infected at the beginning of year 1, i.e. the initial number of infectives:

$$g_1 = \alpha_1 / f_1$$

Since f_1, the probability that an individual develops AIDS during the first year of HIV infection, is very small, the process is ill-conditioned.

Brookmeyer & Gail (1994); Gail & Rosenberg (1992); and Baccheti *et al.* (1993) provide a detailed and informative explanation of the back-calculation method, along with many other publications.

2.1.3 Phylodynamics

Chronic or persistent infections, such as HIV, show a relatively slow increase in the number of cases, without the peaks and the troughs associated with acute infections. Clewly explains, in his 2004 paper entitled: "phylodynamics: a conjunction of epidemiology and evolution?", that, for chronic infections, phylogenetic trees can be constructed based on sequences from different individuals (i.e. between-host population phylogenetics) or sequences evolving within an individual patient (i.e. within-host individual phylogenetics). These two types of trees are not congruent. The population tree reflects the temporal and spatial dynamics of the disease, whereas the individual tree is a reflection of immune selection occurring within the host. Grenfall *et al.* (2004) address the problem of how to construct a model that will accommodate the different phylogenetic trees and temporal and spatial epidemic data – they call this type of modelling, Phylodynamics. A key phylodynamic parameter defined by Grenfall *et al.* is the Evolutionary Infectivity Profile (EIP) which is a measure of the transmission rate of immunologically selected microbial mutations. It may be expressed mathematically, as shown in equation (2.3) below, as a function of the pathogen population size, its mutation rate and the strength of the immune response of the host.

$$EIP \propto mN(x)\int_t N(t)I(t), \quad t = 0 \ldots x \qquad \ldots\ldots (2.3)$$

Where m = mutation rate;

N = viral population size;

t = time.

It is suggested by Grenfall *et al.* that determining the EIP of an infection will help in vaccine design, drug therapy and countering emergent diseases. Different phylodynamic patterns that may be observed are described by Clewly as follows:

- Infection with no immune response and no adaptation occurs;
- Limited immune response and high adaptability of the pathogen, seen in the course of an HIV infection;
- Infection rapidly cleared because of strong immunological response in an experienced host.

Phylodynamics is intended to provide a means whereby phylogenetic and epidemiological models can be unified, thereby allowing a new understanding of the transmission of infectious disease.

2.1.4 Modelling the HIV/AIDS Epidemic

The model building approach, or compartmental modelling, is one of the main methodologies which operational researchers are interested in, in particular of the three aforementioned key methodologies (back-calculation, curve fitting and transmission modelling). It aids comprehension of the structure of the epidemic and understanding of how complicating aspects might affect the global spread of the disease. Such factors may include heterogeneity in sexual behaviour, variable infectiousness, changing sexual behaviour and the nature of partner formation (mixing) (Dangerfield & Roberts 1994). Transmission modelling is significantly useful in view of ambiguity, complexity, inadequate data and resource use. In order for this modelling technique to excel in areas such as: disease prevention; early detection and screening programmes; evaluation of treatments; allocation of resources; and improved patient monitoring and care (Brailsford & Shahani 1994), information on a number of features of the mechanisms concerned (for instance: infection; disease progression; risk group; risk behaviour; and modes of transmission) is necessary. Habitually, models of this type investigate the consequences of various what-if scenarios qualitatively and/or quantitatively (Anderson 1989; Bailey 1992[a]; Dietz 1991; Anderson & May 1992; Druten *et al.* 1990 and; Jager & Ruitenberg

1992). When models are suitably fitted to a particular HIV/AIDS epidemic, they can be used for medium-term forecasts, as illustrated by Bailey (1992[a]) to Switzerland, Hethcote *et al.* (1991) to San Francisco, Heisterkamp *et al.* (1992) to Amsterdam and Verdecchia *et al.* (1992) to Italy.

Assumptions are implied concerning the means by which transmission of HIV occurs. These assumptions also regulate the modelled population characterized by the observed AIDS cases. Thus, dynamic models must be employed to well-defined (e.g. geographically and categorically) real populations adhering to the postulates implied (Jager *et al.* 1993). Bailey (1992[a]) presented a model of HIV/AIDS, intended for practical public health applications, with a close connection between local data and compartmental modelling. This model proposed by Bailey includes different risk-groups (intravenous drug users (IVDU's); homosexual/bisexual men, high and low risk; and heterosexuals); estimates model parameters; and incorporates a correction for reporting delay and under-reporting. Consequently, it utilizes AIDS case data and data from death certificate investigation. Models should employ various sources of information and modify model dynamics and statistical techniques to a specific local situation (Jager *et al.* 1993). More recent methodological progress permits the construction of realistic situations, using (sub) epidemics linked with socio-economic impacts (Boom *et al.* 1992). Mathematical models designed and developed for infectious diseases by researchers since the early 20th century (Bailey 1975; Hethcote & Van Ark 1980 and Anderson 1982) can be invaluable in the creation and justification of theories. Thus, the procedure demands complete understanding of the main dynamics involved in the growth of an infectious disease in order to create a simplified mathematical interpretation of a vastly complex situation with comprehensible assumptions. It is imperative to maintain as simple a model as possible, in spite of how complex the reality of the situation may be. The inclusion of too many non-essential parameters will mean more uncertainty in the model due to the greater amount of estimation required. The invention of a compartmental model of the AIDS epidemic which embraces the three key transmission groups, or exposure categories, affected (male homosexuals, intravenous drug users and non-monogamous heterosexuals) would be moderately complicated. Numerous relations between heterosexuals themselves and with members of other transmission groups (e.g.

the activities of bisexuals and persons who have sex with infected IV drug users) and the larger number of parameters within the model cause difficulties. This generates problems for estimation either by direct methods or by fitting the model to time series data (Dangerfield & Roberts 1994). This work, like that of Dangerfield & Roberts (1989, 1996) and Roberts & Dangerfield (1990[a], 1990[b]) has involved the development of a transmission model of AIDS spread in the male homosexual community only, due to the inherent complexity involved in formulating a transmission model which embraces all three main groups of susceptibles (homosexuals, intravenous drug users and heterosexuals). The research by Dangerfield & Roberts (1996) has three main objectives:

i. An international comparison of the parameter values obtained as a result of fitting a model to time-series data from a number of different countries;
ii. A comparison of the optimised parameter values with those derived from clinical studies and sample surveys;
iii. A comparison with the projections made by the other two approaches to modelling AIDS epidemiology insofar as they offer projections disaggregated by risk group.

2.2 Introduction to the Cardiff HIV/AIDS Epidemic Model

2.2.1 Compartmental modelling of HIV/AIDS

Traditionally, infectious disease is modelled using SIR, or SIS, models. These involve dividing the population into sub-populations, those who are: Susceptible to the disease; Infected with the disease and Recovered from the disease (i.e. once again Susceptible to the disease). For HIV/AIDS, individuals do not recover from the disease; hence we use an SI model. Also, the infected state is divided into HIV infected and AIDS categories due to the significant difference in health status. Plus, we incorporate a 'Death from AIDS' state to signify that AIDS is a terminal illness. Thus, the states considered for modelling the HIV/AIDS epidemic are as shown in Figure 2.1. There are movements between the compartments as illustrated by the directional arrows and, as for any model

consisting of a set of states, there exists a set of rules determining how an individual transfers from one state to another (Brailsford & Shahani 1994).

Figure 2.1 **The four basic states in the epidemiological model for HIV/AIDS.**

These four sub-populations can then be split further to create various other sub-populations, as seen in publications by Hethcote & Van Ark (1980); Griffiths *et al.* (1990); Wheeler (1990); Hethcote *et al.* (1991); Bailey (1993, 1994[a], 1994[b], 1997); Griffiths & Williams (1994); Pasqualucci *et al.* (1998) and Rossi & Schinaia (1998). For the model implemented here, the sub-populations are split into those individuals who indulge in High Risk activities and those who adopt Low Risk behaviour. Roberts & Dangerfield (1990[b]) go even further and divide the sub-populations into three risk behaviour groups: high, moderate and low. Also, the infected sub-population can be sub-divided into a number of smaller sections in order to illustrate the various stages of disease progression that an individual may pass through before being classified as having contracted AIDS. Brailsford & Shahani (1994) provide a description of the natural history models in use during the early 1990's and go into detail explaining three different

types of model that they have developed, with varying degrees of complexity, in order to meet the different needs of their intended users. The Cardiff model shares similarities with these models described by Brailsford & Shahani (1994) since they are essentially semi-Markov processes representing the uncertainty and variability witnessed during the course of HIV infection. Garnett (2002) provides an easily comprehendible description of mathematical models, their creation and use, for the purpose of modelling sexually transmitted diseases, defining all relevant mathematical and technical terms within the article. Garnett reports that mathematical compartmental models "serve a number of roles in understanding sexually transmitted infection epidemiology and control... providing an explicit framework within which to develop and communicate an understanding of infectious disease transmission dynamics." This same article by Garnett goes on to include the construction of a simple deterministic compartmental mathematical model of an infection in a homogenous population and its analytical solution, providing a useful reference for the introduction of the Cardiff model.

2.2.2 The Cardiff HIV/AIDS Epidemic Model

The Cardiff Model is displayed in Figure 2.2 overleaf. Within the Cardiff Model the same principles are applied as discussed previously; the homosexual population is divided into Susceptibles, Infectives, AIDS and Death from AIDS sub-populations, and for each of these states an individual can either be participating in high risk behaviour or low risk behaviour. As displayed in Figure 2.2, the sub-populations are denoted by:

$X(t)$ = The number of High Risk Susceptibles at time t
$Y(t)$ = The number of High Risk Infectives at time t
$A(t)$ = The number of High Risk AIDS cases at time t
$W(t)$ = The number of Low Risk Susceptibles at time t
$V(t)$ = The number of Low Risk Infectives at time t
$Z(t)$ = The number of Low Risk AIDS cases at time t

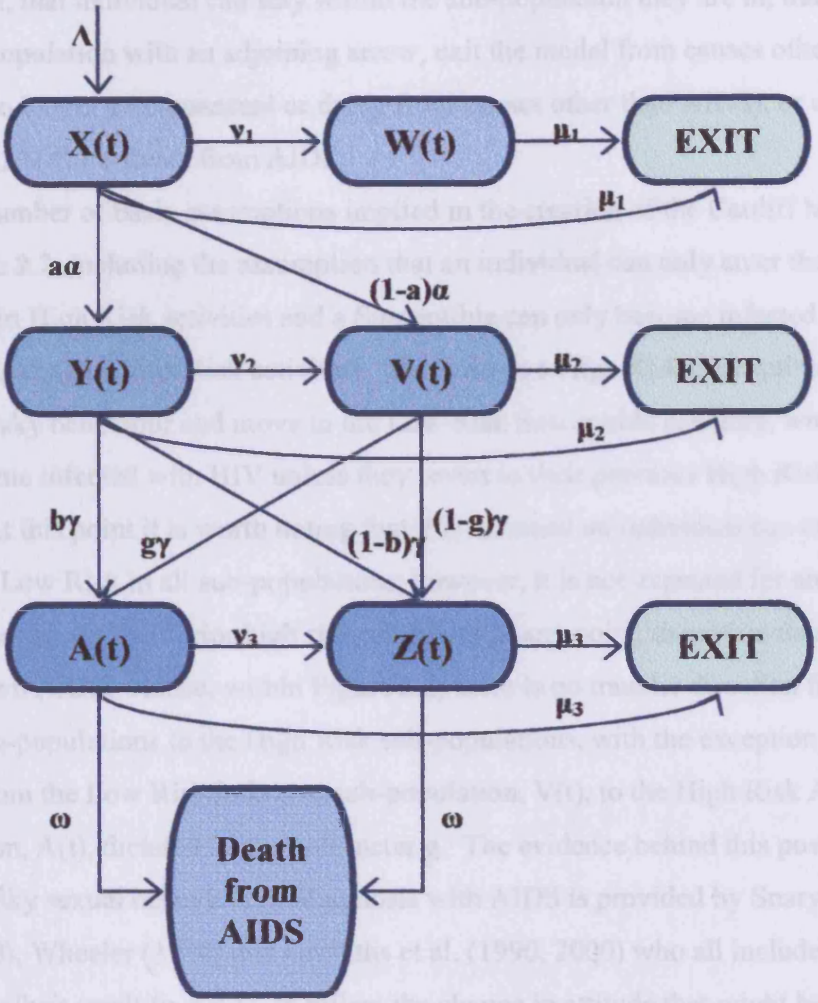

Figure 2.2 **The Cardiff HIV/AIDS Epidemic Model**

When discussing High Risk and Low Risk behaviour amongst homosexual men, what is implied is the significant difference in the degree of exposure to the HIV virus subject to the activities that the individual is participating in at that time. For instance, homosexuals within the High Risk category may be practising unsafe sex with numerous and frequent partners, whilst a homosexual within the Low Risk category might be participating in safe sex, or in a stable long-term relationship. Following an individual through the

Cardiff model, that individual can stay within the sub-population they are in, transfer to another sub-population with an adjoining arrow, exit the model from causes other than AIDS, (e.g. no longer a homosexual or dying from causes other than AIDS), or exit the model due to AIDS i.e. death from AIDS.

There are a number of basic assumptions implied in the creation of the Cardiff Model as seen in Figure 2.2, including the assumption that an individual can only enter the model if participating in High Risk activities and a Susceptible can only become infected with HIV if participating in High Risk activities. This allows a High Risk Susceptible to lessen their risky behaviour and move to the Low Risk Susceptible category, where they will not become infected with HIV unless they revert to their previous High Risk behaviour. At this point it is worth noting that it is assumed an individual can move from High Risk to Low Risk in all sub-populations; however, it is not expected for an individual to return to their prior high risk behaviour at any point, except on contraction with full-blown AIDS. Hence, within Figure 2.2, there is no transfer direction from the Low Risk sub-populations to the High Risk sub-populations, with the exception of the movement from the Low Risk Infective sub-population, V(t), to the High Risk AIDS case sub-population, A(t), dictated by the parameter g. The evidence behind this possible increase in risky sexual behaviour on diagnosis with AIDS is provided by Snary (2000), Lowrie (2000), Wheeler (1990) and Griffiths et al. (1990, 2000) who all include this transfer rate, albeit small ($g = 0.1$), to reflect the change in attitude that might be associated with the prognosis of AIDS. The assumption that an individual will not, otherwise, return to their previous High Risk behaviour follows on from work completed by Snary (2000), who states that 'to keep the compartmental model as simple as possible and to constrain the number of parameters within the model it is assumed that a homosexual will transfer from high to low risk only'.

For each possible movement through the Cardiff model, there is an associated parameter. These parameters are shown in Figure 2.2, placed next to their repective directional arrows. Each is listed and defined on the following page:

Λ = the Entry Rate into the Cardiff model,

μ_1 = the rate that a Susceptible exits the model from causes other than AIDS,

μ_2 = the rate that an Infective exits the model from causes other than AIDS,

μ_3 = the rate that an AIDS case exits the model from causes other than AIDS,

ν_1 = the rate that a High Risk Susceptible transfers to the Low Risk category,

ν_2 = the rate that a High Risk Infective transfers to the Low Risk category,

ν_3 = the rate that a High Risk AIDS case transfers to the Low Risk category,

a = the proportion of High Risk Susceptibles who continue to practice in High Risk behaviour once they become infected with HIV,

b = the proportion of High Risk Infectives who continue to practice in High Risk behaviour once they are diagnosed as AIDS cases,

g = the proportion of Low Risk Infectives who start to practice in High Risk behaviour once they are diagnosed as AIDS cases,

α = the incidence rate, represents the rate at which homosexual men become infected within a time interval, δt,

γ = the incubation rate,

ω = the death rate, or the AIDS Survival Time.

The parameters, Λ and α, will be discussed in much more detail in the following section, but meanwhile, to give an idea of the calculation of Λ and α:

- $\Lambda = \lambda N_{1978}$, where λ is the arrival rate and N_{1978} is the total homosexual population in 1978; and

- $\alpha = \beta c \frac{Y(t)+A(t)}{X(t)+Y(t)+A(t)}$, where βc is the infectivity rate and $\frac{Y(t)+A(t)}{X(t)+Y(t)+A(t)}$ represents the proportion of High Risk HIV infected individuals at time t.

Each of the sub-populations has a differential-difference equation associated with it; these differential-difference equations for the basic Cardiff HIV/AIDS Epidemic model, as seen in Figure 2.2, are given below in equations (2.4*a*)-(2.4*f*):

$$dX(t)/dt = \Lambda - \alpha X(t) - (\nu_1 + \mu_1)X(t) \quad \ldots(2.4a)$$

$$dY(t)/dt = a\alpha X(t) - (\gamma + \nu_2 + \mu_2)Y(t) \quad \ldots(2.4b)$$

$$dA(t)/dt = b\gamma Y(t) + g\gamma V(t) - (\nu_3 + \mu_3 + \omega)A(t) \quad \ldots(2.4c)$$

$$dW(t)/dt = \nu_1 X(t) - \mu_1 W(t) \quad \ldots(2.4d)$$

$$dV(t)/dt = (1-a)\alpha X(t) + \nu_2 Y(t) - (\gamma + \mu_2)V(t) \quad \ldots(2.4e)$$

$$dZ(t)/dt = (1-b)\gamma Y(t) + (1-g)\gamma V(t) + \nu_3 A(t) - (\mu_3 + \omega)Z(t) \quad \ldots(2.4f)$$

Equations (2.4a)-(2.4f) can then be rearranged using first principles to obtain the set of discrete-time equations (2.5a)-(2.5f) seen overleaf:

$$X(t+\delta t) = X(t) + [\Lambda - (\mu_1 + \nu_1)X(t) - \alpha X(t)]\delta t \quad \ldots(2.5a)$$

$$Y(t+\delta t) = Y(t) + [a\alpha X(t) - (\gamma + \nu_2 + \mu_2)Y(t)]\delta t \quad \ldots(2.5b)$$

$$A(t+\delta t) = A(t) + [b\gamma Y(t) + g\gamma V(t) - (\nu_3 + \mu_3 + \omega)A(t)]\delta t \quad \ldots(2.5c)$$

$$W(t+\delta t) = W(t) + [\nu_1 X(t) - \mu_1 W(t)]\delta t \quad \ldots(2.5d)$$

$$V(t+\delta t) = V(t) + [(1-a)\alpha X(t) + \nu_2 Y(t) - (\gamma + \mu_2)V(t)]\delta t \quad \ldots(2.5e)$$

$$Z(t+\delta t) = Z(t) + [(1-b)\gamma Y(t) + (1-g)\gamma V(t) + \nu_3 A(t) - (\mu_3 + \omega)Z(t)]\delta t \quad \ldots(2.5f)$$

Throughout this thesis, the equations have been solved for each time interval δt (δt is taken as 1 week, over a period of 50 years). When solving these equations for each δt, HIV Incidence, HIV Prevalence, AIDS Incidence and AIDS Prevalence can be estimated. HIV Incidence refers to the number of new HIV cases per year and is given by $\alpha \sum_{i=1}^{52} X(i)$, where X(i) (i = 1, 2, ..., 52) denotes the number of High Risk Susceptibles present in week i of the particular year under consideration. Similarly, AIDS Incidence, that is, the number of new cases of AIDS per year (i.e. the rate at which Infectives are diagnosed as AIDS cases multiplied by the total number of High and Low Risk Infectives) is given by $\gamma\left[\sum_{i=1}^{52} Y(i) + \sum_{i=1}^{52} V(i)\right]$, where Y(i) and V(i) denote the total number of High Risk and Low Risk Infectives, respectively, present in week i of the year under consideration. The term prevalence refers to the number of cases alive at time t. Thus, HIV/AIDS Prevalence is given by Y(t) + V(t) + A(t) + Z(t), whereas AIDS Prevalence alone is defined as A(t) + Z(t).

When solving the differential-difference equations via Euler's method (first principles), the value that we choose as our time increment, δt, can have a significant effect on the modelling procedure and output. If too big, then events may occur that are not recognised or noted within the model since occurrence takes place within one time interval i.e. a homosexual may become infected and die from AIDS within one time step.

Alternatively, if δt is too small then rounding errors can take place (Snary 2000). Throughout this thesis, a time interval of 1 week is used (i.e. $\delta t = 1/52$) in accordance with work by Snary and Bailey. Note that England (1997) showed that Euler's method provided sufficient accuracy of results when compared to more sophisticated models of numerical solutions of these equations, such as the Runge-Kutta 4^{th} order method.

2.3 HIV and AIDS data

2.3.1 The Dataset

The Public Health Laboratory Service (PHLS), at the Communicable Disease Surveillance Centre (CDSC), and the European Non-Aggregate AIDS Data Set (ENAADS), gathered by the European Centre for the Epidemiological Monitoring of AIDS, provide UK data which can then be employed for a mathematical and statistical investigation into the HIV/AIDS epidemic. The PHLS collects information including reported HIV infections, AIDS diagnoses, AIDS mortalities, AIDS indicator diseases. It segregates this data into regions within the UK for different transmission groups. Appendix 2.1 tabulates the UK data, for homo/bisexual men, implemented throughout this thesis, with AIDS incidence and HIV incidence extracted from the ENAADS dataset and deaths from AIDS obtained through contact with the CDSC. It is this data that the Cardiff HIV/AIDS model is based on and fitted to, employing maximum likelihood techniques for the estimation of certain parameters and a minimisation of χ^2-square summation to obtain the best fit possible.

ENAADS

Fifty-two countries in the European region of the World Health Organization (WHO) conduct joint surveillance of AIDS at the WHO-EC Collaborating Centre on AIDS/European Centre for the Epidemiological Monitoring of AIDS (ECEMA), Saint-Maurice, established in 1984. Surveillance is based on reporting of anonymous individual data. One institution per country reports AIDS cases to ECEMA and sends anonymous individual data on all AIDS cases reported nationally since the beginning of the epidemic. These data, which are extracted from the national AIDS data sets, are

merged to form the European Non-Aggregate AIDS Data Set (ENAADS). The data in ENAADS were presented quarterly, and more recently at 6-month intervals, in the report 'HIV/AIDS Surveillance in Europe'. A total of 38 countries (including the UK) provide data on each individual AIDS case. The range of the information recorded in the ENAADS data set is listed below:

- Country of national report
- Sex
- Age group at diagnosis
- Year of diagnosis
- Quarter of diagnosis
- Vital Status (classifying an individual as dead or not known to be dead)
- Year of death
- Test for HIV-1
- Test for HIV-2
- Transmission category
- Transmission sub-category or heterosexual contact category
- Transmission category of mother for mother-to-child cases
- Year of national report
- Quarter of national report
- Exact age at diagnosis
- AIDS indicator disease present at the diagnosis of AIDS

The definition used to classify HIV positive individuals as AIDS cases, for this dataset, is described in detail in section 1.1.3, i.e. the 1993 European AIDS Surveillance Case Definition. The dataset is released at half-year intervals with the end of year report for 2003 used within this thesis. As in Snary (2000), it is the UK AIDS cases for homosexual/bisexual men that provide the observed AIDS incidence data for this work and the UK new HIV diagnoses for homosexual/bisexual men that provide the HIV data (from 1995 onwards).

HIV data

Since the use of HAART became widespread in 1996, trends in AIDS incidence numbers have become less reflective of underlying trends in the HIV transmission (CDC 2002). Surveillance data on newly diagnosed HIV infections provide a more complete picture of the epidemic and the need for prevention and care than that provided by data on AIDS cases. Data on newly diagnosed HIV infections, however, should be interpreted with caution since they may not represent HIV incidence (i.e. new infections) and because they depend heavily on patterns of HIV testing and reporting which differ between countries (EuroHIV 2003). Determining HIV incidence (the number of new HIV infections) is difficult due to the long incubation period (IP) and lack of severe symptoms until much later on in the progression of the disease. Hence, many individuals are not aware of their serostatus. At present it is estimated that about a third of HIV-positive people do not know that they are infected, or, if they do know that they are HIV-positive, do not know their exact date of infection. Even though there may be a discrepancy between reported HIV cases and HIV incidence, new HIV diagnoses figures can still provide a rough guide for the number of HIV infections occurring. New diagnoses data on HIV among homo/bisexual men, is provided from the Health Protection Agency (HPA 2003) and EuroHIV (2003). The data dates from 1985 through to 2002, and demonstrates a reasonably stable level of approximately 1500 new diagnoses of HIV per year. It is suspected that HIV incidence prior to 1985 was not as settled as the apparent trend after this date. In fact, back-projections suggest that HIV incidence rose from 1978 onwards, to a peak, at around 1982, with about 3500 to 4000 new cases of HIV infection occurring in this year.

Surveillance programmes on HIV infection include: unlinked seroprevalence surveys (DH 1996); diagnostic HIV-testing reports and laboratory surveillance (Waight *et al.* 1992, Goldberg et al 1992, Van Duynhoven *et al.* 1996, DH 1996, Smith *et al.* 1994 and McDonald *et al.* 1994); as well as anonymous (repeated) surveys and monitoring in targeted sentinel populations, such as attendees of sexually transmitted diseases (STD) clinics, IDU's, and pregnant women (DH 1996, Fennema *et al.* 1995, Wiessing *et al.* 1996 and Bindels *et al.* 1996). For specific purposes, surveillance of HIV infection can be supplemented or extended by immunological or virological data (Lehner *et al.* 1997).

HIV incidence estimates can be obtained from: 1) observing seroconversions in a longitudinal study; 2) inferring incidence from serial cross-sectional surveys; 3) using capture-recapture methods in serial surveys; 4) back-calculation from reported AIDS cases; and 5) identifying recent seroconverters from a cross-sectional sample using two antibody tests of differing sensitivity for HIV antibodies. The fifth method listed here is relatively new and is described by the CDC as the serologic testing algorithm for recent HIV seroconversion (STARHS) (CDC 2002 and Schwarcz *et al.* 2001). STARHS is discussed briefly in section 1.2.1 of this thesis and consists of two HIV enzyme immunoassays: one is a current, highly sensitive, standard test that can detect HIV antibodies within a month of infection and the other has been made an insensitive ("detuned") experimental test that may identify antibodies 129 days to 170 days after the first test. As the measure of antibody in peripheral blood grows progressively in the early weeks and months of HIV infection, a newly infected person will test positive on the sensitive assay and negative on the detuned assay. If the average time a newly infected person will be positive on the first test, and negative on the second, is known, an annualised incidence rate can be extrapolated from the cross-sectional samples. False positive seroconversions can occur in individuals with late-stage HIV infection, in which antibody levels decline, and in persons receiving antiretroviral treatment. However, despite the limitations, STARHS has grown in use because it is the only method that allows an incidence estimate from a single cross-sectional sample and could potentially establish whether infection has occurred within the past year. Public health experts, at the Centres for Disease Control and Prevention, claim that STARHS can assist with tracking trends in HIV infection more accurately by suggesting emerging epidemics, thus improving the focus on intervention efforts. The STARHS technique has been validated for use with HIV subtype B infections, the subtype found in almost all UK born homo/bisexual men. However, when used in determining the incidence of HIV infection among heterosexuals, the reliability of the STARHS technique can be problematic due to the high degree of HIV subtype diversity in this population. Median age and CD4 count at diagnosis can also be employed as indirect markers of HIV incidence as both can be used to specify whether newly diagnosed infections are either predominantly recent or long-standing and to assess how this changes over time (HPA 2003).

HIV prevalence (the number of people living with HIV at a certain time) is easier to calculate than HIV incidence (AIDS Knowledge Base 1999); however, they may not be as informative about the effects of prevention efforts and the future of the epidemic. Prevalence of HIV infection in the United States overall has been estimated by two different methods. The first method is to collect results from serosurveys in different populations and different geographic regions, merge them with estimates of the size of the populations at risk, and produce a total estimate that amalgamates all the data. This method has three main limitations: 1) the majority of serosurveys are not population-based and are difficult to generalise beyond the venue in which the HIV testing was completed; 2) coverage of geographic regions and specific sub-populations at risk is not complete; and 3) the sizes of the populations at risk are not known with any accuracy. The second approach to estimating HIV prevalence uses back-calculation; it combines the available data on the numbers of reported AIDS cases and the IPD of AIDS in order to determine the number of HIV infections occurring in past years (CDC 1995). With information on past HIV infections and AIDS cases, plus the use of the IPD again, current HIV prevalence can be estimated. This approach needs adequately complete surveillance of AIDS cases and an accurate estimate of the IPD. It is limited by its inability to approximate HIV infections in recent years with any precision and, more significantly, the effect of antiretroviral therapy on the IPD has rendered back-calculation currently ineffective in estimating prevalence. Table 2.1 overleaf provides figures of UK HIV prevalence witnessed in the years 1999 (DH 2000); 2001 (DH 2001[a]); and 2002 (HPA 2003). HPA (2003) describes how these figures were calculated, i.e. through combining the data from Unlinked Anonymous Surveys with estimates of the size of the population in various exposure categories derived from the National Survey of Sexual Attitudes and Lifestyles (NATSAL) and Census 2001 population estimates (National Statistics). The total population of England and Wales, aged 16-44, is divided into mutually exclusive behavioural categories relevant to HIV infection risk. The undiagnosed HIV prevalence for each group is multiplied by its population size to get the total number of undiagnosed HIV infections which is then added to the prevalent diagnosed HIV infections from each group, derived from SOPHID (Survey of Prevalent HIV Infections Diagnosed). These estimates are scaled up to include adults aged over 44

Table 2.1 **Estimates of prevalent HIV infections amongst adults in the United Kingdom at the end of 1999; 2001 and 2002, HPA (2003).**

	1999			2001[1]			2002		
Exposure Category	Number Diagnosed[2]	Number Un-diagnosed[3,4]	Total	Number Diagnosed[2]	Number Un-diagnosed[3,4]	Total	Number Diagnosed[2]	Number Un-diagnosed[3,4]	Total
Homo/bisexual men	*12,900*	*4300 (25%)*	*17200*	*15,300*	*4500 (23%)*	*19800*	*17,100*	*5500 (24%)*	*22600*
IDU Males and females	*1500*	*100 (6%)*	*1600*	*1400*	*300 (18%)*	*1700*	*1400*	*300 (18%)*	*1700*
Heterosexuals									
Male	*2800*	*3600 (56%)*	*6400*	*4400*	*4500 (51%)*	*8900*	*5800*	*4800 (45%)*	*10,600*
African				*2700*	*2400*	*5100*	*3800*	*2500*	*6300*
Non-African				*1700*	*2100*	*3800*	*2000*	*2300*	*4300*
Female	*4100*	*3300 (45%)*	*7400*	*6900*	*3700 (35%)*	*10,600*	*9300*	*4600 (33%)*	*13900*
African				*4900*	*2000*	*6900*	*6800*	*2300*	*9100*
Non-African				*2000*	*1700*	*3700*	*2500*	*2300*	*4800*
Total	*6900*	*6900 (50%)*	*13800*	*11,300*	*8200 (42%)*	*19500*	*15100*	*9400 (38%)*	*24500*
Blood Products[5] Male and Female	*600*	*0 (0%)*	*600*	*700*	*0 (0%)*	*700*	*700*	*0 (0%)*	*700*
Grand Total	*21,900*	*11,300 (34%)*	*33,200*	*28,700*	*13,000 (31%)*	*41,700*	*34,300*	*15,200 (31%)*	*49,500*

[1] 2001 re-estimated using newly developed adjustments.

[2] Numbers diagnosed were obtained from SOPHID and SCIEH, adjusted for under-reporting and failure to access services.

[3] Numbers undiagnosed derived for England, Wales and Scotland using data from Natsal 2000 (32) and the Unlinked Anonymous programme in an extension of the method previously described (Petruckevitch *et al.* Genitourinary Medicine 1997; 73: 348-54).

[4] Numbers undiagnosed for Northern Ireland derived by using exposure specific factors.

[5] All cases infected through blood and blood products or tissue were assumed to be diagnosed.

and elsewhere in the UK. Note that since undiagnosed HIV estimates are not available for each of the behavioural groups, prevalence estimates are derived through adjusting the Unlinked Anonymous estimates using behavioural survey data. In 2002, just under half (46%) of the HIV infections in adults were among homo/bisexual men (Table 2.1). 24% (5500) of these homo/bisexual men were unaware of their infection, accounting for 36% of the estimated 15,200 undiagnosed prevalent infections. Another important point to note from Table 2.1 is the estimated 24,500 adults who acquired their infection through heterosexual contact by 2002, of which 9,400 (38%) were unaware of their infection; the highest proportion of undiagnosed infection was in this category with 33% of female and 45% of male heterosexuals unaware of their infection. Black-African men and women accounted for 63% (15,400) of the total prevalent infections in heterosexuals and 51% (4800) of the undiagnosed heterosexual infections. Over all exposure categories, at the end of 2002, an estimated 49,500 adults aged over 15 were living with HIV in the UK, 15,200 (31%) of whom were unaware of their infection.

AIDS data

In comparison to HIV data, AIDS figures can be considered to be fairly reliable. The severe AIDS-defining conditions, such as PCP and KS which necessitate medical intervention, make it much more probable for diagnosis of AIDS to be documented. The changes in the European Centre for the Epidemiological Monitoring of AIDS (Ancelle-Park 1993) definition of AIDS, as discussed earlier in section 1.1.3, have fortunately not had a large impact on the AIDS data; in fact, the surveillance of cases with AIDS has remained important for trend assessment because of the relative constancy of the case-definition and completeness of the data. However, the expansion of the US definition of AIDS in 1993 (CDC 1992[a]) created an immediate artificial increase in AIDS incidence data which then decreased in 1994/1995 (AIDS Knowledge Base 1999). Such fluctuations due to changes in the AIDS definition complicate the interpretation of the AIDS data since the observed data are not consistent over time. Also, datasets based on separate definitions are only examinable in comparison to one another after serious alterations (Jager *et al.* 1993).

Cautious examination of AIDS incidence data can help to depict sub-epidemics, for example, by exposure group, geography, race or ethnicity (Cantoni *et al.* 1995 and CDC

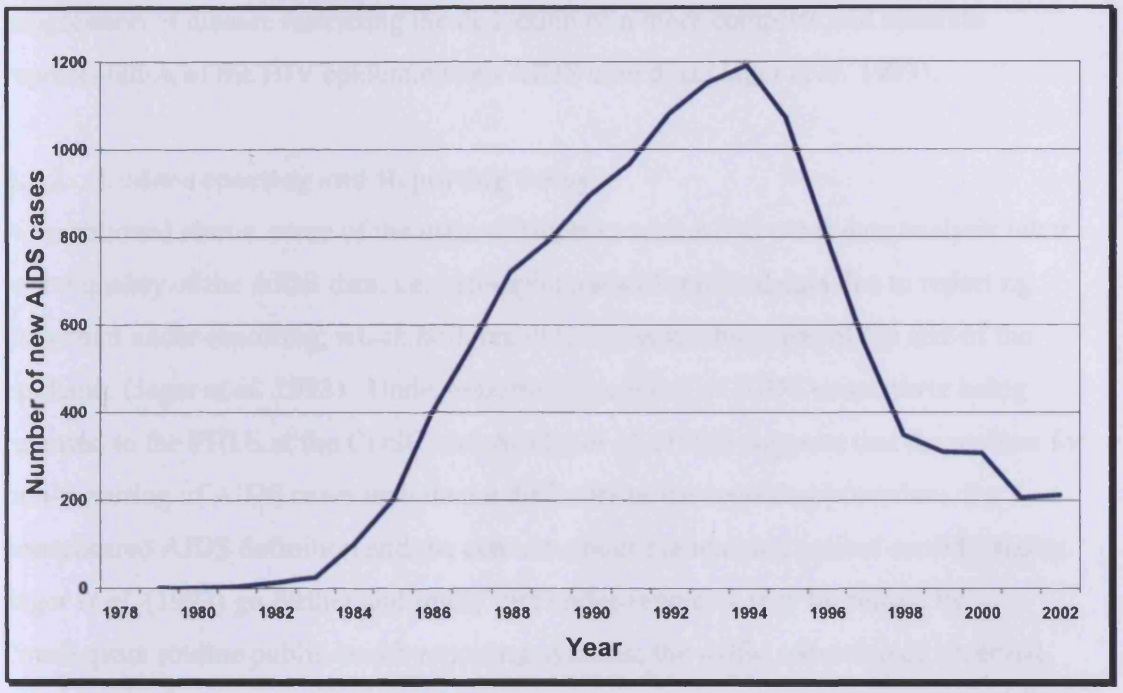

Figure 2.3 **AIDS incidence in homo/bisexual men in the UK by year of diagnosis**

1997[b]). Analysis of AIDS cases in transmission categories labelled 'other' and 'undetermined' has been used to study rare or supposedly new modes of transmission (CDC 1994). Figure 2.3, above, shows the new AIDS cases in homo/bisexual men (excluding homo/bisexual IVDU's) in the UK, by year of diagnosis (EuroHIV 2003). Anonymous, individual data on all cases reported in the UK (and the other 51 countries of the WHO European Region) since the beginning of the epidemic are reported to EuroHIV every 6 months, according to a standard data file specification. After validation, these data merge to form the European Non-Aggregate AIDS Data Set (ENAADS) which is the main dataset used throughout this thesis and which the data applied in Figure 2.3 was extracted from (as listed in Appendix 2.1). The analysis of AIDS case data shown in Figure 2.3 involves empirical problems, such as data quality (AIDS data, despite its improved reliability compared with HIV data, suffers from under-reporting and reporting delay, as discussed below) and the unknown outcomes of human intervention (for instance, prevention and early treatment with antiretroviral drugs), and methodological problems, which may stem from inadequate knowledge about the

progression of disease restricting the deduction of a more complete and accurate representation of the HIV epidemic from AIDS case data (Jager *et al.* 1993).

2.3.2 Under-reporting and Reporting Delay

As mentioned above, some of the main difficulties with AIDS cases data analysis relate to the quality of the AIDS data, i.e. incompleteness of reported data due to reporting delay and under-reporting, which both result in an underestimation of the size of the epidemic (Jager *et al.* 1993). Under-reporting is a result of AIDS cases never being reported to the PHLS at the CDSC. McAnulty *et al.* (1992) suggests that the reasons for non-reporting of AIDS cases include the difficulty of the reporting procedure, the complicated AIDS definition and the concern about maintaining patient confidentiality. Jager *et al.* (1993) go further and imply that under-reporting may be caused by "inadequate routine public health reporting systems; the wilful reduction of observed numbers; inadequate and/or inaccessible health services that fail to detect people with AIDS; lack of standardised procedures (between regions) for the clinical diagnosis of AIDS; and the use of unspecific case definitions". The level of under-reporting is country specific and adjustments in Europe range from 0% to 25% (EuroHIV 2003). For the UK, the Day Report (1993, 1996) assumes an under-reporting rate of 13%, which coincides with estimates produced by Evans & McCormick (1994) who state that 12-14% of AIDS cases are not reported. Chin (1991) proposed that the estimated cumulative numbers of AIDS cases in Africa up to 1991 was 970,000 cases, whereas only 129,066 cases had been reported, suggesting that AIDS case reporting in developing countries is extremely unreliable and are, consequently, of restricted worth in terms of health planning. Under-reporting may have an effect on the reported incidence of AIDS over the entire epidemic and the real magnitude of the HIV epidemic might also be underestimated since infected people could die before acquiring AIDS (Jager *et al.* 1993). It is widely recognised that a reporting delay exists between the time a physician diagnoses a new case of AIDS and reports the fact to the AIDS surveillance centre for the country concerned. This reporting delay results in difficulties for the analysis of AIDS case data, as suggested above. Over 90% of reports of first UK diagnoses of HIV/AIDS for a given year are received at PHLS-CDSC by the end of June in the following year.

The remaining diagnoses may not be reported for several years (CDSC 2002). Modellers invariably work with the data for reported cases of AIDS due to the reliability of the date of report, and the fact that sometimes reported cases are not filed with an associated date of diagnosis. An adjustment is required, of course, either by amending the reported data prior to using them for fitting (this is the method used throughout this thesis) or by specifically modelling the reporting delay endogenously (Dangerfield & Roberts 1994). Downs *et al.* (1988), Rosenberg (1990), Harris (1987), Heisterkamp *et al.* (1989) and Brookmeyer & Liao (1990[a]) have developed techniques for directly estimating AIDS incidence adjusted for delay. Whereas, Cox & Medley (1989) produced expected future AIDS incidence by approximating the delay distribution, and combining this with a relevant curve fit for estimations.

2.4 Parameters within the Cardiff HIV/AIDS Epidemic Model

2.4.1 The Entry Rate

As previously defined, the entry rate term, Λ, is calculated in its simplest form using the expression $\Lambda = \lambda N_{1978}$. We assume that $\lambda = \mu_1$, implying that arrival into the model equals the exit from the model in absence of the HIV/AIDS epidemic i.e. if the HIV/AIDS epidemic was non-existent, then the size of the Susceptible population would be expected to remain relatively stable, with no cause for significant increases or decreases. The term N_{1978}, the size of the high risk homosexual population at the start of the epidemic (at time t = 0), is a constant which involves some difficulty in estimating. The use of N_{1978} is further detailed in work by Anderson (1982) and Bailey (1991, 1992[c], 1993, 1994[a], 1994[b], 1997), who also use the form λN_{1978} for the entry rate. Another expression for the entry rate could be $\Lambda = \lambda[X(t)+Y(t)+A(t)]$, where $X(t)+Y(t)+A(t)$ represents the number of homosexuals taking part in high risk activities at time t. The assumption here is that entry into the High Risk Susceptibles equals deaths in High Risk categories from causes other than AIDS, given that $\lambda = \mu_1 = \mu_2 = \mu_3$. This form of the arrival rate is time-dependent and will decrease as the population decreases, i.e. in the latter stages of the epidemic. Snary (2000) goes into more detail comparing these two

different versions of an entry rate and concludes that the form $\Lambda = \lambda N_{1978}$ is the more realistic option. Later on in this thesis, further discussion of this parameter will take place, including the estimation of λ, N_{1978} and/or A.

2.4.2 The rate of transition from High Risk to Low Risk

An attribute of this HIV/AIDS epidemic model, not evident in all other infectious disease models, is the capability of Susceptibles, Infectives and AIDS cases to move between two levels of at-risk behaviour (Griffiths & Williams 1994). Furthermore, within this model it is only possible to transfer from High Risk to Low Risk behaviour except on diagnosis with AIDS, that is, it is not expected for an individual to revisit their previous risky behaviour once they have relocated into the low risk category. One such circumstance, where an individual may move from a High Risk category to a Low Risk category, could be as a result of media campaigns encouraging homosexuals to change their lifestyles from participating in High Risk sexual activities to Low Risk (Griffiths & Williams 1994). The parameters for each of the sub-populations (Susceptibles, Infectives and AIDS cases) relating to the transition from High Risk to Low Risk, as shown in Figure 2.2 in section 2.2.2, are ν_1, ν_2 and ν_3 respectively. The assumption that homosexuals will not go back to their prior High Risk behaviour, except on diagnosis with AIDS, eases the complexity of the model and restricts the number of parameters to be estimated, which is beneficial. Snary (2000) remarks that there is some suggestion that homosexual men can relapse to their previous unsafe behaviour, as illustrated by the trends in other sexual diseases; in particular, rectal gonorrhoea reports saw a rise in the years 1990 and 1991 (Riley 1991; Waugh 1991; CDR 1998). An alteration in attitudes, and consequently behaviour, of this kind could be caused by a number of factors, including: complacency; lack of concern due to the introduction of new treatments (Kelly *et al.* 1998 and Van de Ven *et al.* 1999) and a drop in media coverage.

2.4.3 The proportions of individuals who become or stay High Risk

Parameters a, b and g, see Figure 2.2, will be discussed here. To begin with, the parameter a is of significance because of the effect it has on the number of newly HIV infected homosexuals who continue to partake in high risk sexual activities, as opposed to changing their behaviour to low risk. Thus, this parameter directly influences the number of infectives in both the High Risk and Low Risk sub-populations. As a consequence of this, the parameter also has an impact on HIV incidence, due to the incidence rate, α, as seen in equation (2.6) below. Furthermore, due to the affect that α has on the other categories in the model, all of the sub-populations will be determined, by some extent, by the value of parameter a. It can be argued that since most individuals are not aware of their precise date of HIV infection, they will continue to practice high risk sexual activities, even after they have contracted HIV. Additionally, even if aware of their new infection status, homosexuals may choose to continue practicing high risk behaviour. Thus, it is expected that a will take a high value; Snary (2000) employs a value of $a = 0.9$. The parameter that represents the proportion of High Risk Infectives, b, who continue to participate in high risk sexual activities on being diagnosed as having contracted AIDS, and the parameter that reflects the proportion of Low Risk Infectives, g, who on diagnosis with AIDS decide to commence participating in high risk sexual activities, are considered next. Any alteration in the value of the parameters b and/or g would mostly affect the two sub-populations A(t) and Z(t); that is, High Risk AIDS cases and Low Risk AIDS cases respectively. To see the effect that these parameters have on the populations, refer to Snary (2000) who experiments with setting $b = g = 0$. This means that all existing AIDS cases are Low Risk, i.e. all in the category Z(t), since no infected homosexuals progressing to AIDS, continued or began participating in high risk sexual activities. More likely than both b and g being equal to zero, are the values $b = 0.5$ and $g = 0.1$, which were suggested by Wheeler (1990); England (1997) and Lowrie (2000). This implies that half of those infected, practising high risk behaviour, will continue to do so once diagnosed with having full blown AIDS, and that 10% of Low Risk Infectives will change their lifestyles and commence high risk behaviour, once AIDS is diagnosed.

2.4.4 The Incidence Rate

Let us consider the parameter denoted by α, which represents the rate at which homosexual men become infected in a time interval δt. In this model, it is assumed that α, denoting the rate at which High Risk Susceptibles move to the infected, takes the form:

$$\alpha = \beta c\,[Y(t)+A(t)]/[X(t)+Y(t)+A(t)] \qquad \ldots (2.6)$$

As is apparent from equation (2.6), α is strongly dependant on the term βc, the infectivity rate where β is the transmission rate per sexual contact and c is the mean number of sexual contacts per unit time. The infectivity rate is discussed in detail in the next section of this chapter, section 2.4.5. The latter term within this expression for α, $[Y(t)+A(t)]/[X(t)+Y(t)+A(t)]$, represents the probability that a particular partner chosen at random is in fact infected with HIV or AIDS (Griffiths & Williams 1994).

2.4.5 The Infectivity Rate

The infectivity rate is a product of the rate at which a Susceptible contracts the virus from an infected partner during each sexual contact, β, and the average number of sexual contacts, or acts, per unit time, c. Anderson (1988) contended that βc is approximately equal to 1, which was initially the value used in the majority of models depicting the epidemic. This suggested value for βc stems from derived estimates of $\beta = 0.1$ and $c = 10$. However, many authors, including Winklestein *et al.* (1988), distinguished a noticeable variation in behaviour from about 1985 onwards, possibly due to the increase in advertising campaigns creating a larger amount of public awareness of the HIV/AIDS virus (Garfield 1994). Consequently, βc was assumed to diminish to a value of approximately 0.4 in the model dating from 1985 (Griffiths & Williams 1994). Snary (2000) shows the significant impact the value of the infectivity rate has on the size of the HIV/AIDS epidemic by implementing different values of βc into a model with all other parameters remaining equal. Within this work by Snary, βc is assumed constant, but due to the possible changes in behaviour, as discussed above, this is not a realistic assumption. In order to assess and quantify these changes in behaviour, the number of reported cases of rectal gonorrhoea in homosexuals can be used as a good indicator of

unprotected sexual activity. Reports to the Communicable Disease Surveillance Centre (CDSC) declined between 1985 and 1989, as expected, however, they then increased in 1990 and 1991. Evans *et al.* (1993) collated information on rectal gonorrhoea; hepatitis B; newly diagnosed HIV; seroconversions in men who have sex with men; and new episodes of gonorrhoea and syphilis, in a study they performed confirming that all of these indicators reveal a consistent trend of worsening sexual behaviour from 1990 onwards, with increasing numbers of individuals participating in risky sexual activities. The improved sexual behaviour and attitudes during the mid and late 1980's meant that the AIDS epidemic did not reach the feared extremes that were originally predicted; however, the relaxation in homosexual routines will cause the course of the epidemic to change once more; any deterioration back to the pre-1985 value of βc would result in another breakout of the epidemic (Griffiths &Williams 1994), this time perhaps reaching the levels that were so feared before.

2.4.6 The Incubation Rate

The AIDS incubation period is classified by Dangerfield (1999) as the delay in time between an individual being infected with HIV and the ensuing diagnosis with AIDS. Thus, the incubation rate is defined as the rate at which HIV Infectives transfer to AIDS cases. Consequently, the incubation time is a vital constituent of any HIV/AIDS epidemic model and is, unfortunately, particularly hard to estimate due to the fact that most infectives are unaware of their exact time of HIV infection. In 1999, Dangerfield assumed the incubation period (IP) to be approximately ten years, with this average duration increasing due to treatment being widely accessible to those who are HIV-positive. Since 1987, studies have shown that treatments have lengthened the incubation period by a significant amount as expected due to their aim of prolonging life (Gail *et al.* 1990 and Keet *et al.* 1996). From the time when cocktail therapies became widely available in 1996, the IP has increased even further; in fact, the increasing length of survival time is ongoing due to the changing population to one starting antiretroviral therapy earlier in the progression of HIV, with more treatment-naïve patients initiating combination therapy. Also, the IP is expected to gradually lengthen over time, due to increased knowledge, experience and understanding of when to start treatments, when to

'switch' treatments (due to lack of virological response or adverse events) and what to switch treatments to, i.e. an unique and different combination of anti-HIV drugs which would be most effective for specific individuals dependant upon such factors as treatment history. The length of the incubation period is discussed in greater detail later on in this thesis, as it poses some of the most important issues within our model.

It is possible for reliable estimates of the incubation period to be obtained; Beral *et al.* (1998) and Porter *et al.* (1999) are two studies amongst many that use dates of seroconversion to estimate the incubation period instead of the exact date of infection whilst Longini *et al.* (1989[a]) estimated the incubation period using a transfusion cohort. Cohorts of haemophiliacs or transfusion recipients are often used to estimate the incubation period as they can offer dependable information on the date of infection with HIV. Also, individuals with both negative and positive HIV tests can also be of use since one can assume the date of infection is the mid-point between these two tests (Brookmeyer & Gail 1994).

Assuming that the incubation period has a negative exponential distribution, the mean incubation rate, γ, is modelled by simply taking the reciprocal of the mean incubation period. The assumption here is that the value γ is independent of whether an infected individual is in either the high or low risk categories. Previously, some researchers have suggested that the Weibull distribution is suitable for modelling the incubation period, maybe due to the fact that this distribution is widely used in other survival studies. Over the years, however, Gamma distributions have become more renowned for their aptness, given that the hazard of AIDS is now known to rise but then plateau after eight years following seroconversion. One reliable estimate was given by Hendriks *et al.* in 1993 who assumed a gamma incubation period distribution (IPD); using data from a cohort of homosexual men they proposed a treatment-free IP of 10.2 years. It is not feasible to depict either a Weibull or a Gamma distribution in integro-differential equation format. However, it is possible to render an Erlang distribution into integro-differential equation format, which is fortunately an appropriate distribution for the incubation period as it is simply a gamma distribution with an integer shape coefficient and presents a hazard function which increases at a slowing rate (Dangerfield 1999).

Heisterkamp *et al.* (1992) discuss the idea of introducing two different time scales into an

HIV/AIDS model; they are calendar time and time since infection for each individual. This development within a model would lead to several integral-differential equations (Blythe & Anderson 1989[b]) which would be complicated to analyse. Nevertheless, by implementing the distributed modelling approach, as shown by Blythe & Anderson (1989[a], 1989[b]) and Bailey (1964), they are easily accommodated. The population segregates into its customary classes (Susceptibles, Infectives and AIDS cases), where each category in turn is split into a series of sub-divisions with incubation duration defined by a negative exponential distribution. Then, since a sum of identical negative exponential distributions is equivalently a gamma distribution (or after a suitable reparameterization, a χ^2-distribution as used by Bailey in 1964), a good estimate to the incubation distribution is achieved, as discussed above. In fact, Blythe and Anderson (1989[b]) demonstrate the use of a weighted sum of negative exponential distributions to account for the distribution of the incubation period. Longini *et al.* (1989[a], 1989[b]) propose a Markov stage model for CDC classes and give estimators for the duration of each stage (Heisterkamp *et al.* 1992). This approach will be incorporated throughout this thesis and is discussed in greater detail within the next section of this chapter.

2.4.7 The Death Rate

The mean death rate (that is, the rate at which AIDS cases die from AIDS), i.e. the reciprocal of the mean AIDS survival time, is another crucial parameter within the HIV/AIDS epidemic model. The official definition of the AIDS survival time is the length of time from the diagnosis of AIDS to AIDS-related death. It permits the calculation of AIDS prevalence, that is, the number of people living with AIDS at a particular point in time. As expected, due to the introduction of recent treatments and therapies for numerous AIDS defining conditions, the value of the death rate has decreased (CDC 1997[c], 1999[a] and Fischl *et al.* 1987). It is expressed by $\omega = 1/(\text{mean AIDS survival time})$ and, unlike for the IP described above, due to the reliability of data on the time of AIDS diagnosis and AIDS death, both AIDS survival time and the death rate, are reasonably uncomplicated to approximate.

In the past the AIDS survival time was predicted at being no longer than a year due to the severity of the damage on the immune system caused by HIV. In fact, the AIDS

Table 2.2 **Median UK AIDS Survival time (years) for year of diagnosis.**

CALENDAR YEAR	ENAADS	BECK *ET AL.* 1994	HILLMAN *ET AL.* 1997	ROGERS *ET AL.* 1997
1982	1.01	1.22		0.887
1983	0.867	1.22		0.887
1984	0.982	1.22	0.783	0.887
1985	1.19	1.22	0.783	0.887
1986	0.968	1.22	0.783	0.887
1987	1.41	1.75	2.27	1.53
1988	1.63	1.75	2.27	1.63
1989	1.78	1.75	2.27	1.69
1990	1.90		2.27	1.62
1991	1.90		2.27	1.62
1992	1.93		2.27	
1993	1.75		2.27	
1994	2.16			

Knowledge base (1999) estimated the mean survival time to be between 10 and 13 months prior to 1986. Many studies note the increase in survival time from 1987 onwards, including those by Beck *et al.* (1994[b]); Hillman *et al.* (1997) and Rogers *et al.* (1997), as shown in Table 2.2 above. Straight comparisons are not applicable between these datasets represented in Table 2.2 since methods of survival analysis, data, risk groups and AIDS defining criteria may differ. However, all datasets agree that from 1987 onwards the AIDS survival has increased.

It is worth noting at this point that although the death rate has a significant effect on the model with respect to the numbers whom die from AIDS and, consequently, the AIDS prevalence, a change in value of the death rate, ω, will not alter the rest of the model predictions by a largely significant amount, i.e. AIDS incidence, HIV incidence and HIV

prevalence. Snary (2000) shows how different values for the death rate affect the AIDS prevalence numbers in her thesis; not surprisingly, Snary illustrates that 'the longer the AIDS survival time (or the smaller the death rate) the higher the peak for the AIDS prevalence'.

2.5 The Introduction of a Staged Incubation Period Distribution

2.5.1 The introduction of Stages

Since the start of the epidemic, the natural history of HIV infection has been viewed as a staged process (Longini *et al.* 1996). This section discusses dividing both the High and Low Risk Infective sub-populations, Y(t) and V(t), into m stages, thus modelling an Erlang type distribution as the incubation period distribution (IPD), as seen in Figure 2.4, overleaf.

The Cardiff HIV/AIDS epidemic model in Figure 2.4 illustrates the incorporation of m stages within the infective categories. This proposal of sub-dividing one of the populations within the model into a number of stages results from the theory of Erlang queues (Snary 2000). The Erlang distribution (E_m) has overall mean rate γ and is mathematically equivalent to m negative exponential phases, each of mean rate $m\gamma$. The probability density function (p.d.f.) of the Erlang distribution is expressed as follows:

$$f(t) = \frac{m\gamma(m\gamma t)^{m-1}e^{-m\gamma t}}{(k-1)!}$$

For notation, let the transition rate per unit time from stage i to stage i+1 be γ_i, where i = 1, ..., m and stage m+1 relates to AIDS. This notation is applied due to the assumption that there is only '1-step' forward movements between stages. Also, we denote $Y_i(t)$ and $V_i(t)$ (with i=1, ..., m) to be the number of HIV Infectives in stage i of the High Risk and Low Risk sub-categories respectively.

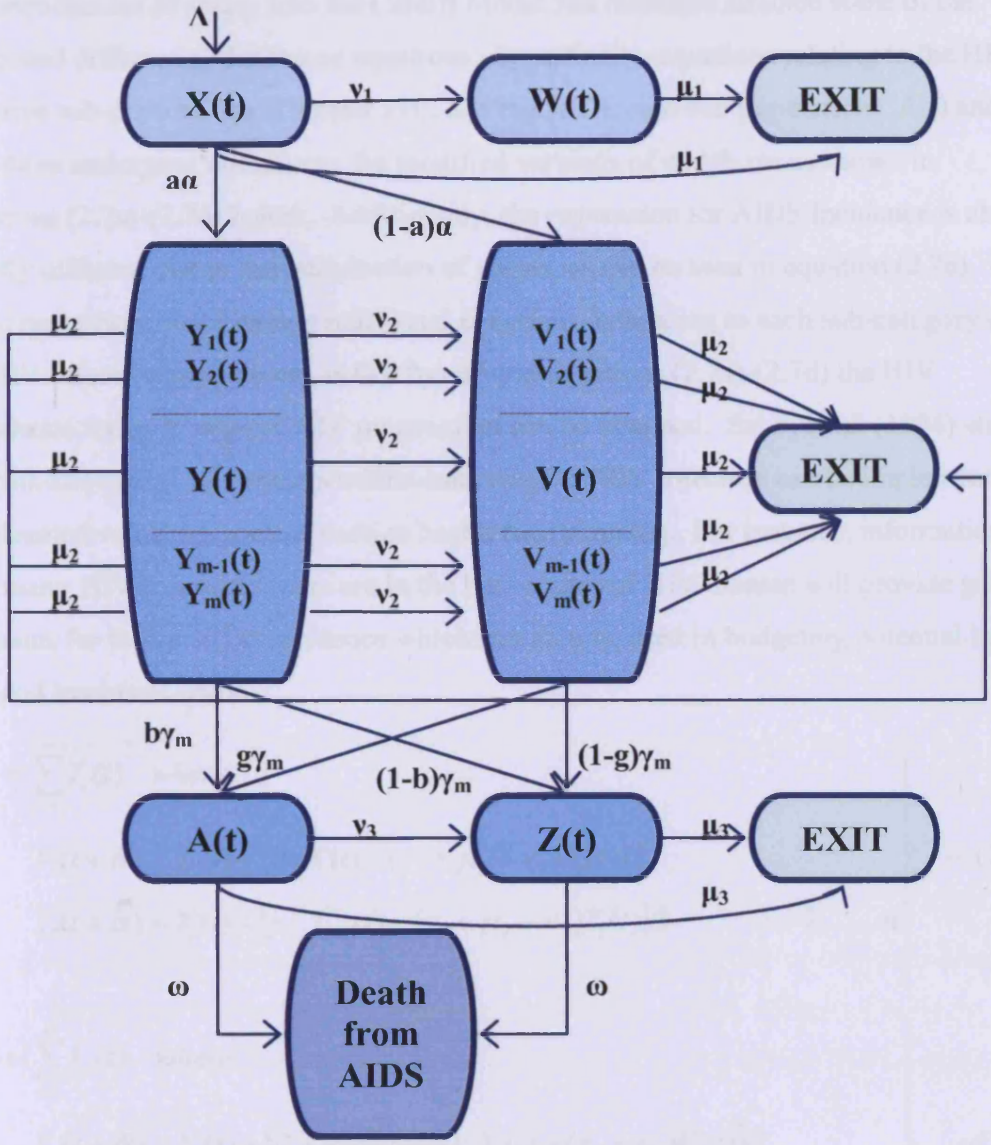

Figure 2.4 **The Cardiff Model with m stages in the Infective sub-populations.**

The same assumptions as previously employed to the basic (one stage) Cardiff HIV/AIDS model are applied here. Further assumptions for this staged model include the concepts that a homosexual will enter the HIV Infective category via stage 1, of either High or Low Risk infection, and must be in the final stage of HIV infection before AIDS can be contracted. In Section 2.5.2, IPD's which permit a progression to AIDS from other stages of HIV infection, as well as the end stage, will be discussed.

The introduction of stages into the Cardiff Model has therefore affected some of the associated differential-difference equations. Specifically, equations relating to the HIV Infective sub-populations, Y(t) and V(t), and the AIDS case sub-populations, A(t) and Z(t), have undergone alterations; the modified versions of which are as shown in equations (2.7a)-(2.7d) below. Additionally, the expression for AIDS Incidence is also slightly different due to the introduction of stages, as can be seen in equation (2.7e). One of the many benefits of having individual equations, belonging to each sub-category of the HIV Infective populations, is that by solving equations (2.7a)-(2.7d) the HIV prevalence for each stage of HIV progression can be obtained. Sabin *et al.* (1994) state that this knowledge of numbers within each stage of HIV infection can be implemented, and deemed valuable, in areas such as health care planning. For instance, information on how many HIV Infectives there are in the later stages of HIV disease will provide good estimates for future AIDS incidence which can then be used in budgeting potential health care and treatment costs.

$$\left.\begin{aligned} &Y(t)=\sum_{i=1}^{m}Y_i(t) \quad \textit{where} \\ &Y_1(t+\delta t)=Y_1(t)+\left[a\alpha X(t)-(\gamma_1+\mu_2+\nu_2)Y_1(t)\right]\delta t \\ &Y_i(t+\delta t)=Y_i(t)+\left[\gamma_{i-1}Y_{i-1}(t)-(\gamma_i+\mu_2+\nu_2)Y_i(t)\right]\delta t \qquad i=2,\ldots,m \end{aligned}\right\} \quad \cdots(2.7a)$$

$$\left.\begin{aligned} &V(t)=\sum_{i=1}^{m}V_i(t) \quad \textit{where} \\ &V_1(t+\delta t)=V_1(t)+\left[(1-a)\alpha X(t)+\nu_2Y_1(t)-(\gamma_1+\mu_2)V_1(t)\right]\delta t \\ &V_i(t+\delta t)=V_i(t)+\left[\gamma_{i-1}V_{i-1}(t)+\nu_2Y_i(t)-(\gamma_i+\mu_2)V_i(t)\right]\delta t \quad i=2,\ldots,m \end{aligned}\right\} \quad \cdots(2.7b)$$

$$A(t+\delta t)=A(t)+\left[b\gamma_mY_m(t)+g\gamma_mV_m(t)-(\nu_3+\mu_3+\omega)A(t)\right]\delta t \qquad \cdots(2.7c)$$

$$Z(t+\delta t)=Z(t)+\left[(1-b)\gamma_mY_m(t)+(1-g)\gamma_mV_m(t)+\nu_3A(t)-(\mu_3+\omega)Z(t)\right]\delta t \qquad \cdots(2.7d)$$

$$\textit{AIDS Incidence}=\gamma_m\left[\sum_{i=1}^{52}Y_m(i)+\sum_{i=1}^{52}V_m(i)\right] \qquad \cdots(2.7e)$$

As for HIV infectives, individuals within the AIDS case population can also be sub-divided into stages of AIDS progression indicating a deterioration of health. However, once an individual has been diagnosed as having contracted full-blown AIDS, it is expected that survival time is relatively short at approximately only 1 or 2 years. For this reason, AIDS stages have not been incorporated in the Cardiff model. In concordance with Snary (2000), the research within this thesis is mostly concerned with the effect that new treatments have imposed on the HIV incubation period and on the AIDS survival time, taken as a whole.

2.5.2 Staged Incubation Period Distributions

In order to create the stages within HIV progression, markers such as CD4 T+ cell count, viral load and the amount of health care that an individual is receiving, offer themselves as natural tools of definition. The most commonly used marker for an incubation period distribution is CD4 T+ cell count; this has been used by Longini *et al.* (1991, 1993, 1996), Hendriks *et al.* (1996), Satten & Longini (1996) and Snary (2000).
The initiative of a staged model has not only been effectively put into operation within the HIV/AIDS epidemic but also other diseases such as cancer (Longini *et al.* 1989[a]).
The Walter Reed staging system was developed in 1986 (Redfield *et al.* 1986), and various staging systems have been in practice ever since. An accepted mathematical tool for modelling a process, such as HIV, is a staged Markov model, which has been exercised in the following fundamental topics, quoted below, of HIV/AIDS research (Longini *et al.* 1996):

'1. To describe the natural history of HIV infection (Longini *et al.* 1989[a], 1989[b], Longini 1990, Longini *et al.* 1991);
2. To evaluate the effect of covariates on stage-specific progression rates, such as therapy (Longini *et al.* 1993);
3. To predict the stage-specific course of the HIV epidemic in selected populations (Longini *et al.* 1992) and in the USA as a whole (CDC 1992[b], Brookmeyer 1991);
4. To estimate HIV incidence from infection surveys (Satten & Longini 1994);

5. To provide estimates for HIV transmission models used to estimate transmission probabilities (Longini *et al.* 1989[b]) and to investigate the dynamics of the HIV epidemic (Hethcote *et al.* 1991, Jacquez *et al.* 1988, Koopman *et al.* 1991).'

Hendriks (1999) states that a staged Markov model consists of the three main aspects listed below:

- A set of stages,
- Waiting time distributions within each stage,
- Probability distributions of transferring stage once the waiting time is over.

Hendriks *et al.* (1996) and Hendriks (1999) affirm that an advantage associated with the use of Markov models is their full use of data. Arguments exist against the use of a Markov chain for the purpose of modelling the HIV IP, including the suggestion that under a Markov model, incorporating CD4+ T cell count, the time until death (or AIDS) is conditionally independent of time since infection (Brookmeyer & Gail 1994). Further discussions on the benefits and limitations of Markov models can be found in the following publications: Brookmeyer & Gail (1994); Hendriks *et al.* (1996); and Satten & Longini (1996).

The application of a staged IP, particularly when stages are defined by CD4+ T cell count, makes it possible for the model to include antiretroviral treatment and prophylaxis against opportunistic infections. In fact, the use of a Markov model, despite the aforementioned disadvantages, allows the absorption of advised disease staging.

The following subsections within this chapter briefly review some of the staged Markov models developed as HIV incubation distributions as proposed by a number of researchers, including Longini *et al.*, Hendriks *et al.* and Satten & Longini. The work undertaken in this thesis incorporates the use of a deterministic model, thus such distributions for the incubation period are not applicable. However, the possible movements of transfer between the stages of HIV can be applied to both stochastic and deterministic models and are, consequently, of interest when investigating the incubation period in greater detail.

Longini et al.

A regular occurrence in Longini's incubation period distributions is the concept of '1-step' forward movements only. For every individual within the model, the length of time in each stage, contained by the Markov chain, is produced by means of the rate associated with that specific stage (obtained via maximum likelihood techniques). Thus, the probability density function (p.d.f.), or probability distribution, can be established; the mean incubation period, the variance and the mean rate (γ) can also be determined. Longini has considered both a 3- and a 6-stage model. The 3-stage IP, as illustrated in Figure 2.5, below, was developed by Longini *et al.* (1989[a], 1989[b]) and was one of the first staged Markov models.

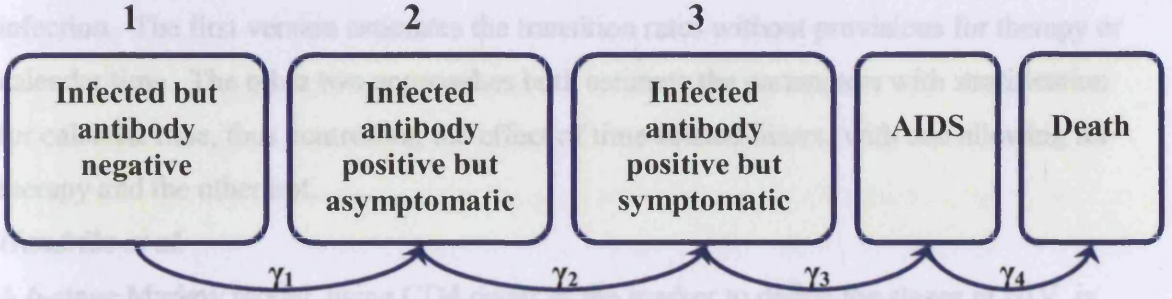

Figure 2.5 **Representation of Longini's 3-stage incubation period distribution.**

The three different states, numbered in Figure 2.5, comprise stages indicative of the progression of HIV infection; the two other stages included within this flow diagram signify the diagnosis of AIDS and where death has resulted due to AIDS.

Snary (2000) provides comparisons between this Longini distribution, the Erlang distribution and 3 Exponential distributions in series; the Longini 3-stage distribution is then incorporated into the Cardiff HIV/AIDS model to demonstrate the use and results when utilizing such an IPD. The same comparisons and analysis are performed by Snary when investigating the Longini 6-stage Incubation Period Distributions (Longini *et al.* 1993, 1996) as illustrated in Figure 2.6 overleaf.

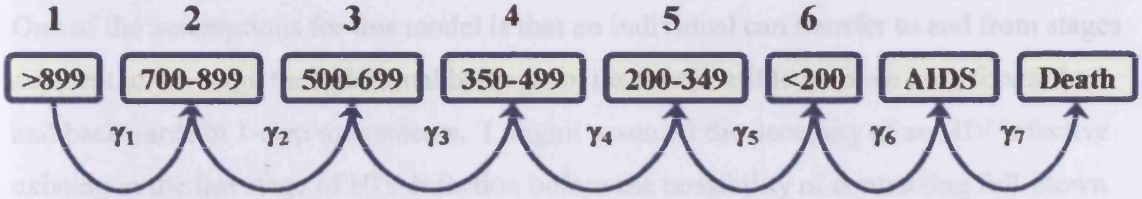

Figure 2.6 **Representation of Longini's 6-stage IPD, stages defined by CD4 Count.**

These use the idea that HIV can be expressed as a chain of advancing, monotonic states, reflected in a mean decline of CD4 cells over time. As with the 3-stage distribution, a Markov model is fitted to the data using maximum likelihood techniques which operate using the formulation of the likelihood function, with respect to an individual's progression through HIV. There are 3 different adaptations of this 6-stage model; each having identical monthly transition rates belonging to the first three stages of HIV infection. The first version estimates the transition rates without provisions for therapy or calendar time. The other two approaches both estimate the parameters with stratification for calendar time, thus controlling the effect of time-related biases, with one allowing for therapy and the other not.

Hendriks et al.

A 6-stage Markov model, using CD4 count as the marker to define the stages in HIV, is employed by Hendriks *et al.* (1996) and Hendriks (1999), in the same way as Longini, as discussed in the previous section. The observed CD4 count data is smoothed before maximum likelihood procedures are put into operation to compute estimates of the transition rates (γ) linking stages. Dissimilar to Longini's '1-step' forward motion only, Hendriks incorporates a more complicated invertible continuous-time Markov model, as displayed in Figure 2.7.

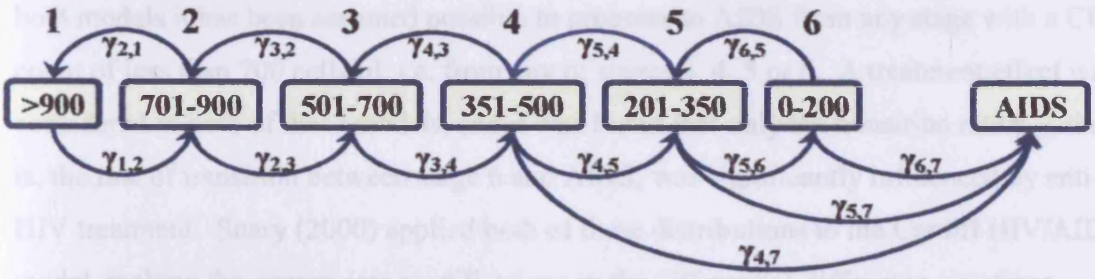

Figure 2.7 **Representation of Hendrik's IPD, stages defined by CD4 count (cells/μl).**

One of the assumptions for this model is that an individual can transfer to and from stages adjacent to the stage the individual belongs to, i.e. it is possible to move both forwards and backwards in 1-step movements. Longini assumed the necessity of an HIV infective existing in the last stage of HIV infection before the possibility of contracting full-blown AIDS, however, as apparent from Figure 2.7, the idea within the Hendriks IPD is that an individual can progress to AIDS from any of the stages 4, 5 or 6, with associated rates of $\gamma_{4,7}$, $\gamma_{5,7}$ and $\gamma_{6,7}$, respectively. The final feature to note, with Hendriks' IPD, is the inclusion of a treatment effect, as with the third Longini 6-stage IPD. Snary (2000) gives a much more in-depth review of this distribution for the incubation period and introduces it to the Cardiff HIV/AIDS epidemic model – resulting in the differential-difference equations being altered to allow for the possible progression to AIDS from stages other than stage 6 and the backward 1-step transitions.

Satten & Longini

These distributions, as illustrated in Figures 2.8(a) and 2.8(b) overleaf, like those produced by Longini and Hendriks, consist of 6 CD4 cell count marker-defined stages. However, one distinct variation, between the Satten & Longini distribution and those created by Longini and Hendriks, is the employment of the statistical procedure of errors-in-variables so as to overcome noisy data and calculate estimates of monthly stage transition rates (Longini and Hendriks conquered this problem by primarily smoothing the data). There are two variations of the Satten & Longini IPD; one is unidirectional (Figure 2.8(a)), whilst the other is bidirectional (Figure 2.8(b)).

The Unidirectional model, as shown in Figure 2.8(a), is composed of forward movements only, progressing one stage at a time through HIV progression. The second model shown here, in Figure 2.8(b), is Satten & Longini's Bidirectional model, which permits a homosexual to transfer to an adjacent stage in either direction, forwards or backwards. In both models it has been assumed possible to progress to AIDS from any stage with a CD4 count of less than 700 cells/μl, i.e. from any of stages 3, 4, 5 or 6. A treatment effect was considered in both of these models, and it was found that only the transition rate $\gamma_{6,7}$, that is, the rate of transition between stage 6 and AIDS, was significantly influenced by anti-HIV treatment. Snary (2000) applied both of these distributions to the Cardiff HIV/AIDS model, making the appropriate modifications in the differential-difference equations,

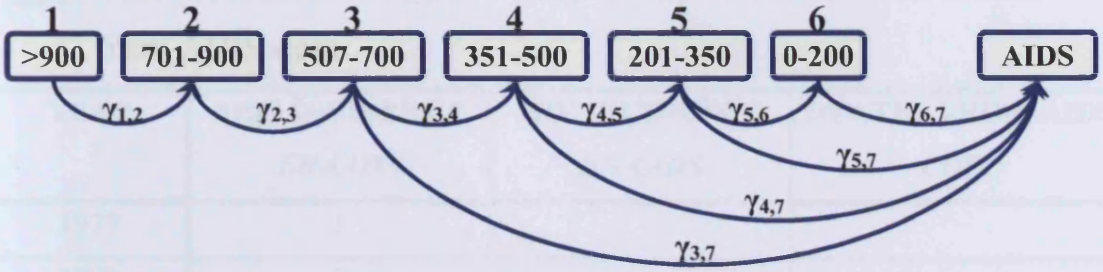

Figure 2.8(a) **Representation of the Unidirectional Satten &Longini IPD.**

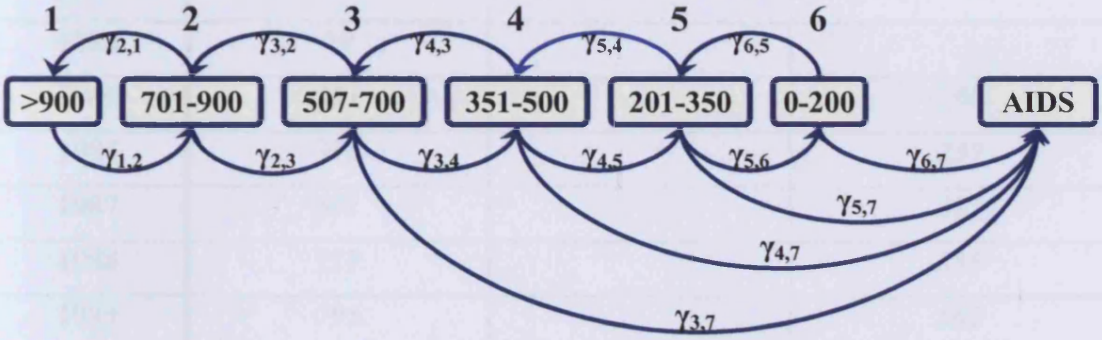

Figure 2.8(b) **Representation of the Bidirectional Satten & Longini IPD.**

noting that the Unidirectional IP is merely a sub-model of the Bidirectional IP, with all backward transition rates set equal to zero. It may also be worth noting at this point that Satten & Longini found the Bidirectional model to create a significantly better fit.

A.2.1 Table of Observed AIDS incidence, HIV incidence and deaths from AIDS data

YEAR	AIDS INCIDENCE *ENAADS*	HIV INCIDENCE *ENAADS*	DEATHS FROM AIDS *CDSC*
1979	*1*		
1980	*0*		
1981	*4*		
1982	*11*		
1983	*24*		
1984	*99*		
1985	*201*		*108*
1986	*396*		*237*
1987	*551*		*317*
1988	*719*		*355*
1989	*795*		*562*
1990	*897*		*654*
1991	*966*		*781*
1992	*1081*		*874*
1993	*1151*		*1056*
1994	*1190*		*1159*
1995	*1071*	*1443*	*1095*
1996	*808*	*1693*	*890*
1997	*559*	*1551*	*390*
1998	*349*	*1506*	*239*
1999	*311*	*1362*	*224*
2000	*308*	*1464*	*215*
2001	*207*	*1534*	*186*
2002	*213*	*1966*	*139*
2003	*179*	*1967*	*155*

CHAPTER 3

5-PARAMETER MAXIMUM LIKELIHOOD TECHNIQUES WITHIN THE CARDIFF MODEL

3.1 Introduction

As previously discussed, numerous parameters within the Cardiff HIV/AIDS Epidemic model are problematical with reference to obtaining reliable values for them. Of particular interest is the infectivity parameter, βc, which denotes the degree of high-risk sexual behaviour that results in the contraction of HIV. As a 'sociological' parameter, βc is dependent on public awareness of HIV infection within the homosexual population and is thus difficult to quantify.

Other parameters of significance within the model that have proven a challenge to estimate include the entry rate into the model, Λ; the initial number of HIV infectives at the start of the epidemic, a_{1978}; and the lengthening proportion, r, placed on the incubation period compared with its duration at the non-treatment stage. In addition, the death rate, ω, despite being measurable through recorded yearly AIDS diagnoses and deaths from AIDS, needs some consideration due to the fact that its value varies over time with the advancement of treatments.

The entry rate, Λ, in its simplest form, is taken as the product of the arrival rate, λ, and the number of High Risk homosexuals in the population at the start of the epidemic, N_{1978}, that is, $\Lambda = \lambda N_{1978}$. The interpretation of the entry rate in this form, however, may be deemed too simplistic and consequently unrealistic. Griffiths *et al.* (1990) question the application of this entry rate within the model, due to the idea that enrolment to the High Risk Susceptible sub-population, X(t), varies over time as a direct result of publicity and changing attitudes towards the virus. One alternative form of the entry rate is $\Lambda = \lambda[X(t)+Y(t)+A(t)]$. This generates a lower peak of the AIDS epidemic than

$\Lambda = \lambda N_{1978}$ produces since the term X(t)+Y(t)+A(t) depicts the total number of individuals within any of the high risk sub-populations at time t. This expression for the entry rate is time-dependant and will decrease as the population decreases accordingly, specifically towards the latter stages of the epidemic. To incorporate the idea of various perceived entry rates into the model, two different methodologies, and consequently two different sets of parameters, have been considered and implemented throughout this work. Firstly, λ and N_{1978} are estimated separately and their product taken to be the total entry rate into the epidemic, Λ. Secondly, the overall entry rate, Λ, is modelled as an independent single parameter, taking on whichever form it may be concluded to hold. In conjunction with this, λ is assumed equal to μ_1 (due to the concept that the constant rate of arriving into the Susceptible category is equal to the constant rate of exiting from the Susceptible category, as a result of natural death or emigration from the model if the AIDS epidemic was not existent), for which the value is derived from population statistics, and N_{1978} is assumed a fixed value of 10,000. This will probably mean that $\Lambda \neq \lambda N_{1978}$, unless due to unlikely coincidence.

The parameter a_{1978}, which refers to the number of HIV positive homosexuals (including AIDS cases) within the UK at the end of 1978, is also subject to interpretation and is consequently problematic in specification. This parameter will be examined in detail within this chapter owing to the fact that the total number of HIV positive homosexuals at the start of the epidemic necessitates distribution over all 6 of the HIV stages, as well as the AIDS stage.

The death rate, ω, can be calculated annually from data given that, by definition, ω = 1 / mean AIDS survival time, with both the date of diagnosis for AIDS and the endpoint of AIDS (death) documented and deemed reliable records. However, due to the continual improvements in treatments, the mean AIDS survival time changes year upon year, thus the death rate varies in accordance with the development of new treatments and therapies. Hence, it is considered here as a parameter for estimation, with data on deaths from AIDS being used to verify, or justify, the results drawn. Later work, in Chapter 4, investigates this parameter in greater detail, including it within the model as a variable parameter, estimated not by the MLE technique but within a separate analysis providing a comparison between its estimated value, as produced by the model, and its computed

value, obtained from available AIDS data.

The final parameter to be considered within this chapter is the parameter r, which is defined as the proportional increase in the length of the HIV incubation period (defined as the time between initial infection with HIV and the eventual onset of AIDS) due to the introduction of antiretroviral treatments prolonging life and postponing the progression to AIDS or any AIDS defining illness. Within the Cardiff model, assuming a constant staged incubation period (where $\gamma_1 = \gamma_2 = \ldots = \gamma_m$), we have:

$$\gamma_i = m/(r \times IP) \qquad i = 1, \ldots, m$$

or

$$r = m/(\gamma_i \times IP) \qquad i = 1, \ldots, m$$

where γ_i are the transition rates between stages assumed equal in value;
m is the total number of stages;
IP is the incubation period prior to treatments;
r is the proportion the IP is lengthened due to the introduction of treatments.

Note that when r = 1, the transition rates are calculated as they were previously, without considering the treatment effect on the IP. Also, note that estimating the parameter r is equivalent to estimating the duration of each of the 6 stages within the lengthened incubation period assuming they are all equal ($1/\gamma_1 = 1/\gamma_2 = \ldots = 1/\gamma_6$), or estimating the transition rates between stages, as formulated above assuming equality ($\gamma_1 = \gamma_2 = \ldots = \gamma_6$). This chapter considers maximum likelihood techniques in order to estimate the parameters discussed above. Numerous researchers, including Bailey (1991, 1992[c]) and Griffiths & Williams (1995), have implemented this method of maximum likelihood to estimate parameters within an epidemic model, such as the Cardiff HIV/AIDS Epidemic model. It is important to note that the practice of maximum likelihood is independent of the model. One limitation of the Maximum Likelihood Estimate (MLE) technique is the assumption that parameters remain static. For many of the parameters within the model this is not the case, predominantly since the introduction of treatments. Moreover,

parameters and distributions are unlikely to be constant due to media campaigns, public awareness and attitudes affecting behavioural patterns over time (Griffiths & Williams 1994). One way of overcoming this disadvantage of the method is to consider a number of MLE's based upon different time eras that are linked together, thus allowing new values for parameters to be investigated at certain time intervals based on behavioural changes and the introduction of treatments. This is contemplated later on in the thesis, specifically within Chapter 4.

Dangerfield & Roberts (1994) used parameter optimisation in a system dynamics approach in order to fit their model (in the analysis of five countries) to the data from each of the five countries individually. Much of the analysis work completed by Dangerfield and Roberts involved optimising the parameters of a transmission model of AIDS spread in the homosexual population (Dangerfield & Roberts 1989; Roberts & Dangerfield 1990[a]). The process of this was described by Dangerfield & Roberts in 1994 as 'numerically intensive work ... where the benefits from the enormous increase in desktop computing power can be realised ... it involves an iterative heuristic search algorithm applied to the multi-dimensional parameter space'. The algorithm employed by Dangerfield & Roberts was originally formulated by Hooke & Jeeves in 1961 and allows the optimisation of parameters as they change value through time; this advantageous characteristic was then instigated by Dangerfield & Roberts (1994, 1996) in their estimation of the following parameters (described here using the notation previously identified within the Cardiff model):

1. c, the mean number of different contacts per unit time,
2. X(t)+W(t), the size of the susceptible population,
3. β, the probability of passing on HIV infection (this differs from that within the Cardiff model; here it is considered as three separate probabilities with respect to the definite stages in the natural history of HIV throughout the long incubation period),
4. The durations of the second and third phases of the assumed three-stage incubation period distribution (that is, $1/\gamma_2$ and $1/\gamma_3$, where $m = 3$).

The nature of the model used by Dangerfield & Roberts (1994), and similarly of the Cardiff model implemented throughout this thesis, permits both prevalence and incidence estimates to be made and, providing the set of parameters are assumed not to vary in the immediate future, it is acceptable to predict the epidemics' outlook over the upcoming years so as to estimate AIDS incidence, as well as HIV incidence, AIDS/HIV prevalence and deaths from AIDS.

The Cardiff HIV/AIDS epidemic model is used to obtain AIDS incidence, HIV incidence and deaths from AIDS, which are attuned consistent with the parameters to be estimated in order to produce an excellent fit with the observed data attained from ENAADS (AIDS and HIV incidence) and CDSC (deaths from AIDS). The observed data utilized for this fit has formerly been adjusted for under-reporting and reporting delays (EuroHIV 2003). However, data over the most recent years may still be deemed unreliable; hence, the model will cover the years 1979-2002 only. Using yearly data from these sources provides 24 observations for AIDS incidence (1979-2002); 18 observations for deaths from AIDS (1985-2002) and only 8 observations for HIV incidence (1995-2002). This small number of observations on which to create the expected AIDS incidence, expected HIV incidence and expected deaths from AIDS, will result in a small number of degrees of freedom within the χ^2 goodness of fit test, if too many parameters are estimated at one time. Snary (2000) investigates using smaller time intervals of 6 months in order to increase the number of degrees of freedom within the χ^2 goodness of fit test. The 6-monthly observed data, however, was somewhat erratic and posed problems when trying to acquire a good, smooth, fit between the observed and the expected data. Comparisons between using different time intervals showed the Maximum Likelihood Estimates to be alike; hence, yearly data and results are stated and analysed within this work.

3.2 The MLE Technique

The first factor within the Maximum Likelihood technique which necessitates deliberation is the statistical distribution to be used to model observed AIDS incidence within each small time period of 1 year, as employed within this work. The Poisson distribution (as implemented by Bailey 1991, 1992[c]; Griffiths & Williams 1995; Griffiths *et al.* 2000; Lowrie 2000; and Snary 2000) offers itself as a suitable distribution to model the number of new AIDS cases for each time period for two main reasons:

A. the AIDS data are fundamentally count data,
B. one essential criterion for the theory of maximum likelihood is that the observed data are independent.

Note, with respect to B above, that the AIDS data may not actually be independent (Bailey 1992[c]); however, in order to adopt the approach of maximum likelihood for the estimation of parameters within the model and to maintain simplicity, the assumption that the observed data are independent is exercised. This assumption is made not only within this thesis, but also in the published accounts of Bailey (1991, 1992[c]); Griffiths & Williams (1995); Griffiths *et al.* (2000); Lowrie (2000); and Snary (2000). The observed AIDS data, used throughout this thesis, is abstracted from the ENAADS dataset (EuroHIV 2003) and is depicted in the probability distribution function (p.d.f.) of the Poisson distribution below (equation (3.1)). Also included within this expression of the p.d.f are the expected AIDS cases which are obtained by solving the differential-difference equations within the epidemic model, i.e. they are the output from the model with which we are creating the best fit possible to the observed data. The probability distribution function (p.d.f.) of the Poisson distribution is as follows:

$$f(\mathrm{a}_i) = \frac{\alpha_i^{\mathrm{a}_i} e^{-\alpha_i}}{\mathrm{a}_i!}, \qquad i = 1,2,...,T \qquad \ldots(3.1)$$

where $a_1, a_2, \ldots, a_T$ = observed AIDS cases for T successive time periods,

$\alpha_1, \alpha_2, \ldots, \alpha_T$ = expected AIDS cases for T successive time periods.

The theory included within this section, describing the MLE technique, is extracted from work by Bailey (1991, 1992[c]). As the title of the estimation method being considered within this chapter suggests, the next step in deriving the maximum likelihood estimates is to determine the expression for the log likelihood of this Poisson model (equation (3.2) below). This log-likelihood is then maximized subject to the expected AIDS cases, that is, the α_i terms.

$$L = \log\left\{\prod_{i=1}^{T} \frac{\alpha_i^{a_i} e^{-\alpha_i}}{a_i!}\right\} = \sum_{i=1}^{T} \{a_i \log \alpha_i - \alpha_i - \log(a_i!)\} \qquad \ldots(3.2)$$

The expected AIDS cases are the terms created by the model itself and from the fact that the model is adjusted in accordance with the parameters to be estimated, it follows that the expected AIDS cases are dependent upon the parameters subject to estimation. In other words, denoting by θ_j, j = 1, ..., n, the set of n parameters in the epidemic model to be estimated, and by $\underline{\theta}$ the vector of these n parameters, we see that the α_i are dependent upon the θ_j. Accordingly, in order to maximise the log-likelihood, the expression L has to be differentiated by each of the parameters to be estimated, θ_j , and the results set to zero to give a set of n simultaneous equations. So, the two vectors below are created:

$$\underline{\theta} = \begin{bmatrix} \theta_1 \\ \theta_2 \\ \vdots \\ \theta_n \end{bmatrix} \qquad \underline{S} = \begin{bmatrix} \delta L/\delta\theta_1 \\ \delta L/\delta\theta_2 \\ \vdots \\ \delta L/\delta\theta_n \end{bmatrix} = \underline{0}$$

If it is not possible to solve these simultaneous equations explicitly, then iterative numerical methods like Newton-Raphson can be used (Kendall & Stuart 1973).
First, consider the scenario of only 1 time period, in which the parameters are to be estimated. This provides an understanding of the basic procedure involved in a clear and uncomplicated notation. After the one-period rationale has been described, the scenario where the parameters are estimated over more than 1 time period is considered.

Univariate scenario

Let θ_0 be the initial approximation to the MLE $\hat{\theta}$. In the univariate case, the vectors $\underline{\theta}$ and $\underline{S}$ consist of the element(s), θ and $\frac{\delta L}{\delta \theta}$ respectively, where L = ln f is the log-likelihood (as derived previously) to be maximised.

$$\left(\frac{\delta \ln f}{\delta \theta}\right)_{\theta=\hat{\theta}} = \left(\frac{\delta \ln f(x;\hat{\theta})}{\delta \hat{\theta}}\right)$$

Given the condition that $\hat{\theta}$ is the maximum likelihood of θ, the result seen in equation (3.3a) is known. Additionally, implementing Taylor's series, the expression for the derivative of the log-likelihood can be approximated as seen in equation (3.3b).

$$\frac{\delta \ln f(x;\hat{\theta})}{\delta \theta} = 0 \qquad \ldots(3.3a)$$

$$\frac{\delta \ln f(x;\hat{\theta})}{\delta \theta} \approx \frac{\delta \ln f(x;\theta_0)}{\delta \theta} + (\hat{\theta} - \theta_0)\frac{\delta^2 \ln f(x;\theta_0)}{\delta \theta^2} \qquad \ldots(3.3b)$$

Furthermore, by rearranging equation (3.3b) in terms of $\hat{\theta}$, using the fact that the subject derivative at present in equation (3.3b) is equal to zero (as shown in equation (3.3a)), we obtain equation (3.4) below. Of particular interest in equation (3.4) is the comparison between the denominator on the right hand side of the formulae and the definition of the information matrix, I, identified below equation (3.4), where E denotes the expected value of the function.

$$\hat{\theta} \approx \theta_0 - \frac{\dfrac{\delta \ln f(x;\theta_0)}{\delta \theta}}{\dfrac{\delta^2 \ln f(x;\theta_0)}{\delta \theta^2}} \qquad \ldots(3.4)$$

$$I = -E\left[\frac{\delta^2 \ln f(x;\theta)}{\delta \theta^2}\right]$$

It is apparent from this comparison that the expected value of the second derivative term shown in equation (3.4) is equivalent to $-I(\theta_0)$, and since a change in the value of θ has little, or no, effect on this second derivative term, the expected value can replace this derivative within the equation for $\hat{\theta}$. Thus, for the univariate case, the iterative procedure is expressed as follows:

$$\theta_{n+1} = \theta_n + \frac{\delta \ln f(x;\theta_n)}{\delta\theta} \Big/ I(\theta_n) \qquad \ldots(3.5)$$

Multivariate scenario

Let θ_j be the initial approximation to the MLE $\hat{\theta}_j$. Then, for large enough T (i.e. a large number of successive time periods), $\hat{\theta}_j$ is asymptotically unbiased and efficient, that is:

$$\hat{\theta}_j \sim N\left\{\theta_j, \underline{I}(\theta_j)^{-1}\right\}$$

Next, for the multivariate case, it can be noted that the variance-covariance matrix, $\underline{V}$, is equal to the inverse of the information matrix, $\underline{I}$, which is defined in the multivariate case as:

$$\underline{I} = -E\left[\frac{\delta^2 L}{\delta\theta_j \delta\theta_k}\right] = \underline{V}^{-1}$$

By using the theory on approximate solutions of likelihood equations (Kendall & Stuart 1973), as seen in the description for the univariate scenario, the iterative procedure, using the same notation as above, is thus evaluated to be:

$$\underline{\theta}_{n+1} = \underline{\theta}_n + \frac{\delta \ln f(x;\underline{\theta}_n)}{\delta\underline{\theta}} \Big/ \underline{I}(\underline{\theta}_n)$$

To simplify, the vector $\underline{S}$, is reintroduced into the notation: $\underline{S} = \begin{bmatrix} \delta L/\delta\theta_1 \\ \delta L/\delta\theta_2 \\ \vdots \\ \delta L/\delta\theta_n \end{bmatrix} = \frac{\delta \ln f(x;\underline{\theta}_n)}{\delta \underline{\theta}}$

Then, the iterative procedure seen in equation (3.6) below, commonly known as the method of scoring for parameters, is formed and implemented to calculate the estimates of the parameters $\underline{\theta}_j$, j = 1, 2, ..., n.

$$\underline{\theta}_{n+1} = \underline{\theta}_n + \underline{S}_n / \underline{I}(\underline{\theta}_n) = \underline{\theta}_n + \underline{S}_n \underline{I}^{-1}(\underline{\theta}_n) = \underline{\theta}_n + \underline{I}^{-1}\underline{S} \qquad \ldots(3.6)$$

3.3 5-Parameter MLE

Section 3.2 demonstrates the theory behind the computation involved within the maximum likelihood technique and shows the scoring method iterative formula to be:

$$\underline{\theta}_{n+1} = \underline{\theta}_n + \underline{I}^{-1}\underline{S} \qquad \ldots(3.7)$$

In order to perform MLE on the parameters to be estimated, the theory within section 3.2 needs to be put into effect. This is accomplished using Visual Basic (VB), employing Excel Spreadsheets as the output domain, i.e. a program is written in VB incorporating all the differential-difference equations (thus creating the model of expected AIDS, HIV and deaths) and computing the theory of MLE, as seen in section 3.2. The aim of the program is not only to illustrate the expected HIV/AIDS epidemic against the observed HIV/AIDS epidemic, but also to incorporate the method of maximum likelihood to model the expected data on to the observed data by providing a guide for changes in value of particular, chosen, parameters and, thus, producing better, and eventually the best, possible fits between Observed and Expected HIV, AIDS and deaths data.

In this section, the theory presented in part 3.2 is explored to determine the equivalent computational formulae that can be put into practice. Then, finally, this computational method is utilized to estimate 5 different parameters within the model, at the same time.

From section 3.2, it is known that $L = \sum_{i=1}^{T} L^{(i)}$, thus $\frac{\delta L}{\delta \theta_j} = \sum_{i=1}^{T} \frac{\delta L^{(i)}}{\delta \theta_j}$. Hence, for the univariate case, the log-likelihood expression, assuming the Poisson distribution, is:

$$L^{(i)} = a_i \log \alpha_i - \alpha_i - \log(a_i!)$$

Differentiating this log-likelihood, $L^{(i)}$, with respect to the parameters to be estimated, θ_j, using the chain rule (since α_i is a function of θ_j) gives the elements in matrix $\underline{S}$:

$$S_j^{(i)} = \frac{\delta L^{(i)}}{\delta \theta_j} = a_i \frac{1}{\alpha_i} \frac{\delta \alpha_i}{\delta \theta_j} - \frac{\delta \alpha_i}{\delta \theta_j} = \left(\frac{a_i}{\alpha_i} - 1 \right) \frac{\delta \alpha_i}{\delta \theta_j} \qquad \ldots(3.8)$$

It is worth noting, at this point, that since there is no unequivocal expression for α_i, there is no explicit expression for $\frac{\delta \alpha_i}{\delta \theta_j}$. For the work within this model, a more liberal interpretation of these partial derivatives is adopted. In real terms, the partial derivatives, $\frac{\delta \alpha_i}{\delta \theta_j}$, represent a measurement of effect that a small change in parameter value, θ_j, has on the expected AIDS cases, α_i. In other words, $\frac{\delta \alpha_i}{\delta \theta_j}$ requires calculation by first principles from the differential-difference equations in the epidemic model. This is input into the VB program using the following operation:

$$\frac{\textit{AIDS Cases with old parameter value - AIDS Cases with new parameter value}}{\textit{Small Change in parameter value}}$$

This evaluation of the partial derivatives allows a numerical approximation of the partial derivative terms to be made, thus enabling the completion of the calculation of the elements within $\underline{S}$. See Appendix 3.1 for the VB script of these partial derivatives and their role in the MLE process.

The product of $\underline{S}$ and $\underline{I}^{-1}$, within the iterative formula (equation (3.7)), also needs evaluating in order to be computed numerically. In the univariate case, it is known from the definition of $\underline{I}$, that:

$$I_{jk}^{(i)} = -E\left(\frac{\delta^2 L^{(i)}}{\delta\theta_j \delta\theta_k}\right)$$

Hence, the second derivative term needs to be investigated in order to determine $\underline{I}$ in computational form. This means differentiating $S_j^{(i)}$ with respect to θ_k, using the product rule, such that:

$$\frac{\delta^2 L^{(i)}}{\delta\theta_j \delta\theta_k} = \left(\frac{a_i}{\alpha_i} - 1\right)\frac{\delta^2 \alpha_i}{\delta\theta_j \delta\theta_k} - \frac{a_i}{\alpha_i^2}\frac{\delta\alpha_i}{\delta\theta_j}\frac{\delta\alpha_i}{\delta\theta_k}$$

Now, using the knowledge that, by definition, $E(a_i) = \alpha_i$, the univariate case gives:

$$I_{jk}^{(i)} = -E\left(\frac{\delta^2 L^{(i)}}{\delta\theta_j \delta\theta_k}\right) = -E\left(\left(\frac{a_i}{\alpha_i} - 1\right)\frac{\delta^2 \alpha_i}{\delta\theta_j \delta\theta_k} - \frac{a_i}{\alpha_i^2}\frac{\delta\alpha_i}{\delta\theta_j}\frac{\delta\alpha_i}{\delta\theta_k}\right) = \frac{1}{\alpha_i}\frac{\delta\alpha_i}{\delta\theta_j}\frac{\delta\alpha_i}{\delta\theta_k}$$

Again, the partial derivatives, within this computation of the $I_{jk}^{(i)}$ elements, have no explicit expression and so the same principle of interpretation is imposed, as it was for the partial derivatives within the calculation of the $S_j^{(i)}$ elements. Finally, generalizing for the multivariate case gives equations (3.9):

$$\left.\begin{aligned} \underline{S} &= \sum_{i=1}^{T}\left[\left(\frac{a_i}{\alpha_i} - 1\right)\frac{\delta\alpha_i}{\delta\theta_j}\right], \quad \text{where } j = 1,2,\ldots,n. \\ \underline{I} &= \sum_{i=1}^{T}\left[\frac{1}{\alpha_i}\frac{\delta\alpha_i}{\delta\theta_j}\frac{\delta\alpha_i}{\delta\theta_k}\right], \quad \text{where } j,k = 1,2,\ldots,n. \end{aligned}\right\} \quad \ldots(3.9)$$

Applying this computation to the scenario where n = 5, that is, there exist 5 parameters to be estimated at the same time, involves the inversion of a 5x5 matrix (i.e. I^{-1}). This inversion slows the length of time the VB program takes to run; the formula for the inversion is complicated and, subsequently, time consuming to ascertain the procedure is working correctly and accurately. Alternatively, outputting the $\underline{I}$ elements into an Excel Spreadsheet, inverting the matrix within the sheet and then reading back into the program the $\underline{I}^{-1}$ elements, is a much more efficient method for completion of the inverse. Also, another advantage of computing the 5 x 5 inverse in this manner is the ease of assessment; by simply performing a multiplication of the matrices I and I^{-1} within the Excel Spreadsheet one can ensure the result is always equal to the Identity matrix. Hence, the approach involving the interaction with an Excel Spreadsheet is employed throughout this MLE work.

3.4 Estimating Parameters in the Cardiff Model

This section describes the creation of the Cardiff HIV/AIDS model, the computation of the differential-difference equations and the application of MLE theory for 5 parameters, as seen in sections 3.2 and 3.3, within a VB program. The underlying assumptions must be clarified and any restrictions on the parameter values require declaration. See Appendix 3.1 for snippets of the VB program script that are employed for this work. The first set of 5 parameters to be estimated is:

- N_{1978} = the number of high-risk homosexuals in 1978,
- λ = the arrival rate of homosexuals into the Susceptible sub-population,
- a_{1978} = the number of HIV positive homosexuals at the end of year 1978,
- βc = the infectivity parameter,
- r = the proportion the IP lengthens due to the introduction of treatments.

Then, to incorporate the concept of estimating the entry rate, Λ, as a single entity without strict definition, λ and N_{1978} are withdrawn from the estimation process and replaced by

Λ. In addition, the death rate, ω, is introduced into the MLE procedure to make up the 5 parameters. That is, the second set of 5 parameters for estimation is:

- Λ = the entry rate into the High Risk Susceptible sub-population,
- a_{1978} = the number of HIV positive homosexuals at the end of year 1978,
- βc = the infectivity parameter,
- r = the proportion the IP lengthens due to the introduction of treatments,
- ω = the death rate from the AIDS case sub-populations.

In order to perform this estimation, primarily the models' initial conditions need to be set. The initial parameter values and settings for the program are as follows, based upon a combination of work by Snary (2000), Lowrie (2000) and Griffiths *et al.* (2000) or gained directly from population statistics.

- IP = Mean length of incubation period in years prior to the introduction of treatments = 11.4 (Snary 2000),
- μ_1 = rate at which homosexuals exit the susceptible category from causes other than AIDS = 0.003 (DH1 2002),
- μ_2 = rate at which homosexuals exit the High and Low Risk Infective categories from causes other than AIDS = 0.03 (Snary 2000 and Lowrie 2000, to 2.d.p.),
- ν_2 = rate at which High Risk Infectives become Low Risk Infectives = 0.1 (Snary 2000),
- ν_3 = rate at which High Risk AIDS cases become Low Risk AIDS cases = 0.5 (Snary 2000 and Griffiths *et al.* 2000),
- b = proportion of High Risk Infectives whom, on diagnosis with AIDS, continue their High Risk behaviour = 0.5 (Snary 2000),
- g = proportion of Low Risk Infectives whom, on diagnosis with AIDS, change their behaviour to High Risk = 0.1 (Snary 2000),
- ω = death rate = 1 (Snary 2000),
- m = number of stages in HIV infection = 6 (Snary 2000).

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Inspecting the values of the parameters listed on the previous page, it is apparent that they have been rounded to a small degree of accuracy. Whilst a few of the parameter values already possess this nicety with no need for adjustment, others have been subject to rounding due to the notion that the parameter values are estimations. A sensitivity analysis on all the parameter values listed on the previous page was completed, taking it in turn to change the value of each parameter and running the program, noting the effect on the previously minimised chi-square. In general, a change in parameter value, for most of the parameters, by 0.01 resulted in the MLE chi-square increasing by no more than 0.00001. Hence, it was decided that the parameter values do not need to be valued to a large number of decimal places within the work since small differences in value do not have a significant effect on the HIV/AIDS model outputs.

In Chapter 2 of this thesis, all parameters within the Cardiff HIV/AIDS model were listed. It is worthy of note that not all those parameters are apparent in the initial conditions listed here, even when allowing for the 5 parameters to be estimated. This is partly due to the assumption that Low Risk Susceptibles play no part within this model, i.e. W(t) is not considered here, or more precisely, the transfer allowed from X(t) to W(t) at rate ν_1 is designated a value of 0. This simplification has meant that the exit rate from the (High Risk) Susceptibles within the model considered here, μ_1, is the only exit rate from this sub-population without an individual progressing further through the model and contracting HIV. Consequently, within the programming of this model, the differential-difference equation relating to W(t) is not included. The value of μ_1 was determined from population statistics (DH1 2002) by calculating a ratio for the number of deaths within the total population, aged 15-64, in the UK. This figure, averaged over all age groups, was approximately 3 in 1000, hence $\mu_1 = 0.003$. Note that for the male homosexual population the death rate from causes other than AIDS may be marginally greater than for the general UK population taken as a whole. However, any evidence of this is not supported by the list of reported causes of death attained from the Department of Health (DH1 2002). As for the other parameters, a sensitivity analysis has been performed with respect to the value of the parameter μ_1 and it was confirmed that a small change in value does not significantly affect the model outputs. Consequently, any minor difference in the value of μ_1 that may be observed, when considering the male

homosexual population only, is deemed negligible, hence μ_1 is designated the value of 0.003. Other missing parameters within this model include: the proportion, a, of High Risk susceptibles who on diagnosis with HIV maintain their High Risk behaviour, which is assumed a value of 1 since no immediate change in behaviour (from High Risk to Low Risk) can be expected when a High Risk Susceptible becomes infected with HIV due to the principle that an homosexual is not immediately aware of their status change, i.e. HIV diagnosis is rarely at the same time as infection; and the rate at which homosexuals exit the High and Low Risk AIDS categories, μ_3, from causes other than AIDS, which is deemed negligible in comparison with the size of the death rate, ω, and consequently is assumed a value of 0.

The above assumptions create a model that is easy to understand and allows attention to be paid to the HIV infective sub-populations and the movements between the stages of HIV. Note that these assumptions do not affect the expected AIDS incidence, HIV incidence or death figures, which are the numbers that the model produces with the objective of fitting the relevant observed data. Nor should these assumptions interfere with other outputs of the program, such as HIV prevalence statistics. Figure 3.1, overleaf, provides a diagrammatic view of the simplified Cardiff HIV/AIDS model that is being instigated throughout this chapter, with the dashed directional arrows and faded compartments representing the movements which no longer occur subject to the above named assumptions.

Using the ENAADS dataset as the source of the observed AIDS incidence data, the first reported case of AIDS in the UK was in 1979. Thus, this is considered as the first year of the HIV/AIDS epidemic and so 1978 is employed as the base year (i.e. when $t = 0$). One notion in operation for the construction of the model is that during the base year, since the HIV/AIDS epidemic has not yet begun, all individuals would be assumed to be partaking in high-risk sexual activities, due to the lack of awareness of HIV/AIDS. This means that all homosexuals who are HIV positive in 1978 are considered to belong to one of the High Risk sub-populations. Therefore, it is assumed that $V(1978) = Z(1978) = 0$, that is, all Low Risk sub-population groups within the model of HIV/AIDS are assumed to be empty. Following this conjecture, that all homosexuals are High Risk at the start of the epidemic, is the assumption that $N_{1978} = X(1978)+Y(1978)+A(1978)$.

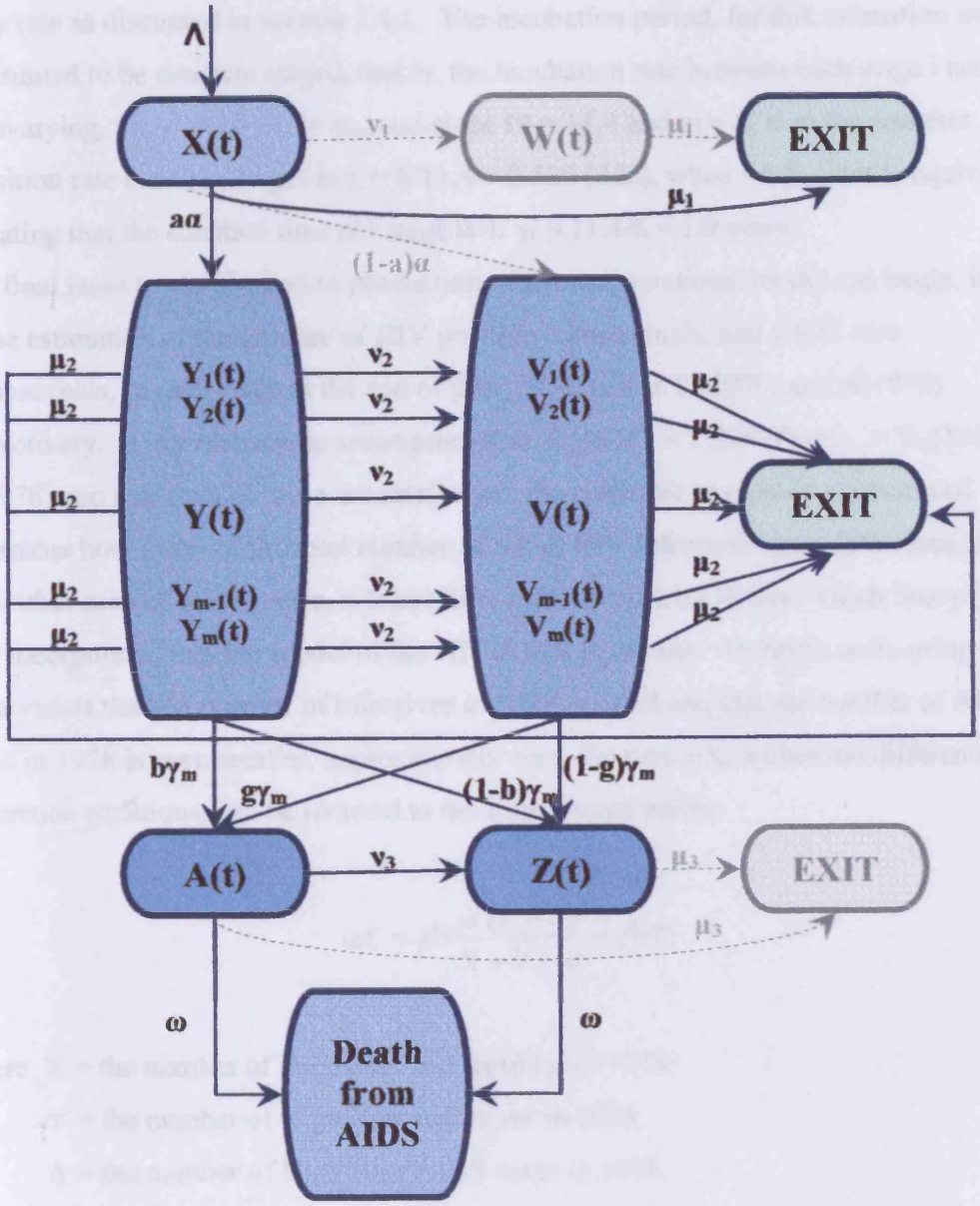

Figure 3.1 Simplified version of the Cardiff HIV/AIDS Epidemic model.

For the estimation of the first set of 5 parameters, listed previously, the entry rate into the model is assumed to be $\Lambda = \lambda N_{1978}$, adhering to the first methodology for categorizing the entry rate as discussed in section 2.4.1. The incubation period, for this estimation work, is assumed to be constant staged, that is, the incubation rate between each stage i and i+1 is unvarying, i.e. $\gamma_1 = \gamma_2 = \ldots = \gamma_m$, and since IP = 11.4 and m = 6, then the constant transition rate between stages is $\gamma_i = 6/11.4 \approx 0.526$ (3dp), when r = 1. This is equivalent to stating that the constant time per stage is $1/\gamma_i = 11.4/6 = 1.9$ years.

The final issue to clarify, before production of the computational model can begin, is that of the estimation of the number of HIV positive homosexuals, and AIDS case homosexuals, in each stage at the end of year 1978, that is $Y_i(1978)$ and A(1978) respectively. It is a reasonable assumption that $Y_1(1978) > Y_2(1978) > \ldots > Y_m(1978) >$ A(1978) and that each of these are small since the epidemic has barely commenced. To determine how many of the total number of initial HIV infectives and AIDS cases, a_{1978}, are within each of these stages, it is useful to refer to work by Bailey, which Snary (2000) also incorporated into her model of the HIV/AIDS Epidemic. To begin with, using the observation that the number of infectives in 1978 is small and that the number of AIDS cases in 1978 is even smaller, approximately zero, the term αX, within the differential-difference equations, can be reduced to the form shown below:

$$\alpha X = \beta c \frac{X(Y+A)}{X+Y+A} \approx \beta c Y$$

where X = the number of High Risk Susceptibles in 1978;

Y = the number of High Risk Infectives in 1978;

A = the number of High Risk AIDS cases in 1978.

Substituting this expression for αX back into the original differential-difference equations linearises them into the system of equations shown overleaf, with the same notation as used above.

$$\frac{dX}{dt} = \Lambda - \beta cY - \mu_1 X$$

$$\frac{dY_1}{dt} = \beta cY - (\gamma_s + \mu_2)Y_1$$

$$\frac{dY_i}{dt} = \gamma_s Y_{i-1} - (\gamma_s + \mu_2)Y_i, \quad i = 2,\ldots,m$$

$$\frac{dA}{dt} = \gamma_s Y_m - (\omega + \mu_3)A$$

In order to create an expression for $\frac{dY}{dt}$, all equations for Y_i above (i = 1, ..., m) must be summed together, i.e. $Y = \sum_{i=1}^{m} Y_i$, and simplified to give:

$$\begin{aligned}\frac{dY}{dt} &= \sum_{i=1}^{m} \frac{dY_i}{dt} \\ &= \beta cY - (\gamma_s + \mu_2)Y_1 + \gamma_s Y_1 - (\gamma_s + \mu_2)Y_2 + \gamma_s Y_2 - (\gamma_s + \mu_2)Y_3 + \ldots + \gamma_s Y_{m-1} - (\gamma_s + \mu_2)Y_m \\ &= \beta cY - \mu_2 \sum_{i=1}^{m} Y_i - \gamma_s Y_m \\ &= (\beta c - \mu_2)Y - \gamma_s Y_m \qquad \ldots(3.10)\end{aligned}$$

Noting that Y_m, in 1978, is small, Bailey decided to abandon the term $\gamma_s Y_m$ from this simplified expression for $\frac{dY}{dt}$. Thus,

$$\frac{dY}{dt} \approx (\beta c - \mu_2)Y \qquad \ldots(3.11)$$

Consequently, the solution of this variable separable type differential equation is found to be $Y = ke^{(\beta c - \mu_2)t}$, where k is the constant of integration. This solution was acquired by reorganising and integrating both sides of the differential equation (3.11), before taking

anti-logs. Then, this expression for Y can be substituted back into the equations for Y_i to give the final proportions. Taking the scenario where i = 1, we get:

$$\frac{dY_1}{dt} = \beta ck e^{(\beta c-\mu_2)t} - (\gamma_s + \mu_2)Y_1$$

or

$$\frac{dY_1}{dt} + (\gamma_s + \mu_2)Y_1 = \beta ck e^{(\beta c-\mu_2)t}$$

The (integrating-factor type) differential equation shown here can be solved at time t = 0, as seen below, where $\rho = \frac{\beta c}{\gamma_s}$:

$$\left.\begin{aligned} Y_1 &= \frac{\beta ck}{(\gamma_s + \beta c)} = \frac{\rho k}{1+\rho} \\ &\textit{Similarly,} \\ Y_i &= \frac{\rho k}{(1+\rho)^i}, \qquad i = 2,\ldots,m \\ A &= \frac{k}{(1+\rho)^m} \end{aligned}\right\} \qquad \ldots(3.12)$$

Next, the constant of integration, k, needs to be evaluated. One suggestion for the value of k is based upon the dependence of the formulae on the number of stages, m. To illustrate this, imagine the case where $m \to \infty$ and $k \neq 0$; for each stage there exists a constant of integration, thus, when summed over all m stages, the total constant of integration tends to infinity. This is not a feasible option and so, assuming k = 0 seems a reasonable assumption. Another way of evaluating k is accomplished by assuming an infinite number of HIV stages when investigating the relationship $Y = \sum_{i=1}^{m} Y_i$, such that equations (3.12) hold.

$$Y = \sum_{i=1}^{\infty} Y_i$$

$$= \frac{\rho k}{(1+\rho)} + \frac{\rho k}{(1+\rho)^2} + \frac{\rho k}{(1+\rho)^3} + \cdots$$

$$= \frac{\rho k}{(1+\rho)} \left\{ 1 + \frac{1}{(1+\rho)} + \frac{1}{(1+\rho)^2} + \ldots \right\}$$

$$= \frac{\rho k}{(1+\rho)} \left\{ \frac{1}{1 - 1/(1+\rho)} \right\}$$

$$= k$$

Also,

$$A = \underset{m \to \infty}{\text{Lim}} \left\{ \frac{k}{(1+\rho)^m} \right\} = 0$$

Next, drawing on the assumption stated previously, that $a_{1978} = \sum_{i=1}^{m} Y_i + A$, it becomes apparent that $a_{1978} = k$. With this finding, the argument for the assumption that $k = 0$ is supported when considering the situation before the epidemic begins when there are no HIV infectives or AIDS cases.

Now that it has been identified that $a_{1978} = k$, the proportions for the number of High Risk Infectives in each of the stages of HIV infection and AIDS, at the start of the epidemic, with $m = 6$ in the Cardiff model, are as shown in equations (3.13), in the form of the geometric distribution:

$$\left.\begin{aligned} Y_i &= \frac{a_{1978}\rho}{(1+\rho)^i}, \qquad i = 1,\ldots,6 \\ A &= \frac{a_{1978}}{(1+\rho)^6} \end{aligned}\right\} \qquad \ldots(3.13)$$

3.5 Fitting the Cardiff Model

The initial conditions, assumptions and proportions, as discussed thus far, are stated in Appendix 3.1 where the program for the model and consequent MLE calculations is summarised. The differential-difference equations for X, Y, V, A and Z are also depicted in Appendix 3.1, as are the calculations for the 5-parameter MLE, i.e. the partial derivatives; the elements within the $\underline{I}$ matrix; the elements within the $\underline{S}$ matrix; and the subsequent correction values.

Another mechanism to solve this optimization problem (other than MLE in VB), is to use an 'add-in' called Solver within Microsoft Excel (Microsoft Excel User's Guide 1993-1994). In order to use this application, however, the entire model must be formulated and inputted into the cells of an Excel Spreadsheet. The differential-difference equations, the objective function, variables and constraints, are entered directly into the worksheet. This process is incredibly extensive and becomes extremely convoluted, as the model gets more and more complex. Consequently, the method of Solver can be considered as error-prone, especially in comparison to the much simpler and easier to understand method of formulation within a computer program. Solver also has the disadvantage that, other than an estimate for each parameter, no other deductions within the model can be acquired; the method of scoring, on the other hand, allows much further investigation to be undertaken due to the availability and accessibility of the calculated information matrix and its inverse, I and I^{-1}.

Nevertheless, Solver is a very powerful tool and its use within the modelling of the HIV/AIDS epidemic should not be underestimated. The objective function can be set as the log-likelihood (L) and maximized subject to changing the parameter values. This is in accordance with the method of MLE, with the exception that the optimization is performed by Solver and not by the scoring method as shown in equation (3.7). Within this thesis, Solver is used as a tool for verification, whilst the method of scoring is the predominant technique applied for estimating parameters.

In either approach (whether using Solver or the iterative formula seen in equation (3.7)), the parameters to be estimated are subject to constraints. That is, they are bound by predetermined conditions such that they remain realistic in value. At present, within this simplified model, where each parameter is to be estimated only once at the start of the

epidemic, the restrictions placed upon them are as shown below:

- $\Lambda > 0$, non-negativity (or, if considered individually, $N_{1978} > 0$ and $\lambda > 0$ for non-negativity),
- $0 < a_{1978} \leq 1000$, non-negativity plus an upper boundary for realism,
- $0 < \beta c \leq 2$, non-negativity (since both $\beta > 0$ and $c > 0$) plus an upper boundary for realism,
- $r \geq 1$, r restricted to only *increase* the IP due to the introduction of treatments,
- $\omega > 0$, non-negativity.

Note that as the model becomes more complicated, the number of constraints will increase. For instance, if the total time period of the epidemic (1979-2002) is split into two time eras, pre-treatment (1979-1995) and post-treatment (1996-2002), relating to the introduction of highly effective combination treatments, and if the parameters were re-estimated for the second time period, it would be expected that ω would decrease and r would increase in value. Hence, the constraints $\omega_0 > \omega_1$ and $r_0 < r_1$ would be introduced, where ω_0 relates to the death rate prior to the introduction of treatments; ω_1 to the death rate after the introduction of treatments; r_0 to the proportion of increase of the IP prior to the introduction of treatments; and r_1 to the proportion of increase of the IP after the introduction of treatments.

Within this section the Cardiff model, as shown in Figure 3.1, is fitted to the yearly AIDS, HIV and deaths data for Calendar years 1979-2002, 1995-2002 and 1985-2002, respectively, to calculate estimates of 5 parameters over the entire time period. Firstly, the parameters N_{1978}, λ, a_{1978}, βc and r are considered, under the assumption that $\Lambda = \lambda N_{1978}$. The results for this estimation and consequent fit are shown and investigated in section 3.5.1. Secondly, the parameters Λ, a_{1978}, βc, r and ω are estimated, where, here, the assumption is of a more complex entry rate, specifically, $\Lambda \neq \lambda N_{1978}$. The results for this estimation are shown and investigated in section 3.5.2.

3.5.1 Estimation of the 5 parameters: N_{1978}, λ, a_{1978}, βc and r.

Applying the initial conditions for parameters, as displayed in section 3.4, and the assumption that $\gamma_1 = \gamma_2 = \ldots = \gamma_m$, where in this case m = 6 (based on a constant staged incubation period of length 11.4 years, in accordance with Snary (2000) who extracted the figure from work by Bailey (1992[9])), the iterative formula in equation (3.7), $\underline{\theta}_{n+1} = \underline{\theta}_n + \underline{I}^{-1}\underline{S}$, is employed to create a set of estimates for the parameters N_{1978}, λ, a_{1978}, βc and r. These parameter estimates are calculated from yearly AIDS incidence data (1979-2002) using maximum likelihood techniques, with HIV incidence data (1995-2002) and deaths from AIDS data (1985-2002) included in the calculation of the chi-square value to be minimised. The program was run through numerous iterations before arriving at a set of optimal parameter values creating the best combined fit for AIDS incidence and HIV incidence data. The program was then run a second time, this time including deaths from AIDS data into the fitting process, producing the best combined fit for AIDS incidence, HIV incidence and deaths from AIDS data. The two resultant sets of parameter values, subject to constraints, are as listed in Table 3.1, overleaf. Note that the only changes in MLE value, including deaths from AIDS data into the overall fit of the model, are with respect to the parameters N_{1978} and λ, that is, with regards to the entry rate into the High Risk Susceptible sub-population, which reduces its value from $\Lambda = \lambda N_{1978} = 1298$ to 1149 (a decline of about 11.5% on its original value). Also, both a_{1978} and βc reach their upper limits, as defined in the constraints imposed to ensure realism and reduce ambiguity. If these restrictions were not enforced then both a_{1978} and βc would have increased to values greater than 1000 and 2, respectively.

The respective minimised chi-square values, for these sets of parameters observed in Table 3.1, are arranged in Table 3.2 on the next page. It is noticeable from this table that the introduction of the deaths from AIDS data into the overall fit compensates the fit between observed and expected HIV incidence for an improvement in fit for both AIDS incidence and deaths from AIDS. In fact, the lack of fit between observed and expected new HIV cases more than doubles (from a chi-square value of approximately 640 to about 1437), whilst for both AIDS cases and deaths from AIDS the fit improves by a count of over 400 and 500 respectively in terms of their chi-square sums. The χ^2 figure subject to optimization for each case is highlighted in Table 3.2. In general, the effect of

	Model fitted to AIDS incidence and HIV incidence	Model fitted to AIDS incidence, HIV incidence and deaths from AIDS
N_{1978}	11,800	11,490
λ	0.11	0.1
a_{1978}	1000	1000
βc	2	2
r	1.27	1.27

Table 3.1 **Final Parameter Estimates as produced for the Cardiff Model using MLE.**

	Model fitted to AIDS incidence and HIV incidence	Model fitted to AIDS incidence, HIV incidence and deaths from AIDS
AIDS incidence χ^2	2938.735	2512.975
HIV incidence χ^2	639.946	1436.800
AIDS +HIV incidence χ^2	*3578.681*	3949.775
Deaths from AIDS χ^2	3793.855	3260.507
Total Overall χ^2	7372.536	*7210.282*

Table 3.2 **Total χ^2 values relating to final MLE's.**

allowing for deaths from AIDS data, in the fitting of the model, is of a fall in total overall chi-square by 162.254, suggesting an improvement in the HIV/AIDS epidemic model taken as a whole when compared to just fitting HIV and AIDS incidence data. Consequently, a lower level of entry rate, as implied by the second set of parameter values listed in Table 3.1, suggesting smaller amounts for N_{1978} and λ, can be viewed as more preferable than that suggested during the fit of AIDS and HIV data alone.

Also, it is important to note that the total chi-square can equal different values dependent on whether the observed and expected data, over all three datasets, were summed over time prior to or after the chi-square calculation, as shown in equation (3.14).

$$\sum(O_A - E_A)^2 / E_A + \sum(O_H - E_H)^2 / E_H + \sum(O_D - E_D)^2 / E_D \qquad \ldots(3.14)$$

$$\neq \sum[(O_A + O_H + O_D) - (E_A + E_H + E_D)]^2 / (E_A + E_H + E_D)$$

where,

O_A = Observed AIDS incidence data

O_H = Observed HIV incidence data

O_D = Observed Death from AIDS data

E_A = Expected AIDS incidence data

E_H = Expected HIV incidence data

E_D = Expected Death from AIDS data

For the chi-square summation, and minimization, here, the first form of the total chi-square, on the left hand side of equation (3.14), is utilized, as apparent in Table 3.2.
In Appendix 3.1, it is seen that the partial derivatives within the MLE methodology incorporate AIDS incidence data only, i.e. the effect a small change in parameter value has on new AIDS cases over the time period 1979-2002. The other datasets (HIV incidence and deaths from AIDS) are introduced into the fit via the chi-square calculation and minimisation. Also, in later work, for some parameters a small change in value will have little effect on the expected AIDS incidence data and hence will result in near zero value partial derivatives, which then gives rise to difficulties within the program due to the attempt to divide by zero. In particular, ω only marginally affects AIDS incidence and HIV incidence, thus, it only significantly affects the model when deaths from AIDS data is included in the chi-square optimisation. This is discussed in more detail in the next sub-section of this chapter.
The fit between expected and observed AIDS Incidence, HIV Incidence and deaths from AIDS is illustrated in Figures 3.2a, 3.2b and 3.2c respectively.

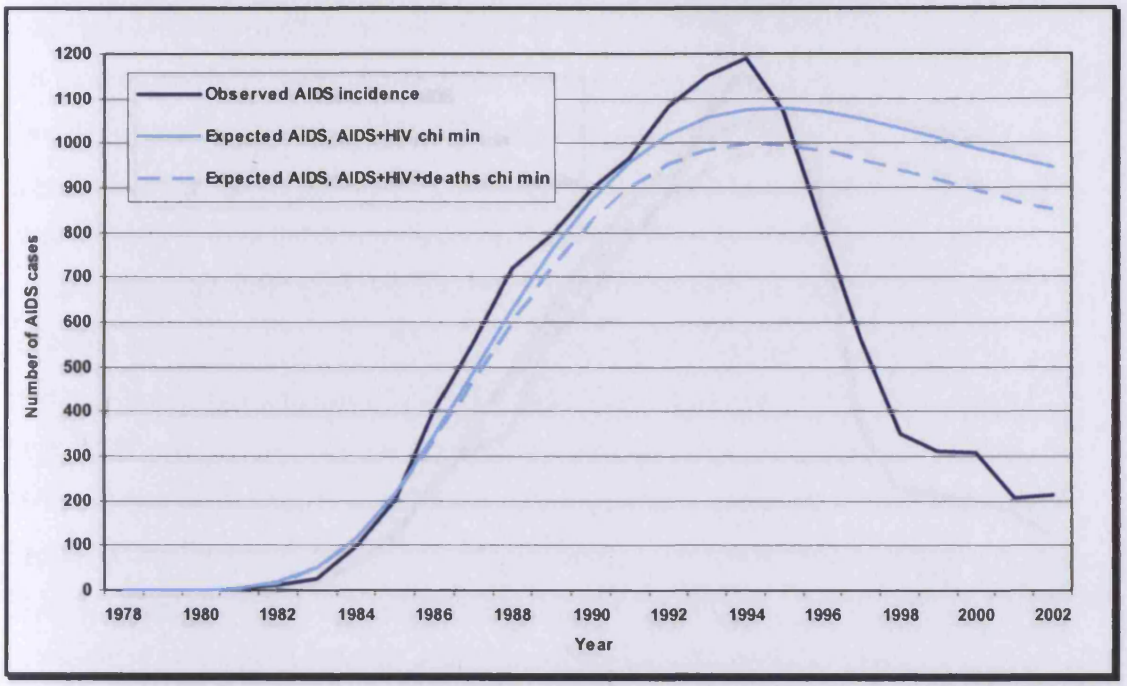

Figure 3.2a **Fit between expected and observed AIDS incidence subject to 5-parameter estimation on N_{1978}, λ, a_{1978}, βc and r.**

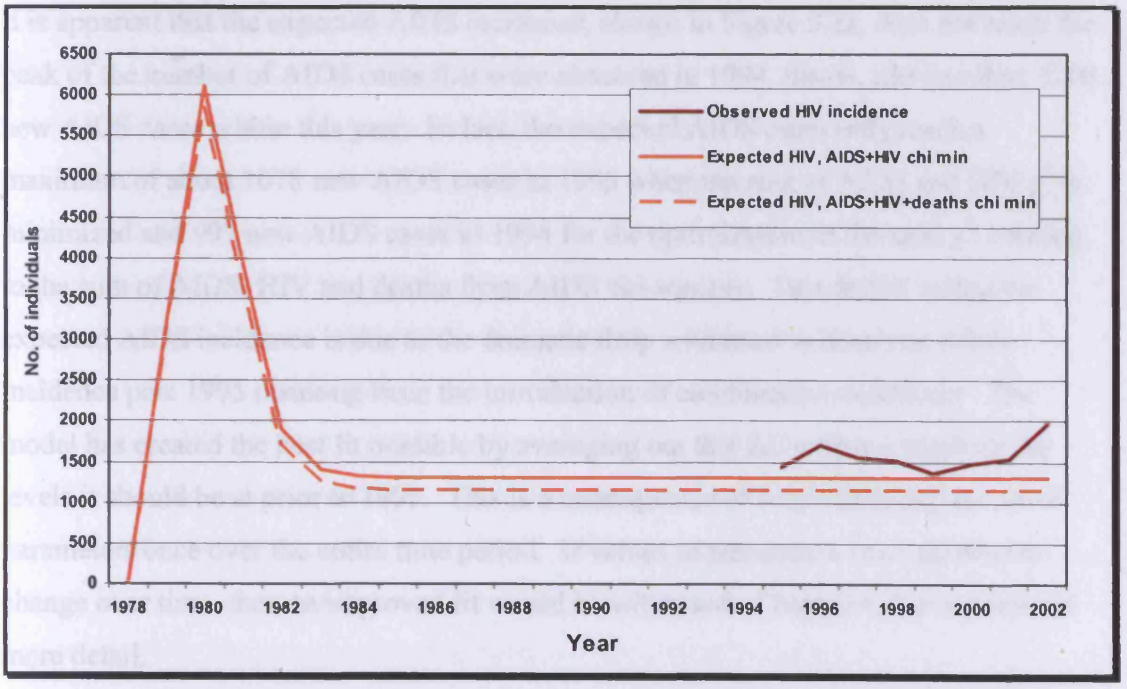

Figure 3.2b **Fit between expected and observed HIV incidence subject to 5-parameter estimation on N_{1978}, λ, a_{1978}, βc and r.**

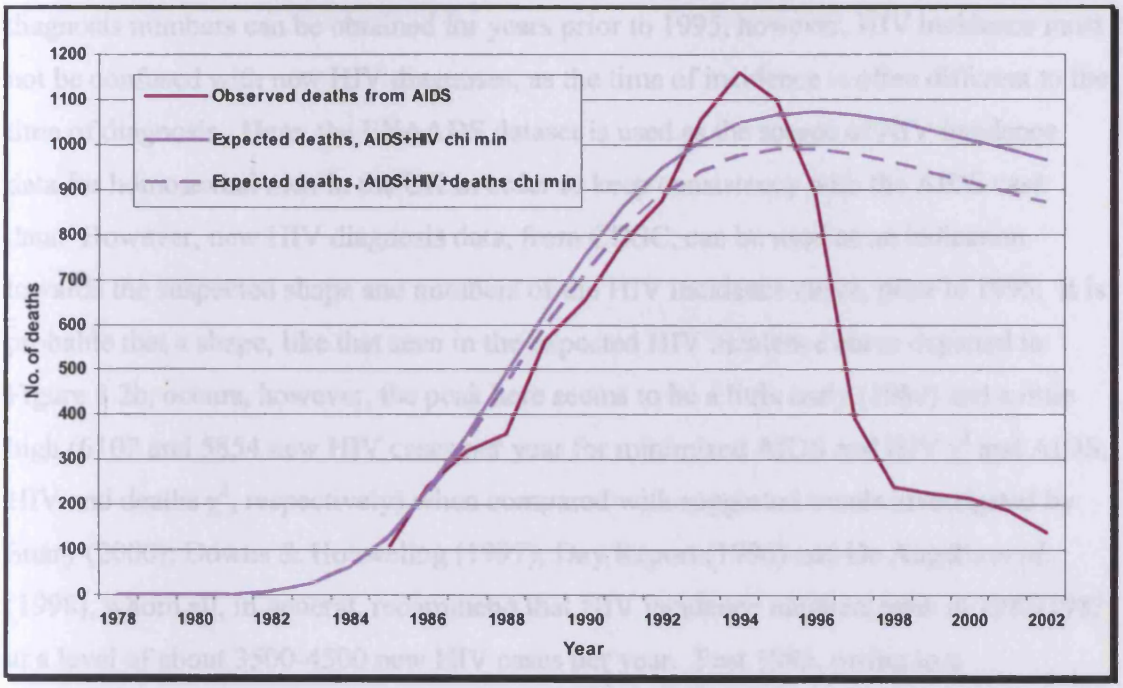

Figure 3.2c **Fit between expected and observed deaths from AIDS subject to 5-parameter estimation on N_{1978}, λ, a_{1978}, βc and r.**

It is apparent that the expected AIDS incidence, shown in Figure 3.2a, does not reach the peak of the number of AIDS cases that were observed in 1994, that is, just less than 1200 new AIDS cases within this year. In fact, the expected AIDS cases only reach a maximum of about 1078 new AIDS cases in 1995 when the sum of AIDS and HIV χ^2 is minimized and 997 new AIDS cases in 1994 for the optimization of the total χ^2, relating to the sum of AIDS, HIV and deaths from AIDS chi-squares. This deficit within the expected AIDS incidence is due to the dramatic drop witnessed in observed AIDS incidence post 1995 resulting from the introduction of combination treatments. The model has created the best fit possible by averaging out this fall with not reaching the levels it should be at prior to 1995. This is a consequence of only estimating the set of parameters once over the entire time period. If values of parameters were allowed to change over time, then an improved fit would be witnessed. Chapter 4 goes into this in more detail.

HIV incidence, seen in Figure 3.2b, is more difficult to get a known good fit for due to the fact that only data from 1995 onwards is available from the ENAADS dataset. HIV

diagnosis numbers can be obtained for years prior to 1995, however, HIV incidence must not be confused with new HIV diagnoses, as the time of incidence is often different to the time of diagnosis. Here, the ENAADS dataset is used as the source of HIV incidence data for homosexual men in the UK in order to keep consistency with the AIDS case data. However, new HIV diagnosis data, from CDSC, can be used as an indication towards the suspected shape and numbers of the HIV incidence curve, prior to 1995. It is probable that a shape, like that seen in the expected HIV incidence curve depicted in Figure 3.2b, occurs, however, the peak here seems to be a little early (1980) and a little high (6107 and 5854 new HIV cases per year for minimized AIDS and HIV χ^2 and AIDS, HIV and deaths χ^2, respectively) when compared with suggested trends investigated by Snary (2000); Downs & Houweling (1997); Day Report (1996) and De Angelis *et al.* (1998), whom all, in general, recommend that HIV incidence numbers peak in 1982/1983 at a level of about 3500-4500 new HIV cases per year. Post 1983, owing to a government campaign promoting safe sex in 1985/1986 (Johnson & Gill 1989; Evans *et al.* 1993), levels of HIV incidence are assumed to have fallen quite rapidly and, in more recent years, have maintained their reasonably low, and stable, levels of about 1500 new cases of HIV each year.

The fit for deaths from AIDS, Figure 3.2c, is similar to that for AIDS incidence, in that post-1995 there exists a sharp decline in the number of deaths observed in accordance with the introduction of highly active antiretroviral treatments. The number of deaths from AIDS reaches a peak of approximately 1150 homosexuals in 1994, and drops to a rate of just over 200 individuals per year by 1998. The model has tried to compensate for this dramatic fall by limiting the peak of the expected number of deaths to 1071 for the optimization of the AIDS and HIV χ^2 and 989 for the optimization of the AIDS, HIV and deaths from AIDS χ^2, thus creating an averaging effect over the entire time period. Again, this lack of capability of the model to reach the levels it needs in order to create a good fit with the observed data is due to the static nature of the parameter values within the model. Yet, due to the introduction of new therapies and changing sexual behaviours, the assumption that parameters remain constant over time is unrealistic.

Figure 3.3, overleaf, shows the expected numbers within the sub-populations, X(t), Y(t), V(t), A(t) and Z(t), as the epidemic progresses through time. Each of these sub-

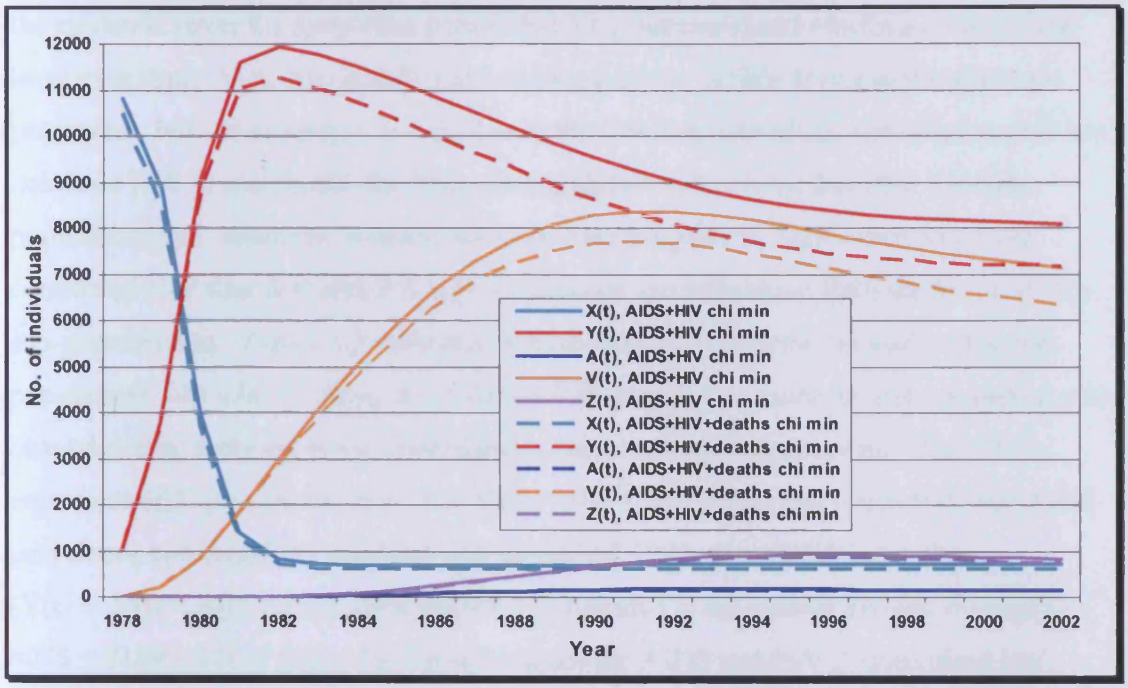

Figure 3.3 **Sub-population prevalence trajectories subject to 5-parameter estimation on N_{1978}, λ, a_{1978}, βc and r.**

populations (High Risk Susceptibles, High Risk and Low Risk Infectives and High Risk and Low Risk AIDS cases respectively) follow a plausible trend in numbers, as evident in Figure 3.3, when considering that each curve in the diagram illustrates the prevalence of individuals in their respective category. That is: X(t) represents the number of people susceptible to the HIV/AIDS virus at time t; Y(t) represents the number of people who are infected with HIV and are participating in High Risk sexual activities at time t; V(t) represents the number of individuals who are infected with HIV and are participating in Low Risk sexual activities at time t; A(t) represents the number of homosexuals who are living with AIDS and are participating in High Risk sexual activities at time t; and Z(t) represents the number of homosexuals who are living with AIDS and are participating in Low Risk sexual activities at time t. It would be anticipated that Y(t) would increase rapidly over the first few years of the epidemic (1978-1984) before slowing its growth and maintaining a reasonably high level of High Risk individuals living with HIV. Accordingly, as the total population begins to be infected with HIV, the number of susceptible individuals within X(t) would be expected to decrease rapidly at the start of

the epidemic (over the same time period that Y(t) increases) and remain a constant low level over time. V(t), A(t) and Z(t) are all likely to rise in their levels as the epidemic progresses, but not as steeply as Y(t) due to the fact that individuals can only become low risk once HIV is contracted (the V(t) sub-population is extracted from the Y(t) sub-population) and, similarly, homosexuals can only progress to AIDS once they have contracted HIV (the A(t) and Z(t) sub-populations are withdrawn from the Y(t) and V(t) sub-populations). Figure 3.3 coincides with the assumed patterns for each of the sub-populations, but when looking at combined HIV prevalence numbers and comparing with observed data, there are some discrepancies with the model predictions. Y(t) + V(t) represents HIV prevalence alone and Y(t) + V(t) + A(t) + Z(t) represents HIV and AIDS prevalence combined. In the final year modelled, 2002, overall HIV prevalence (Y(t) + V(t) + A(t) + Z(t)), from Figure 3.3, rounded to the nearest integer, is roughly 8075 + 7119 + 120 + 822 = 16,136 individuals for AIDS and HIV χ^2 minimised and approximately 7153 + 6343 + 120 + 740 = 14,356 individuals for AIDS, HIV and deaths from AIDS χ^2 minimised. However, statistics from the Department of Health (DH 2002) present HIV prevalence as 17,100 individuals diagnosed and living with HIV in 2002. This figure does not allow for the proportion of homosexuals believed to be unaware of their infection, thus an approximated 5500 (24%) is added to the diagnosed amount to obtain an estimate for total HIV prevalence in 2002 of 22,600 homo/bisexual men living with HIV. This means the expected prevalence figures created by the model with 5-parameter estimation, are significantly understated. This is not the only cause for concern with the expected prevalence numbers, when comparing the expected prevalence figures, as represented in Figure 3.3, with the observed HIV prevalence data that can be obtained from publications by the Department of Health (DH), the CDSC and the PHLS, over the last few years, it is apparent that the observed data suggest an increasing trend in prevalence figures, whilst the Cardiff model, within this chapter, has produced decreasing prevalence estimates over the most recent years. These are both problems created by the restriction on the parameters to maintain one value over the entire time period (1979-2002), work later on in the thesis investigates this further.

3.5.2 Estimation of the 5 parameters: Λ, a_{1978}, βc, r and ω.

For the estimation of the 5 parameters, Λ, a_{1978}, βc, r and ω, the same initial conditions hold as they did in section 3.5.1. However, here, we use additional fixed parameter values; $\lambda = 0.003$ (in accordance with μ_1) and $N_{1978} = 10{,}000$, since these two values are no longer being estimated within the MLE process. This abides by the idea that $\Lambda \neq \lambda N_{1978}$, since the entry rate, Λ, is being estimated as a separate entity within the MLE process. The implication of the fixed value for N_{1978}, is that the initial value of the susceptible population, X(t), is equal to N_{1978} - YOLDSUM (see Appendix 3.1), where YOLDSUM is the total number of HIV infectives at the start of the epidemic, with N_{1978} = 10,000, as opposed to $N_{1978} = \Lambda / \lambda = \Lambda / 0.003$. This is the only point within the model differential-difference equations that N_{1978} is considered as an independent parameter; elsewhere it is always assumed to be a function of Λ. The fixed value of $\lambda = 0.003$, has no influence on the differential-difference equations at any stage throughout the model, since it is only considered within the expression for Λ. This means that defining $\lambda = \mu_1$ is trivial within this computation of the model, and has no effect on the model outputs. Yet, the concept that $\lambda = 0.003$, does allow the assumption that $\Lambda \neq \lambda N_{1978}$ while maintaining the theory that $\lambda = \mu_1$, thus modelling a scenario where the entry rate is more complex. The parameter estimates creating the best fit subject to the minimization of two different χ^2 values are shown in Table 3.3, with the respective chi-square figures represented in Table 3.4, including the highlighted summed χ^2's exposed to optimization. As mentioned before, the effect of a small change in value of ω on AIDS and HIV incidence is minimal, thus, when optimizing the parameter values subject to the minimization of the AIDS and HIV χ^2, altering the value of the death rate from its original value of 1 has no impact on the χ^2 sum of 3429.969. Consequently, for the consideration of AIDS and HIV incidence alone, in the minimization of the chi-square, the death rate has kept its value of 1 since changing this parameter value has no effect. When deaths from AIDS are brought into consideration, the value of the death rate reduces to its new optimal value of 0.97 to create a minimized overall χ^2 value of 6944.805. Therefore, the change in value of ω specifically affects the deaths from AIDS χ^2. Together with this modification in the value of the death rate, the only other parameter included in the estimation process that changes value with the introduction of deaths from AIDS into the χ^2 calculations, is the overall

	Model fitted to AIDS incidence and HIV incidence	Model fitted to AIDS incidence, HIV incidence and deaths from AIDS
Λ	1350	1210
a_{1978}	1000	1000
βc	2	2
r	1.23	1.23
ω	1	0.97

Table 3.3 **Final Parameter Estimates as produced for the Cardiff Model using MLE.**

	Model fitted to AIDS incidence and HIV incidence	Model fitted to AIDS incidence, HIV incidence and deaths from AIDS
AIDS incidence χ^2	2965.181	2585.294
HIV incidence χ^2	464.788	1050.858
AIDS +HIV incidence χ^2	*3429.969*	3636.152
Deaths from AIDS χ^2	3764.150	3308.653
Total Overall χ^2	7194.119	*6944.805*

Table 3.4 **Total χ^2 values relating to final MLE's.**

entry rate into the High Risk Susceptibles, Λ, which falls from a value of 1350 to 1210. In accordance with these alterations in parameter values, the HIV incidence fit has worsened (with the HIV chi-square sum more than doubling, from a value of roughly 465 to 1051) whilst both the AIDS incidence fit and deaths from AIDS fit have improved. The overall minimized total χ^2 value of about 6945 is the lowest of all the scenarios considered within this chapter; this suggests that the entry rate, Λ, is best considered as a

single quantity within the estimation process and not as a product of λ and N_{1978}, and that deaths from AIDS data, as well as HIV incidence and AIDS incidence data, should be incorporated within the chi-square minimisation process in order to obtain the best overall fit.

Figures 3.4a, 3.4b and 3.4c show the fits for AIDS incidence, HIV incidence and deaths from AIDS respectively. Due to the similarity within both sets of 5-parameter MLE's, the expected AIDS cases, new HIV cases and deaths from AIDS numbers, together with their consequent fits to the observed data, are very similar. Additionally, identical lines of reasoning as those proposed in section 3.5.1 explaining the poor fit between observed and expected AIDS incidence and deaths from AIDS, post-1995, are applicable here also. Namely, the lack of fit for each dataset can be associated with the assumption that all parameter values remain constant over time, despite the introduction of highly active antiretroviral treatments. Consequently, averaged parameter estimates during the MLE process are created, resulting in the expected data curves not reaching the extreme values, and not rapidly declining after the introduction of treatments, as witnessed in the observed data. In general, the main noticeable difference between the trajectories of AIDS incidence, HIV incidence and deaths from AIDS seen in Figures 3.2a, 3.2b and 3.2c, respectively, and those seen in Figures 3.4a, 3.4b and 3.4c, is that when the second set of parameters is estimated all peaks of new AIDS cases, new HIV cases, new deaths from AIDS and sub-population prevalence's are lower than they are for the estimation of the first set of parameters. Keeping the same scale on the paired graphs makes this disparity more obvious to the eye. Figure 3.3, as seen in section 3.5.1, also shares strong similarities with the model outputs produced with the 5-parameters estimated in this section, as seen in Figure 3.5. The shape of the prevalence curves for this set of 5-parameter estimation, for each of the sub-populations X(t), Y(t), Y(t), A(t), and Z(t) are the same as seen in Figure 3.3, with a marginal improvement in height i.e. total HIV prevalence in 2002 (rounded to nearest integer) = Y(2002) + V(2002) + A(2002) + Z(2002) = 8288 + 6978 + 129 + 829 = 16,224 (compared with 16,136 in section 3.5.1) for the minimization of the AIDS and HIV χ^2 and 7432 + 6290 + 129 + 779 = 14,630 (compared with 14,356 in section 3.5.1) for the minimization of the AIDS, HIV and deaths from AIDS χ^2. However, the expected prevalences still show a slight

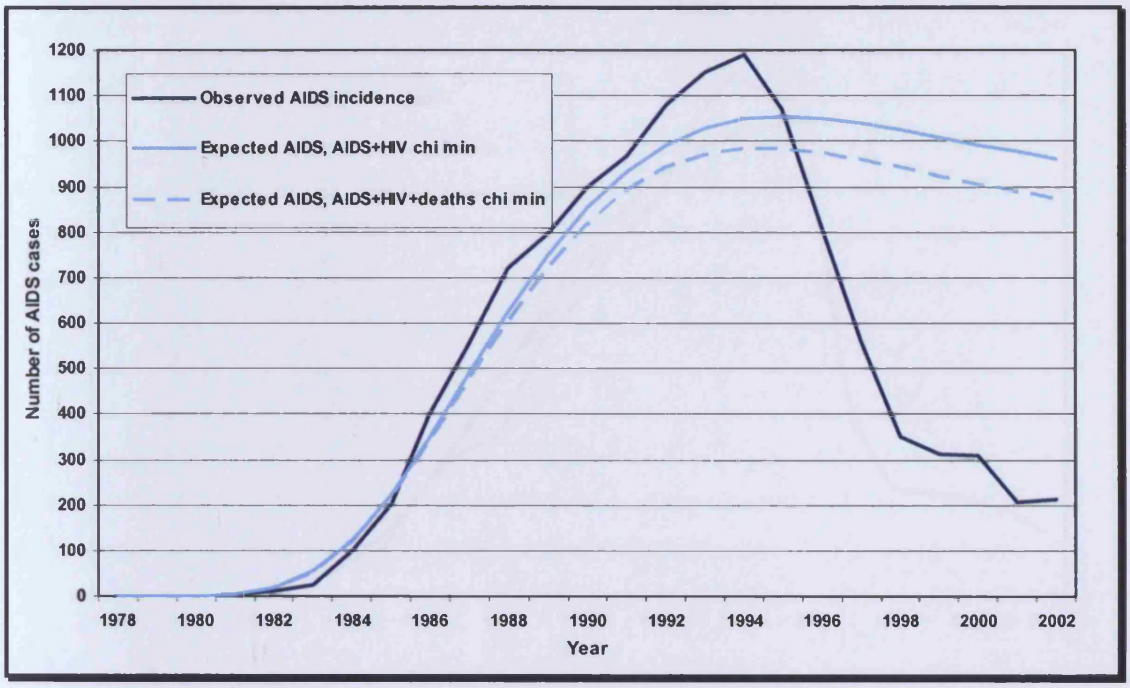

Figure 3.4a **Fit between expected and observed AIDS incidence subject to 5-parameter estimation on Λ, a_{1978}, βc, r and ω.**

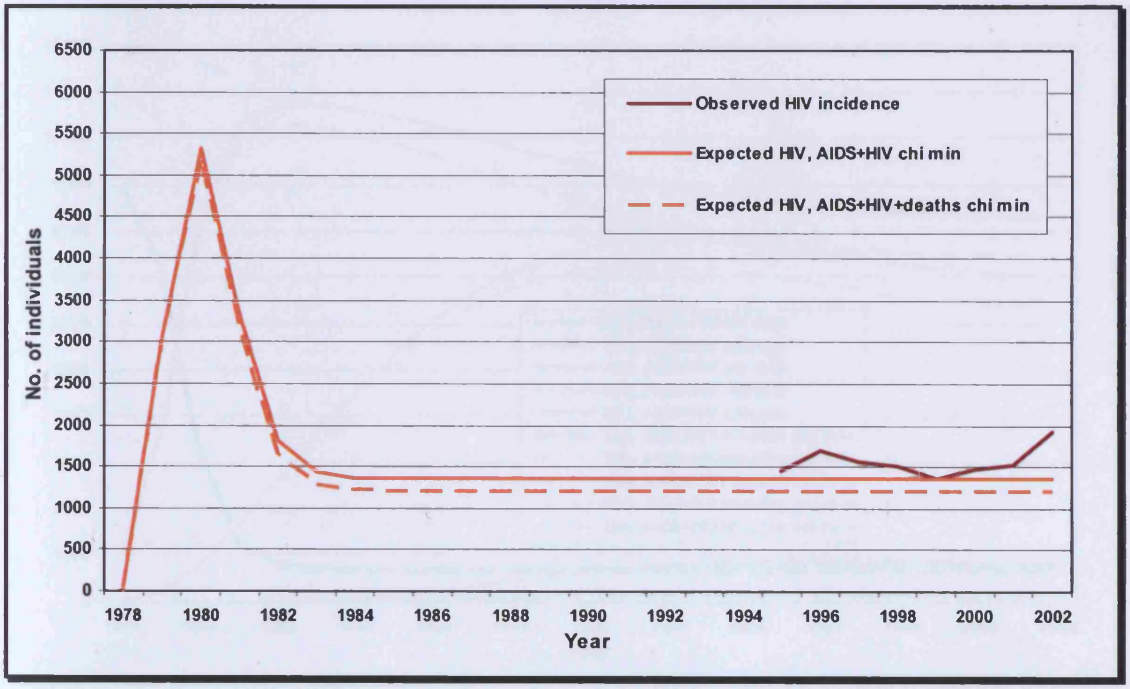

Figure 3.4b **Fit between expected and observed HIV incidence subject to 5-parameter estimation on Λ, a_{1978}, βc, r and ω.**

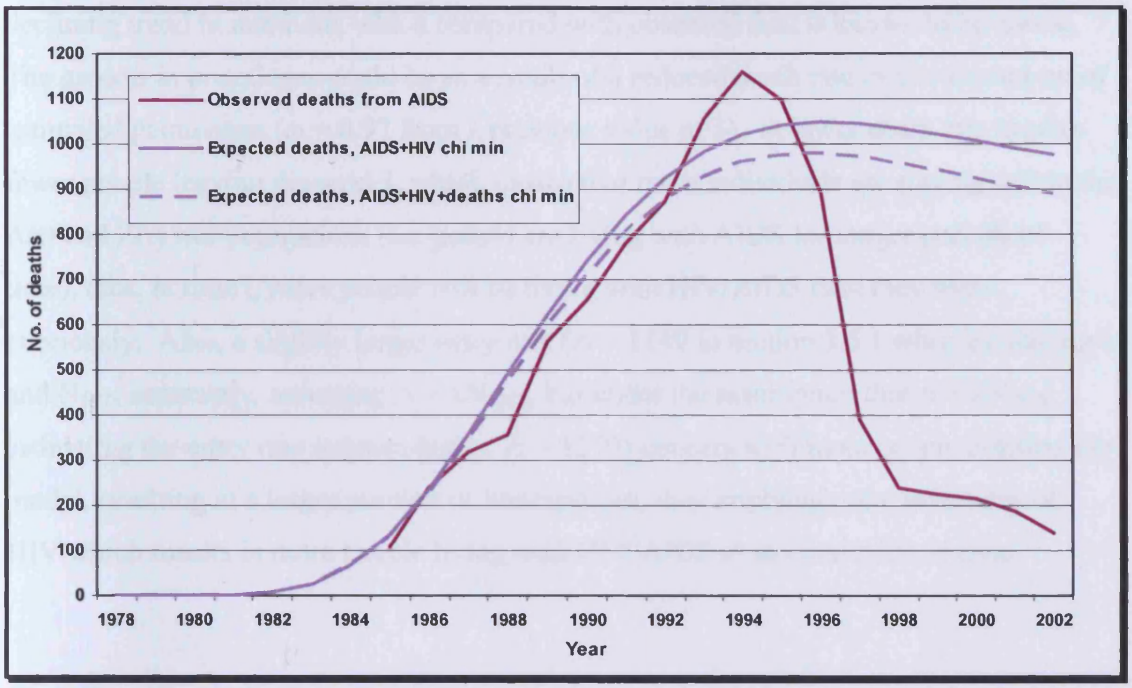

Figure 3.4c **Fit between expected and observed deaths from AIDS subject to 5-parameter estimation on Λ, a_{1978}, βc, r and ω.**

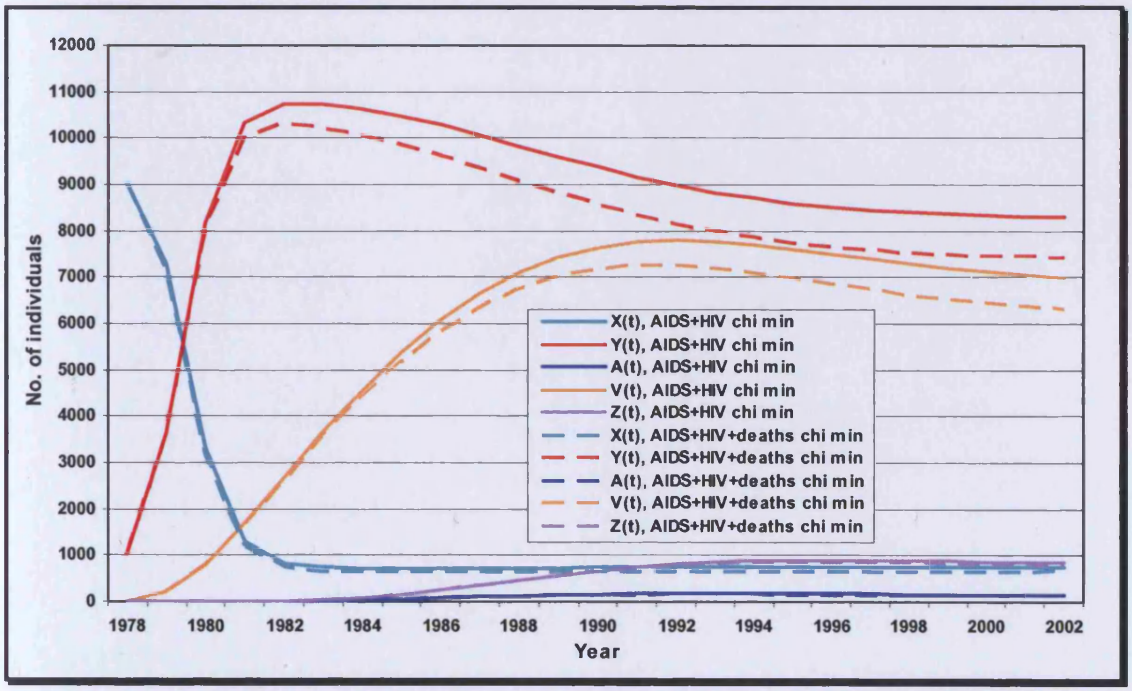

Figure 3.5 **Sub-population prevalence trajectories subject to 5-parameter estimation on Λ, a_{1978}, βc, r and ω.**

declining trend in numbers, which compared with observed data is known to be untrue. The growth in prevalence could be as a result of a reduced death rate in this second set of estimated parameters ($\omega = 0.97$ from a previous value of 1). A lower death rate implies fewer people leaving the model, which means that more individuals are staying within the A(t) and Z(t) sub-populations (i.e. people are living with AIDS for longer periods of time), thus, at time t, more people will be living with HIV/AIDS than they were previously. Also, a slightly larger entry rate ($\Lambda = 1149$ in section 3.5.1 when estimating λ and N_{1978} separately, assuming $\Lambda = \lambda N_{1978}$, but under the assumption that $\Lambda \neq \lambda N_{1978}$, estimating the entry rate independently, $\Lambda = 1210$) concurs with more people entering the model, resulting in a larger number of Susceptibles, thus implying more infections of HIV which results in more people living with HIV/AIDS at any one point in time.

A.3.1 Visual Basic Script within the program of the Cardiff Model

Within this appendix, only the most important parts of the program are depicted since the program in its entirety is extremely long, totalling more than 1000 lines of code. The Visual Basic Script within the program of the Cardiff Model and subsequent MLE code was developed completely from scratch for the purpose of this work, taking more than 12 months to yield the final version. A copy of this program is available from the author on request; contact the School of Mathematics, within Cardiff University, for further details at: Mathematics@cardiff.ac.uk.

.....

First, define the initial conditions. The parameters that are to be estimated are shown in coloured text.

.....

```
NDT% = 52                    'number of time steps per year
DT = (1 / NDT%)              'time increment
nyrs% = 50                   'duration in years
Incub = 11.4                 'incubation period (in yrs)
lam = 0.1                    'arrival rate per year to susceptibles, λ
LAMSTOR = lam                'store value of λ
mu1 = 0.003                  'exit rate per year from susceptibles, μ1
mu2 = (0.03 + 0.1)           'exit rate from High Risk Infectives, μ2 + υ2
nu2 = 0.1                    'entry rate to LR infectives from HR infectives, υ2
nu3 = 0.5                    'entry rate to LR AIDS cases from HR AIDS cases, υ3
theta = 0.03                 'exit rate from low risk infectives, μ2
b = 0.5        'proportion of HR infectives who stay HR on diagnosis with AIDS
g = 0.1        'proportion of LR infectives who become HR on diagnosis with AIDS
omeg = 1                     'death rate, ω
m% = 6                       'number of incubation stages
r = 1.27                     'treatment effect on all γi
RSTOR = r                    'store value of r
rI = r * Incub               'lengthened incubation period due to treatment
gam = (m% / rI)              'incubation rate per stage, γi
Betac = 2                    'Infectivity rate, βc
BETACSTOR = Betac            'store value of βc
N = 11490                    'Initial size of high-risk population, N1978
NSTOR = N                    'store value of N1978
LN = N * lam                 'calculation of the entry rate, Λ
year0% = 1978                'start year
YINIT = 1000                 'initial number of high-risk infectives, a1978
YINITSTOR = YINIT            'store value of a1978
NOBS% = 24                   'Number of years of AIDS data
```

```
    NHOBS% = 24                 'Number of years of HIV data
    NDOBS% = 24                 'Number of years of Deaths data
    INCN = 0.001                'Increment for N
    INCB = 0.01                 'Increment for βc
    INCY0 = 0.01                'Increment for Y0
    INCR = 0.01                 'Increment for r
    INCLAM = 0.01               'Increment for λ
.....
```

Next, definition of arrays, including the observed data sets, before initial conditions and values for all sub-populations, including the allocation of the initial infectives, are set.

```
.....
    Rho = Betac / gam                   'calculation of ρ
    Rho1 = 1 + Rho                      'calculation of ρ1 = 1 + ρ

    YOLD(1) = (YINIT * Rho) / Rho1      'allocation of initial infectives

    For J2% = 2 To m%:
      YOLD(J2%) = YOLD(J2% - 1) / Rho1:
    Next J2%

    YOLDSUM = 0                         'calculation of total number of infectives

    For J2% = 1 To m%:
      YOLDSUM = YOLDSUM + YOLD(J2%):
    Next J2%

    XOLD = N – YOLDSUM                  'initial value for the susceptible population
.....
```

Main Program, calculation of differential-difference equations.

```
.....
For J% = 1 To nyrs% * NDT%

    Year% = Int((J% / NDT%) + 0.001)

    MX = mu1 * XOLD

    BCXY = (Betac * XOLD * SYOLD / (XOLD + SYOLD))

    XNEW = XOLD + ((LN - MX - BCXY) * DT)
                                                    'calculation of X(t)
    YNEW(1) = YOLD(1) + (BCXY - ((gam + mu2) * YOLD(1))) * DT
                                                    'calculation of Y1(t)
```

```
VNEW(1) = VOLD(1) + (nu2 * YOLD(1) - (gam + theta) * VOLD(1)) * DT
                                                    'calculation of V1(t)

For i% = 2 To m%

    YNEW(i%) = YOLD(i%) + (gam * YOLD(i% - 1) - (gam + mu2) * YOLD(i%)) *
               DT
                                                    'calculation of Yi(t), i=2,...,6
    VNEW(i%) = VOLD(i%) + (gam * VOLD(i% - 1) + nu2 * YOLD(i%) - (gam +
               theta) * VOLD(i%)) * DT
                                                    'calculation of Vi(t), i=2,...,6
Next i%

    For i% = 1 To m%
     SYNEW = SYNEW + YNEW(i%)
     SVNEW = SVNEW + VNEW(i%)
    Next i%

    AZNEW = AZOLD + (b*gam*YOLD(m%) + g*gam*VOLD(m%) – (omeg + nu3) *
            AZOLD) * DT
                                                    'calculation of A(t)
    ZNEW = ZOLD + ((1 - b)*gam*YOLD(m%) + (1 - g)*gam*VOLD(m%) + nu3 *
           AZOLD – omeg * ZOLD) * DT
                                                    'calculation of Z(t)
    NEWAZ = gam * (YOLD(m%) + VOLD(m%)) * DT
                                                'new AIDS cases per time increment
    NEWY1 = BCXY * DT
                                            'new HIV infectives per time increment
    NEWD = (omeg * (AZOLD + ZOLD)) * DT
                                                'new deaths per time increment
    AIDSUM = AIDSUM + NEWAZ                     'total AIDS cases
    HIVSUM = HIVSUM + NEWY1                     'total HIV infectives
    DEATHSUM = DEATHSUM + NEWD                  'total deaths

    If J% Mod NDT% = 0 Then
      J1% = J1% + 1

       NEWAIDS(J1%) = AIDSUM – CUMAIDS          'New expected AIDS cases

       NEWHIV(J1%) = HIVSUM – CUMHIV            'New expected HIV infections

       NEWDEATHS(J1%) = DEATHSUM – CUMDEATH     'New expected Deaths
.....
Re-set values before next iteration.  5 parameter MLE calculations.

.....
```

```
    For i% = 1 To nyrs%

        NEWAIDSTOR(i%) = NEWAIDS(i%)
        NEWDEATHSTOR(i%) = NEWDEATHS(i%)

        NEWHIVSTOR(i%) = NEWHIV(i%)

    Next i%     'storing values of AIDS, HIV and Deaths for comparison with small
                changes in parameter values, i.e. partial derivatives and calculation of
                chi-square.

        N = N * (1 + INCN)

For i% = 1 To nyrs%:
DABYDN(i%) = (NEWAIDS(i%) - NEWAIDSTOR(i%)) / (INCN * NSTOR): Next i%

        N = NSTOR

        Betac = Betac * (1 + INCB)

For i% = 1 To nyrs%:
DABYDB(i%) = (NEWAIDS(i%) - NEWAIDSTOR(i%)) / (INCB * BETACSTOR):
                                                                    Next i%
        N = NSTOR
        Betac = BETACSTOR

        YINIT = YINIT * (1 + INCY0)

For i% = 1 To nyrs%:
DABYDY0(i%) = (NEWAIDS(i%) - NEWAIDSTOR(i%)) / (INCY0 * YINITSTOR):
                                                                    Next i%
        N = NSTOR
        Betac = BETACSTOR
        YINIT = YINITSTOR

        r = r * (1 + INCR)

For i% = 1 To nyrs%:
DABYDR(i%) = (NEWAIDS(i%) - NEWAIDSTOR(i%)) / (INCR * RSTOR):  Next i%

        N = NSTOR
        Betac = BETACSTOR
        YINIT = YINITSTOR
        r = RSTOR

        lam = lam * (1 + INCLAM)
```

```
For i% = 1 To nyrs%:
DABYDLAM(i%) = (NEWAIDS(i%) - NEWAIDSTOR(i%)) / (INCLAM *
                                                          LAMSTOR)
    N = NSTOR
    Betac = BETACSTOR
    YINIT = YINITSTOR
    r = RSTOR
    lam = LAMSTOR

.....
```

Calculation of the Information matrix elements using partial derivatives.

```
.....

  I11 = I11 + (DABYDN(I2%) ^ 2) / NEWAIDSTOR(I2%)
  I12 = I12 + (DABYDB(I2%) * DABYDN(I2%)) / NEWAIDSTOR(I2%)
  I13 = I13 + (DABYDY0(I2%) * DABYDN(I2%)) / NEWAIDSTOR(I2%)
  I14 = I14 + (DABYDR(I2%) * DABYDN(I2%)) / NEWAIDSTOR(I2%)
  I15 = I15 + (DABYDLAM(I2%) * DABYDN(I2%)) / NEWAIDSTOR(I2%)
  I21 = I12
  I22 = I22 + (DABYDB(I2%) ^ 2) / NEWAIDSTOR(I2%)
  I23 = I23 + (DABYDY0(I2%) * DABYDB(I2%)) / NEWAIDSTOR(I2%)
  I24 = I24 + (DABYDR(I2%) * DABYDB(I2%)) / NEWAIDSTOR(I2%)
  I25 = I25 + (DABYDLAM(I2%) * DABYDB(I2%)) / NEWAIDSTOR(I2%)
  I31 = I13
  I32 = I23
  I33 = I33 + (DABYDY0(I2%) ^ 2) / NEWAIDSTOR(I2%)
  I34 = I34 + (DABYDR(I2%) * DABYDY0(I2%)) / NEWAIDSTOR(I2%)
  I35 = I35 + (DABYDLAM(I2%) * DABYDY0(I2%)) / NEWAIDSTOR(I2%)
  I41 = I14
  I42 = I24
  I43 = I34
  I44 = I44 + (DABYDR(I2%) ^ 2) / NEWAIDSTOR(I2%)
  I45 = I45 + (DABYDLAM(I2%) * DABYDR(I2%)) / NEWAIDSTOR(I2%)
  I51 = I15
  I52 = I25
  I53 = I35
  I54 = I45
  I55 = I55 + (DABYDLAM(I2%) ^ 2) / NEWAIDSTOR(I2%)

.....
```

Calculation of elements in vector S.

```
.....
```

```
   DLBYDN = DLBYDN + (O(I1%) / NEWAIDSTOR(I2%) - 1) * DABYDN(I2%)
   DLBYDB = DLBYDB + (O(I1%) / NEWAIDSTOR(I2%) - 1) * DABYDB(I2%)
   DLBYDR = DLBYDR + (O(I1%) / NEWAIDSTOR(I2%) - 1) * DABYDR(I2%)
   DLBYDY0 = DLBYDY0 + (O(I1%) / NEWAIDSTOR(I2%) - 1) * DABYDY0(I2%)
   DLBYDLAM = DLBYDLAM + (O(I1%) / NEWAIDSTOR(I2%) -1) *
                                                        DABYDLAM(I2%)
.................
```

MINVERSE performed on excel Sheet1 before reading in values, also MMult of inverse and S matrix performed on excel Sheet1 to get correction values.

```
.............
    NCOR = Worksheets("Sheet1").Cells(2, 15)

    BCOR = Worksheets("Sheet1").Cells(3, 15)

    Y0COR = Worksheets("Sheet1").Cells(4, 15)

    RCOR = Worksheets("Sheet1").Cells(5, 15)

    LAMCOR = Worksheets("Sheet1").Cells(6, 15)


    N1 = NSTOR + NCOR                 'new suggested value for N1978

    BETAC1 = BETACSTOR + BCOR         'new suggested value for βc

    R1 = RSTOR + RCOR                 'new suggested value for r

    YINIT1 = YINITSTOR + Y0COR        'new suggested value for a1978

    LAM1 = LAMSTOR + LAMCOR           'new suggested value for λ
..............
End Sub
```

CHAPTER 4

THE FINAL FIT OF THE CARDIFF HIV/AIDS EPIDEMIC MODEL

The previous chapter brings to light some limitations of implementing a 5-parameter MLE process within the fitting of the HIV/AIDS Epidemic model, i.e. the assumption of constant parameter values over all time. Also, assessing a large number of parameters at once may increase uncertainty in their final estimated value due to the interactions between parameters that occur during the estimation process and the fact that less is assumed known within the epidemic model. Furthermore, the question of which 5 parameters to estimate needs to be considered. Some parameters, such as the death rate, ω, cause complications if introduced into the MLE technique due to the lack of effect a change in value of this parameter has on the estimated AIDS Incidence. In addition, the death rate in particular can be analysed directly from AIDS data by investigating the ratio between the numbers of deaths from AIDS and the total number of people living with AIDS, within a time period of a year. However, due to the introduction of treatments, it is unrealistic to assume an average constant estimate for the death rate based on all time, 1979-2002. Consequently, further work on the death rate is undertaken within this chapter, including a comparison between values of ω estimated within the model and extracted directly from observed AIDS data.

Within this chapter, AIDS Incidence is the observed dataset extracted from EuroHIV (2003), which the expected AIDS Incidence, generated by the Cardiff HIV/AIDS model, is fitted to, subject to alterations in parameter values. Additionally, HIV Incidence (extracted from the same dataset) can be incorporated into this fit by measuring a combined goodness of fit between observed and expected AIDS, and HIV, Incidence. A chi-square value is calculated over all time periods for the fit between AIDS Incidence (1979-2002) and HIV Incidence (1995-2002). This total χ^2 is then minimised to obtain the best compromised fit for AIDS and HIV data. In addition, later on in this chapter, the involvement of a chi-square value with respect to observed and expected deaths from AIDS is considered.

4.1 Parameter Estimation

The model is split into time eras to overcome the limitation of maximum likelihood estimation, i.e. that of constant parameter values over all time. For each time period separate MLE's are calculated, then all time eras are linked together, using smoothing techniques, to create a unified time model. The HIV/AIDS Epidemic lends itself to the division of time in accordance with the introduction of treatments in 1987 and 1995, as well as observed changes in behaviour and attitudes towards the disease. Consequently, the Cardiff model has been split into three different time eras: Pre-treatment era (1978-1986) - which covers the period from the start of the epidemic, before any treatments were available; Early Treatment era (1987-1994) - relating to the founding of the first antiretroviral drug, zidovudine (AZT) in 1987, the start of mono-therapy and the commencement of treatments such as prophylaxis in 1988; and Combination Treatment era (1995-2002) – concurrent with the introduction of combination 'cocktail' therapies in 1995 and the instigation of highly active antiretroviral treatments (HAART). Figure 4.1, overleaf, demonstrates the separating of these time eras and the order of estimation that is employed for the work within this chapter. The four parameters chosen for estimation, Λ, a_{1978}, βc and r, were chosen due to their difficulty to be evaluated from other resources and their significance within the model, in particular with regard to changing behaviours and the effect of new treatments being introduced. The entry rate into the High Risk Susceptibles, Λ, and the number of High Risk Infectives at the end of year 1978, a_{1978}, can both be assumed to uphold a constant value over all time, 1978-2002, and so are estimated only once throughout the entire stretch of the model. The infectivity parameter, βc, however, is expected to have significantly reduced in value (Winkelstein *et al.* 1988) after public awareness campaigns and media attention were directed towards the HIV/AIDS disease in the mid 1980's. Specifically, in 1985/1986, a government operation promoting safe sex (Johnson & Gill 1989; Evans *et al.* 1993) is believed to have changed the attitudes and behaviours of homo/bisexual men in the UK, resulting in a reduction in the number of sexual contacts per individual, c, and thus, a fall in the total value of βc. Thus, βc is estimated twice throughout the entire time period, firstly from 1978-1986 (βc_1) and secondly from 1987-2002 (βc_2), with this second value of βc assuming a value smaller than, or equal to, that of the first, i.e. $\beta c_1 \geq \beta c_2$. Of course, the

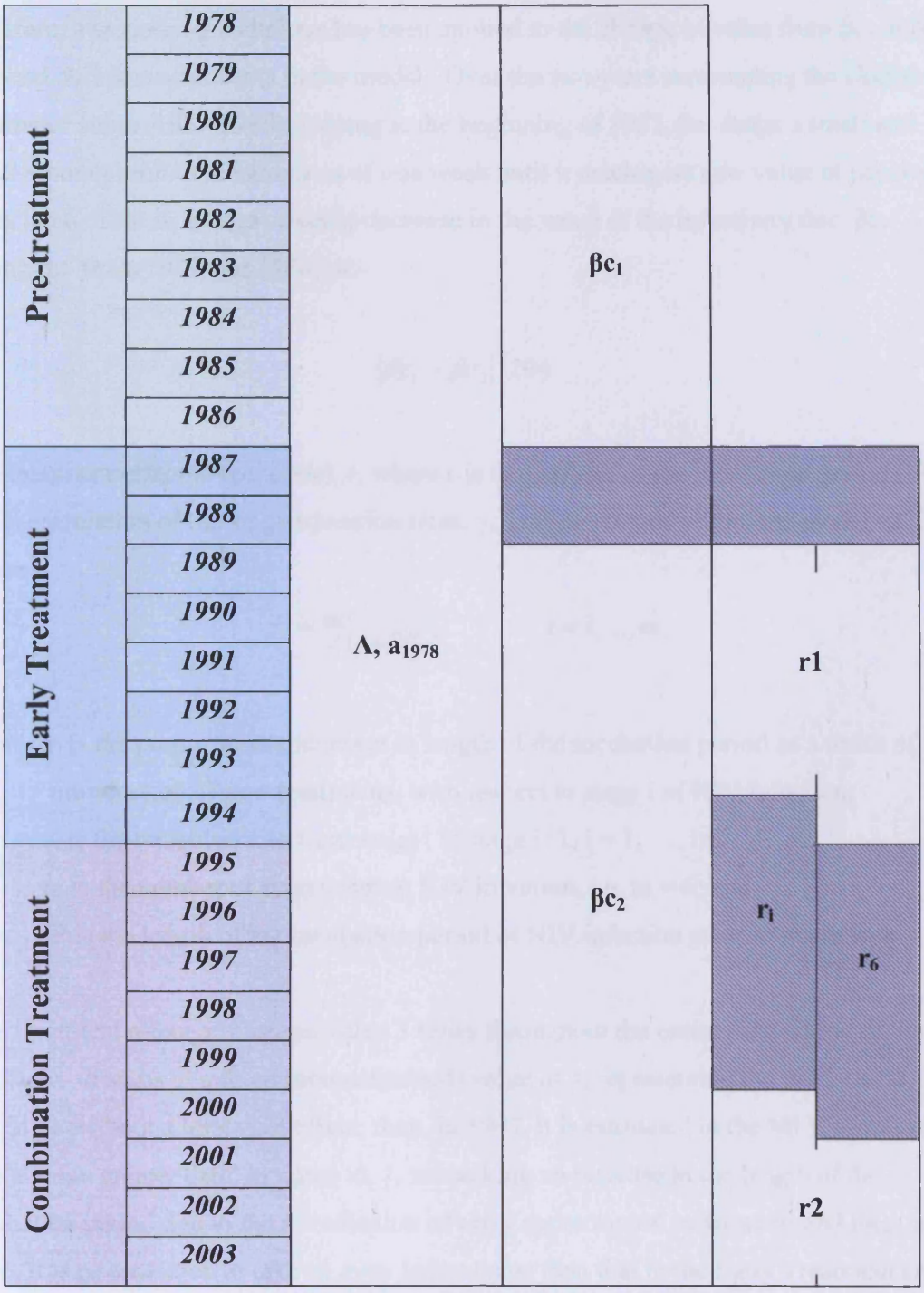

Figure 4.1 **Order of parameter estimation within MLE process**

change in behaviour of the homo/bisexual population in the UK did not occur overnight; therefore, a smoothing technique has been applied to the change in value from βc_1 to βc_2 to avoid abrupt amendments in the model. Over the two years surrounding the change in parameter value (1987-1988), starting at the beginning of 1987, βc_1 drops a small and equal amount each time increment of one week until it reaches its new value of βc_2 two years later. That is, a linear weekly decrease in the value of the infectivity rate, βc, during the years 1987 and 1988, of:

$$|\beta c_1 - \beta c_2|/104$$

The treatment effect in the model, r, where r is the product of the incubation period (IP) in the calculation of the stage transition rates, γ_i, is incorporated within the model as follows:

$$\gamma_i = {}^{m}\!/_{(r_i x IP)}, \qquad i = 1,\ldots,m$$

where r_i is the proportionate increase in length of the incubation period as a result of the introduction of new treatments, with respect to stage i of HIV infection;
γ_i is the transition rate from stage i to stage i+1, i = 1, ..., m;
m is the number of stages during HIV infection, i.e. m = 6; and
IP is the length of the incubation period of HIV infection prior to treatments.

This treatment effect, r, changes value 3 times throughout the entire time period of the epidemic. It starts at a fixed (non-estimated) value of 1, representing the model as it would be without a treatment effect; then, in 1987, it is estimated in the MLE process to take a value greater than, or equal to, 1, mimicking an increase in the length of the incubation period due to the introduction of early antiretroviral treatments; and then, in 1995, it is re-estimated to take an even larger value than that in the Early Treatment era, with respect to the introduction of combination treatments. In other words, each new estimation of r assumes that the IP is increasing in length subject to the two levels of treatment introduction, one in 1987 and the next in 1995, i.e. $r \leq r1 \leq r2$, where r = 1 in

the Pre-treatment era (1978-1986), r1 relates to the first estimation of r for the Early Treatment era (1987-1994) and r2 represents the second estimation of r for the Combination Treatment era (1995-2002). The effect of treatments would not be immediate and so, again, a smoothing technique is applied for each transition of value of r (from r to r1, and then from r1 to r2). A two year smoothing period, from 1987 to 1988, is employed for the conversion of r, in the Pre-treatment era, to r1, in the Early Treatment era, where the additional linear weekly increments in the value of r, starting at the beginning of 1987, are:

$$|r - r1|/104$$

For the initiation of combination treatments in 1995, a longer time for the changeover in value of r is incorporated within the model due to the fact that the effect of new remedies is not just witnessed in the initial impact of highly active antiretroviral therapies but also in the changing infective population to one in an earlier stage of HIV infection, implying that as time progresses the effect of treatments continues to lengthen the incubation period. That is to say, as a result of the introduction of cocktail medications in 1995, a larger proportion of the population of HIV infectives remain in the earlier stages of HIV infection, whilst those in the later stages of HIV infection gradually progress to AIDS, resulting in enhanced effectiveness of the new treatments since more of the population have an improved health status to work with. Plus, as new HIV infections occur, additional benefits are observed due to drug naivety, where individuals have no treatment history thus boasting a lack of resistance to antiretrovirals resulting in greater effectiveness of combination treatments. Furthermore, the increase in expertise and knowledge when treating individuals with a blend of antiretrovirals permits even more substantial results as advanced combinations are being formed and information on drug resistance and treatment history is being more efficiently implemented for each individual. Consequently, this prolonged effect of new combination medicines is represented using a smoothing period of six years. That is, r1 increases to its new value, r2, over six years, with each weekly rise in value equated by:

$$|r1 - r2|/312$$

Moreover, previously it was assumed that each stage within the HIV infective category was of equal length, that is, the IP was constant staged (with 6 stages in total). However, the introduction of highly active antiretroviral therapies have confirmed this assumption to be unrealistic due to the fact that an individual living with stage 1 of HIV infection will be expected to react differently to the new treatments than an individual living with stage 6 of HIV infection. It is likely that an individual in the last stage of progression through the course of HIV will have a poorer health status and will consequently not react as well to new-found medications when compared to a healthier individual. Also, an individual in stage 6 of HIV infection will have lived with the virus for some time, say approximately 10 years, and have been administered throughout most of this time with early treatments such as single dose antiretrovirals (mono-therapy), thus the occurrence of complications with drug resistance and toxicities might be apparent, resulting in a less reactive response to the new combination therapies. This idea of a delayed impact on those in the final stage of HIV infection is incorporated within the parameter estimation process by allowing r to take two values at the same time; r_i relating to stages 1 to 5 of HIV infection and r_6 relating to stage 6 of HIV infection, as demonstrated in equation 4.1 below.

$$\left.\begin{aligned} \gamma_i &= m/(r_i \times IP), \quad i = 1,\ldots,5 \\ \gamma_6 &= m/(r_6 \times IP), \end{aligned}\right\} \qquad \cdots(4.1)$$

Identical smoothing increments are added to r1 for each of the transition paths, r_i and r_6. However, the smoothing process is employed one year later for r_6 than it is for r_i to reproduce the concept of delayed reaction times to treatments concerning those individuals in the last stage of HIV infection, as illustrated in Figure 4.1. Then, once the transition from r1 to r2 has taken place (that is, from 2001 onwards), the stages are assumed to revert back to being equal, that is, $\gamma_1 = \gamma_2 = \ldots = \gamma_6$ once more, thus the incubation period is assumed to return to being constant staged.

Finally, during the estimation of parameters certain constraints need to be enforced in order to maintain realism within the model. For instance, neither of the parameters, the entry rate into the High Risk Susceptibles, Λ, or, the number of High Risk Infectives at

the start of the epidemic, a_{1978}, can take a value of less than zero, as this would suggest that individuals are leaving the model before they have entered, or that a negative number of people were living with HIV at the end of year 1978. As neither of these circumstances is plausible, a non-negativity constraint is placed upon both Λ and a_{1978}. The infectivity parameter, βc, is also subject to a non-negativity restriction, in fact, for the work within this chapter, it is limited to a value no smaller than 0.5. This is due to the assumption that infectivity never drops below this amount, even after the variation in behaviours and attitudes that occurred after the mid 1980's. Reports have suggested, however, that βc could drop to as low as a fifth (Griffiths *et al.* 2000) after public awareness of the virus increased due to advertising campaigns around 1985 (Garfield 1994). Lastly, the treatment effect, r, is given an upper boundary of 5, since it is deemed unrealistic for the effect of treatments to increase the length of the incubation period by more than 5 times its original length, suggesting that an individual could potentially live with HIV for more than 57 years on average (since, r x IP = 5 x 11.4 = 57 years). The complete list of constraints is provided below:

- $\Lambda, a_{1978} \geq 0$, non-negativity,
- $\beta c_1, \beta c_2 \geq 0.5$, non-negativity (since both $\beta > 0$ and $c > 0$) plus boundary for realism,
- $\beta c_1 \geq \beta c_2$, where βc_1 is the first estimate of βc and βc_2 is the second,
- $1 \leq r1 \leq r2 \leq 5$, ensuring that as time progresses the value of r is restricted to only *increase* the IP further due to the introduction of treatments, plus an upper boundary for realism.

4.2 The Final Fit

Employing maximum likelihood techniques on the parameters, Λ, a_{1978}, βc and r, with the order of parameter estimation as described in the previous section of this chapter, improves the fit between the expected AIDS incidence and the observed AIDS incidence data, as attained from the ENAADS dataset (EuroHIV 2003), by suggesting alterations in parameter values until the best fit is obtained. The initial conditions and parameter

values are as listed in Chapter 3, with $\omega = 1$ (Snary 2000, Griffiths *et al.* 2000 and Lowrie 2000), and all model assumptions remain as previously announced. The goodness of fit is measured and the subsequent total χ^2 value is minimised for AIDS and HIV incidence data over the sum of all years; 1979-2002 for the AIDS incidence fit and 1995-2002 for the HIV incidence fit. The final estimated parameter values, that created the best fits for AIDS and HIV Incidence, are as follows:

$$\Lambda = 1665$$
$$a_{1978} = 405$$
$$\beta c_1 = 1.28$$
$$\beta c_2 = 0.5$$
$$r1 = 1.23$$
$$r2 = 4.89$$

The entry rate into the High Risk Susceptibles, Λ; the number of HIV positive individuals at the beginning of the epidemic, a_{1978}; and the infectivity parameter from the start of the epidemic, prior to a change in behaviour, βc_1, all coincide with reported suggested values. If we take the entry rate in its simplest form, $\Lambda = \lambda N_{1978}$, and assume that $\lambda = \mu_1$ such that the arrival rate equals the exit rate of the susceptible sub-population as it would if the HIV/AIDS epidemic was not being considered, then $\lambda = \mu_1 = 0.003$, as obtained from population statistics (DH1 2002) for the exit (death) rate from the general population. This means that the total number of homosexuals in the population at the beginning of the epidemic is equal to $N_{1978} = \Lambda/\lambda = 1665/0.003 = 555{,}000$. For comparison, looking at population statistics, the UK has a total male population (aged 15-64) of about 17 million (DH1 2002). If we then assume an approximate 2-4% of these men partake in homosexual activities (these percentages of homosexual behaviour are based on NATSAL surveys undertaken by Wellings *et al.* 1994 and, more recently, by Erens *et al.* 2003, with the results tabulated in section 5.1 of this thesis) then we have a population of 340,000-680,000 homosexual/bisexual men in the UK. Thus, the estimate of 1665, for the entry rate, Λ, seems to be realistic. In work completed by Snary (2000), the MLE for a_{1978} was found to be 379, calculated from the yearly AIDS data 1979-1994, and the MLE

for βc was derived to be 1.257, assuming a constant value over the years 1979-1994. Griffiths *et al.* (2000) set βc equal to 1, before reducing it when a behavioural change occurred in 1985. Thus, the MLE's obtained during the work in this chapter, based on years 1979-2002, have proven to coincide approximately with other work.

During the estimation process, only one of the constraints listed in the previous section was put into action; the value of βc_2 reached its lower limit of 0.5. Outside of this, all other boundaries that were built in to the model for the estimation procedure were adhered to with no need for enforcement. The value of βc was expected to fall from its previous value, and the constraint was placed in order to prevent the new value of βc to drop by too much. In fact, other work by researchers suggests that βc could drop to a value of about 0.4 (Griffiths & Williams 1994); Griffiths *et al.* (2000) even propose using a value of 0.22 for βc after the change in behaviour witnessed in the mid 1980's, so it is not surprising that, in the work within this chapter, βc_2 wants to fall to a value below 0.5. The value of βc_1 is supported by the idea that the probability of transmission per contact with the virus, β, is approximately 0.1 (Griffiths *et al.* 2000) and the mean number of sexual contacts per homosexual, c, is about 10-12 per year prior to prevention tactics in the 1980's. Dangerfield *et al.* (2001) explore varying infectivity dependent upon the stage of HIV infection; they consider three infective stages within 3 models. Model 1 assumes a patient moves to a state of advanced HIV disease in the event of therapy breakdown; Model 2 assumes a patient moves to a state of late-stage AIDS in the event of therapy breakdown; and Model 3 involves separating out patients on HAART according to their disease state at the commencement of therapy. Within this work by Dangerfield, β is allocated a value of 0.125 for stage 1 of HIV infection in Models 1 and 2 and a value of 0.126 in Model 3. The rate of transmission, β, would not be expected to change value subject to changes in attitudes or to the introduction of treatments; it is the mean number of contacts, c, which is deemed influential throughout this work. With $\beta c_2 = 0.5$, we are suggesting that the mean number of sexual encounters each year has reduced from about 12 to 5, due to the impact of government campaigns exposing the virus, how it is transmitted and how individuals can prevent transmission.

The increase in value of r from 1 to 1.23, in congruence with the introduction of the first antiretroviral drug in 1987, ziduvodine (AZT), and the commencement of other early

treatments such as prophylaxis against opportunistic infections, relates to an increase in the length of the HIV incubation period of 23%. The incubation period (IP) was given an initial value of 11.4 years (derived from Snary 2000) for the Pre-treatment era (1979-1986). This new value of r (r1) has meant that the HIV IP over the years 1987-1995, in the Early Treatment era, is assumed to be 11.4 x 1.23 ≈ 14.022 years; meaning an individual being treated with early treatments, such as monotherapy, can live with HIV more than 2 1/2 years longer than they could before the introduction of treatments. Then, in 1995, with the beginning of the Combination Treatment era, the value of r increases to 4.89 resulting in an increased IP of 11.4 x 4.89 = 55.746 years, postponing the onset of AIDS by more than 44 years in comparison to the Pre-treatment era and by a further 41.5 years in comparison to the Early Treatment era. This implies that an individual contracting HIV today can potentially live with HIV infection for 55 years before progressing to diagnosis of AIDS. This may seem initially unrealistic, but, in fact, holds true to what is being witnessed in clinical research and findings, which suggest the HIV incubation period has been lengthened to such an extent that some patients of the virus die from non-AIDS causes (Sabin 2002).

These final parameter estimations result in a total minimized χ^2 value of: 177.3, made up of a χ^2 value of 32.8 (1dp), summed over the years 1979-2002, for the fit between observed and expected AIDS incidence and a χ^2 value of 144.5 (1dp), summed over the years 1995-2002, for the fit between observed and expected HIV incidence. Within the total AIDS incidence fit, as seen in Figure 4.2, overleaf, separate values for each treatment era can be withdrawn as follows: Pre-treatment era (1979-1986) AIDS $\chi^2 = 9.5$ (1dp); Early Treatment era (1987-1994) AIDS $\chi^2 = 4.8$ and Combination Treatment era (1995-2002) AIDS $\chi^2 = 18.5$. It is worthy of note that due to the inclusion of HIV data into the fitting process, the original possible overall fit for AIDS incidence is compromised somewhat. However, the overall benefits to the model observed when including the HIV data, far outweigh this slight cost in AIDS fit, which is still outstandingly good. As can be seen from the χ^2 values, the majority of the 'bad fit' for the AIDS Incidence data stems from the Combination Treatment era, this could be due to a number of reasons, the first being that this time era is coincident with the years for which the HIV Incidence fit is also taken into account (1995-2002); the second being that

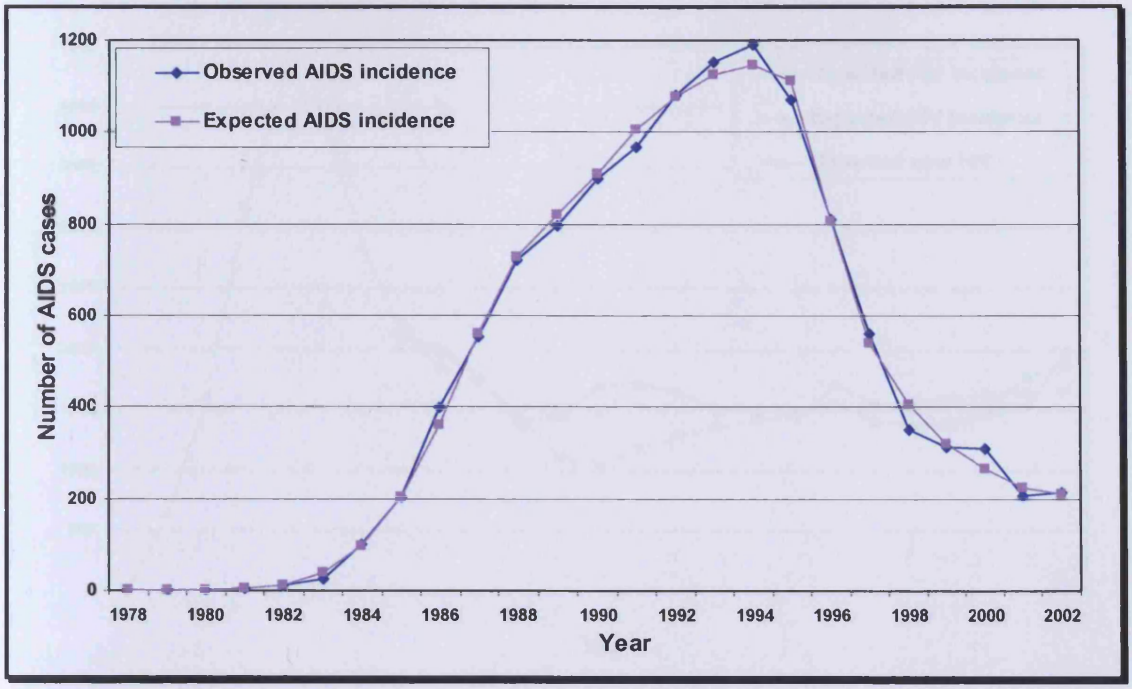

Figure 4.2 **Fit between Observed and Expected AIDS Incidence**

the observed data for the years 1999 onwards are erratic and do not follow a smooth trend line, thus resulting in difficulty in matching exact numbers; and thirdly, the last few years of observed AIDS data may still be subject to some amount of ambiguity due to under-reporting and reporting delays.

The fit between observed and expected HIV incidence data is represented in Figure 4.3 overleaf. This fit is not as close as that of the AIDS Incidence fit partly because HIV incidence data is only available for the years 1995-2002 from the ENAADS dataset (maintaining consistency with the dataset from which observed AIDS cases were extracted). In addition, as with AIDS Incidence, if the HIV Incidence chi-square had been minimized independently, without the inclusion of the AIDS Incidence data, then a better fit to the eight observed HIV data points would have been witnessed. Thus, the fit between observed and expected HIV data is compromised, creating a more accurate and realistic overall model of the HIV/AIDS epidemic. Note that HIV data, in general, is more uncertain than AIDS data due to the difficulties in ascertaining the date of infection, thus it is of greater significance that the model fits the AIDS data than the HIV data. Included in Figure 4.3 is the count of new diagnosed cases of HIV, obtained from HPA

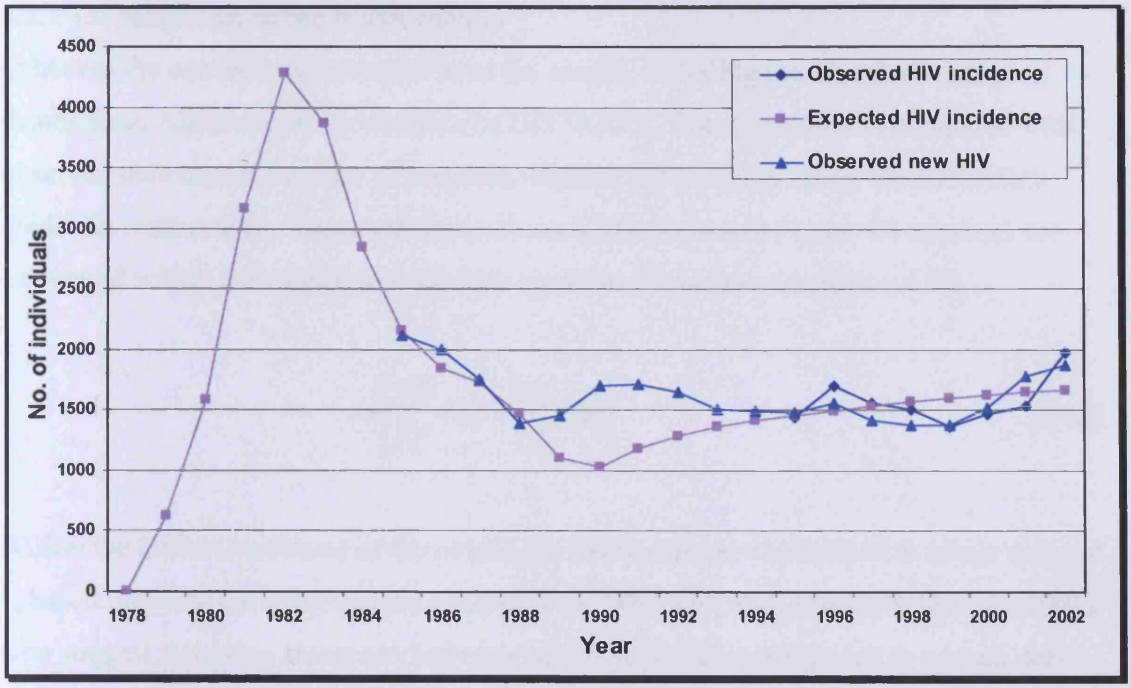

Figure 4.3 **Fit between observed and expected HIV Incidence**

(2005) and by direct contact with the CDSC, which date back to 1985. It is important to realize that new HIV diagnoses and HIV incidence are often not consistent with one another due to the incongruity between diagnosis of HIV and the point at which HIV infection actually occurs mainly resulting from the latent period of HIV, as explained in greater detail in section 2.3.1 of this thesis. However, numbers of newly diagnosed HIV cases can still be a good approximation to HIV incidence figures; hence, comparisons between the expected HIV incidence produced by the model and the observed new diagnosed HIV infections attained from HPA, can be of use. Prior to 1985, it is probable that a shape, like that seen in the expected HIV incidence curve depicted in Figure 4.3, occurs when compared with suggested trends investigated by Snary (2000); Downs & Houweling (1997); Day Report (1996); and De Angelis *et al.* (1998), whom all, in general, recommend that HIV incidence numbers peak in 1982/1983 at a level of about 3500-4500 new HIV cases per year. Post 1983, owing to a government campaign promoting safe sex in 1985/1986 (Johnson & Gill 1989; Evans *et al.* 1993), levels of HIV incidence are assumed to have fallen quite rapidly and, in more recent years, have maintained their reasonably low, and stable, annual levels of about 1600 cases each year.

4.2.1 Investigation of the death rate, ω

Other results can also be extracted from the model, including the expected number of deaths from AIDS and the prevalence of HIV/AIDS. These can also be compared with observed data counts in order to establish whether the model is fitting the HIV/AIDS epidemic realistically. Expected deaths from AIDS, shown in Figure 4.4 overleaf, are calculated within the model described by equation 4.2 below, where $\delta t = 1/52$.

$$\omega\left[\sum_{i=1}^{1/\delta t} A(i) + \sum_{i=1}^{1/\delta t} Z(i)\right] \qquad \ldots(4.2)$$

Within the initial conditions of the model, the death rate, ω was defined to take a value of 1, based on work by Snary (2000) and Lowrie (2000) and, also, Dangerfield et.al. (2001) who suggest a starting mean survival time of 0.9 yr, which corresponds to a mean death rate of 1.1i (since mean survival time = 1 / mean death rate). The value of ω has not been altered or estimated within the model and, consequently, has kept its value as 1 throughout the fitting process. This may be deemed as unrealistic due to the introduction of treatments in 1987 and 1995, which have strong associations with a much reduced death rate. Looking at the trajectory of the expected deaths from AIDS numbers with ω = 1, in Figure 4.4, it is seen that the estimated amounts continually overestimate that which is documented by the CDSC to be the actual numbers of deaths from AIDS that occur for the years 1985-2002. To improve this fit, as performed for AIDS and HIV incidence, observed deaths from AIDS figures, obtained from the CDSC, can be employed to investigate a new variable value for ω for different time eras throughout the epidemic using a goodness of fit measurement for the observed and expected deaths data and minimizing the consequent total χ^2 subject to changes in the value of the death rate, ω. This process of minimizing the χ^2 has been performed and the results exemplified in Figure 4.4 overleaf. The total χ^2 value for the fit of deaths from AIDS data reduced from 817 (when ω was fixed at a value of 1 over the entire time period, 1979-2002) to nearly a sixth of the amount, 138 (rounded to nearest integer). The improvement in fit was created by ω initializing at a fixed value of 1 for the Pre-treatment era (1979-1986), reducing to a value of 0.6 in the Early Treatment era (1987-1994) and then dropping,

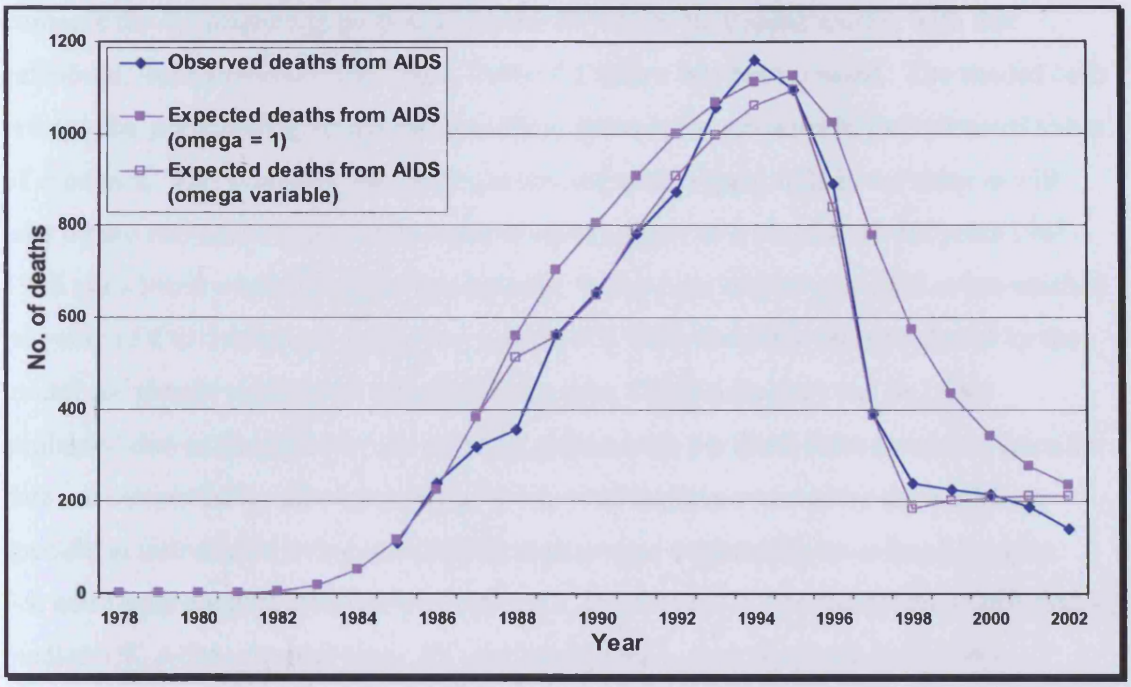

Figure 4.4 **Comparison between observed and expected deaths from AIDS cases**

even further, to a value of 0.09 in the Combination Treatment era (1995-2002). As previously, smoothing techniques are employed for each change in value of ω; a smoothing period of 2 years was utilized, (i.e. smoothing periods over the years 1987-1988 for the first change in value and 1995-1996 for the second) with the weekly decrease in value of ω calculated to be:

$$|\omega_{old} - \omega_{new}|/104$$

The first reduction in the value of ω, due to the introduction of AZT in 1988, coincides with work by Dangerfield *et al.* (2001) whom assume a change in mean survival from 0.9 yr to 1.8 yr, equivalently reducing the mean death rate from $1.1\dot{1}$ to $0.5\dot{5}$. Referring to the AIDS/HIV Quarterly Surveillance Tables (HPA 2005), the yearly number of AIDS diagnoses and deaths, for all exposure categories, can be found dating back to 1989, as well as a cumulative total for the years up to and including 1988. From this, AIDS prevalence can be calculated and consequently an average death rate for all years prior to 1988 and individual death rates for each year 1989-2002 can be produced. In order to

compare the estimated value of ω, as produced within the Cardiff model, with that calculated from available AIDS data, Table 4.1 below has been created. The shaded cells refer to the years during which the smoothing process for a change in the estimated value of ω occurs. The value for the death rate labeled within these cells is the value ω will take by the end of that year, i.e. ω reduces from a value of 1 to 0.6 over the years 1987-1988 via a linear weekly incremental process, thus by the end of year 1988 ω has reached its value of 0.6. Note that, during the years 1989-1994, the death rates produced by the model are almost twice those extracted from data, this discrepancy can be partly explained due to the difference in point of application; the death rates computed from the data are calculated by date (or year) of death whereas those created by the model are specific to individuals living with AIDS, thus are not expected to be as large in value. For additional support refer back to Table 2.2, in section 2.4.7 of this thesis, which details median UK AIDS survival times for year of diagnosis, over the years 1982-1994.

Table 4.1 **Comparison of the value for the death rate, ω**

Year	Death Rate calculated from observed AIDS data (3.d.p.)	Death Rate estimated from Cardiff HIV/AIDS Model
1988 or earlier	0.591	→ 0.6
1989	0.355	0.6
1990	0.345	0.6
1991	0.357	0.6
1992	0.347	0.6
1993	0.379	0.6
1994	0.386	0.6
1995	0.383	→ 0.345
1996	0.348	→ 0.09
1997	0.193	0.09
1998	0.131	0.09
1999	0.113	0.09
2000	0.106	0.09
2001	0.099	0.09
2002	0.099	0.09

4.2.2 HIV Prevalence investigation

Figure 4.5 illustrates the fit for HIV/AIDS Prevalence, as produced by the model with ω variable. Data on observed HIV/AIDS prevalence only dates back to 1996, stemming from a variety of sources: PHLS (2002[b]) provided diagnosed figures for years 1996-1998 and 2000; CDSC (2000) and DH (2000) provided the 1999 prevalence figure; DH (2002) and CDSC (2002) provided data for 2001 and 2002. In addition to these diagnosed prevalence figures, it is expected that a number of HIV positive individuals are unaware of their status; for the years 1999-2002, total prevalence estimates can be obtained from DH (2000) and CDSC (2000) for 1999; PHLS (2002[b]) for 2000; and DH (2002) and CDSC (2002) for 2001 and 2002. These total prevalence estimates (diagnosed and undiagnosed), as obtained from the sources listed above for the years 1999-2002, assume the following percentages of homosexuals are unaware of their serostatus: 25%; 19%; 23% and 24% respectively. Figure 4.5 also shows the expected HIV/AIDS Prevalence as produced by the model for each year 1996-2002. This is the sum of the prevalence at time t in the four infective sub-populations, as defined in equation (4.3).

$$\text{HIV Prevalence} = Y(t) + V(t) + A(t) + Z(t) \qquad \ldots(4.3)$$

Comparison between observed and expected prevalence is difficult due to the few observed statistics available and their inconsistency in origin. However, as an example of a possible good fit the percentage of homo/bisexual men unaware of their infection status is fixed at a decreasing linear amount each year, starting at 49% unaware in 1996 and reducing to 28% unaware by 2002 (falling by 3.5% each year). The reduction in the proportions of individuals unaware of their serostatus each year can be argued partly due to the improvements in surveillance and testing over time, but also as a result of the introduction of treatments; the fear of testing and diagnosis of HIV may have diminished due to an increase in confidence of the new treatments available. A proportion of the population as large as 49% being unaware of their infection in 1996 can not be validated by published literature on the topic; conversely, there is no evidence against this estimate of undiagnosed cases.

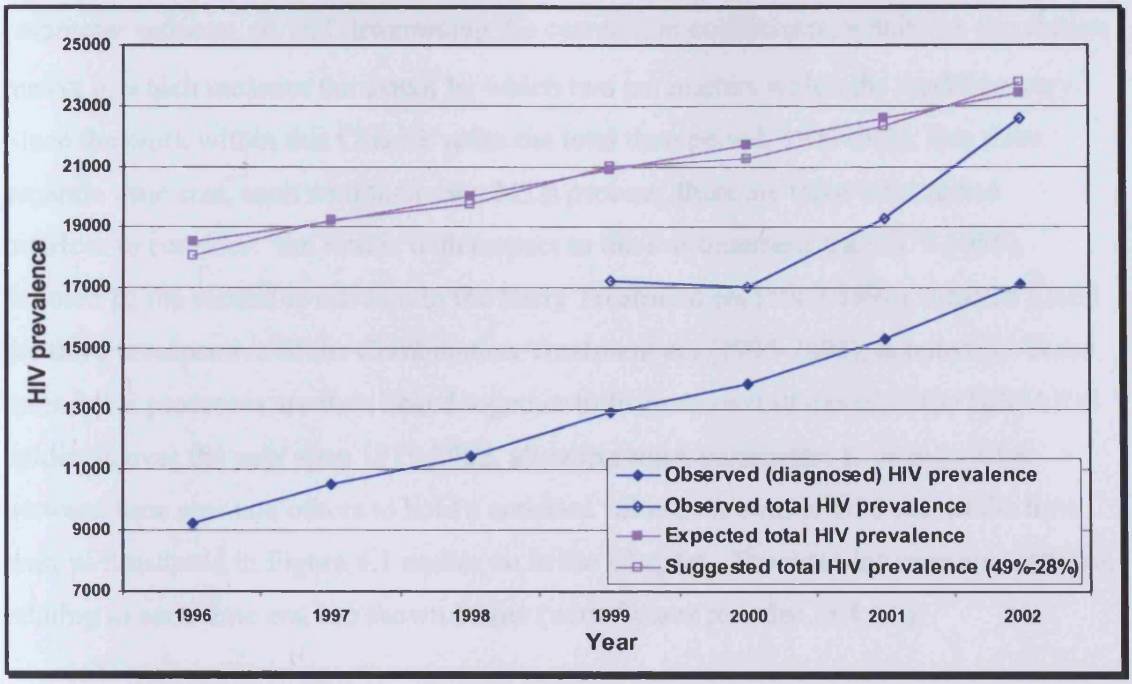

Figure 4.5 **Comparison between observed and expected HIV Prevalence**

The fit between expected and observed HIV prevalence proposed in Figure 4.5 is subject to debatable assumptions and inconsistent data sources and so is deemed to be questionable. Nevertheless, the apparent fit serves the purpose of acknowledging that the expected HIV prevalence, obtained via the model equations, is not too dissimilar from the true HIV prevalence that may exist.

4.2.3 The Information Matrix

As an integral part of the MLE process, the information matrix, as defined and discussed in Chapter 3, is formulated within the iterative procedure $\underline{\theta}_{n+1} = \underline{\theta}_n + \underline{I}^{-1}\underline{S}$. This information matrix is reproduced inside an Excel Spreadsheet, where it is inverted and read back into the VB script for the deduction of parameter correction values to create new and improved estimates, i.e. the multiplication of $\underline{I}^{-1}$ with the matrix containing partial derivatives of the log-likelihood function by each parameter to be estimated, $\underline{S}$. At this point in the program the information matrix and its inverse can be investigated, noting that $\underline{I}^{-1} = \underline{V}$ where $\underline{V}$ is the variance-covariance matrix, in order to calculate the standard error (S.E.), as well as forming subsequent confidence intervals (C.I.'s), for each

parameter estimate, $\underline{\hat{\vartheta}}$, and determining the correlation coefficients, within the correlation matrix $\underline{\rho}$, which measure the extent by which two parameters within the model co-vary. Since the work within this Chapter splits the total time period, 1979-2002, into three separate time eras, each with their own MLE process, there are three information matrices to consider: the first is with respect to the Pre-treatment era (1979-1986), denoted $\underline{I}_p$; the second is relevant to the Early Treatment era (1987-1994), denoted $\underline{I}_e$;and the third is respective of the Combination Treatment era (1995-2002), denoted $\underline{I}_c$. These three MLE processes are then linked together to form an overall model of the HIV/AIDS epidemic over the year span 1979-2002, allowing some parameters to change value between time eras and others to hold a constant value over two, or all three, of the time eras, as illustrated in Figure 4.1 earlier on in the Chapter. The three information matrices, relating to each time era, are shown below (with figures rounded to 4.s.f.):

$$\underline{I}_p = \begin{array}{c} \\ \Lambda \\ \beta c_1 \\ a_{1978} \end{array} \begin{array}{c} \begin{array}{ccc} \Lambda & \beta c_1 & a_{1978} \end{array} \\ \begin{bmatrix} 255.4 & 33210 & 105 \\ 33210 & 4318000 & 13650 \\ 105 & 13650 & 43.13 \end{bmatrix} \end{array}$$

$$\underline{I}_e = \begin{array}{c} \\ \Lambda \\ \beta c_2 \\ a_{1978} \\ r1 \end{array} \begin{array}{c} \begin{array}{cccc} \Lambda & \beta c_2 & a_{1978} & r1 \end{array} \\ \begin{bmatrix} 2640 & 826000 & 976.5 & 287700 \\ 826000 & 267900000 & 303500 & 95650000 \\ 976.5 & 303500 & 368.4 & 105300 \\ 287700 & 95650000 & 105300 & 34730000 \end{bmatrix} \end{array}$$

$$\underline{I}_c = \begin{array}{c} \\ \Lambda \\ \beta c_2 \\ a_{1978} \\ r2 \end{array} \begin{array}{c} \begin{array}{cccc} \Lambda & \beta c_2 & a_{1978} & r2 \end{array} \\ \begin{bmatrix} 3142 & 990800 & 1028 & 304800 \\ 990800 & 321900000 & 320500 & 101300000 \\ 1028 & 320500 & 378.9 & 107000 \\ 304800 & 101300000 & 107000 & 35310000 \end{bmatrix} \end{array}$$

The respective inverted information matrices, that are the variance-covariance matrices for each time era, are then as shown below (to 4.s.f.), using the same sub-script notation as previously. From these matrices, the first point to note is the significant difference between the variances seen in the Pre-treatment era against those seen in either of the Early Treatment era or Combination Treatment era. When calculating the standard error (S.E.) for each parameter (to 4.s.f.), those within the Pre-treatment era are found to be 13.16 for the entry rate, Λ; 0.1381 for the infectivity rate, βc_1; and 13.15 for the number of HIV positive individuals at the start of the epidemic, a_{1978}. The S.E.'s relating to Λ and a_{1978} are comparatively much larger than the S.E.'s calculated for the other two eras. This is due to the fact that the model has only reached the year 1986 in its computations, at which point the information matrix is extracted for investigation. This means that the model has only had 8 years of data to obtain estimates for Λ, βc_1 and a_{1978}. Since both Λ and a_{1978} are eventually being estimated over all three time eras, the larger standard errors witnessed in the Pre-treatment era are not of concern, particularly when noting the S.E.'s seen for the same parameters within the later Treatment eras.

$$\underline{I}_p^{-1} = \underline{V}_p = \begin{array}{c} \\ \Lambda \\ \beta c_1 \\ a_{1978} \end{array} \begin{array}{c} \begin{array}{ccc} \Lambda & \beta c_1 & a_{1978} \end{array} \\ \begin{bmatrix} -173.3 & 1.795 & -146.1 \\ 1.795 & -0.01908 & 1.67 \\ -146.1 & 1.67 & -172.8 \end{bmatrix} \end{array}$$

$$\underline{I}_e^{-1} = \underline{V}_e = \begin{array}{c} \\ \Lambda \\ \beta c_2 \\ a_{1978} \\ r1 \end{array} \begin{array}{c} \begin{array}{cccc} \Lambda & \beta c_2 & a_{1978} & r1 \end{array} \\ \begin{bmatrix} 0.3404 & -0.002222 & -0.1101 & 0.003634 \\ -0.002222 & 0.00001581 & 0.0003591 & -0.00002623 \\ -0.1101 & 0.0003591 & 0.155 & -0.0005466 \\ 0.003634 & -0.00002623 & -0.0005466 & 0.00004382 \end{bmatrix} \end{array}$$

$$\underline{I}_c^{-1} = \underline{V}_c = \begin{array}{c} \\ \Lambda \\ \beta c_2 \\ a_{1978} \\ r2 \end{array} \begin{array}{c} \begin{array}{cccc} \Lambda & \beta c_2 & a_{1978} & r2 \end{array} \\ \begin{bmatrix} 0.04994 & -0.000161 & -0.05534 & 0.0001983 \\ -0.000161 & 0.0000005543 & 0.0001695 & -0.0000007141 \\ -0.05534 & 0.0001695 & 0.08191 & -0.0002567 \\ 0.0001983 & -0.0000007141 & -0.0002567 & 0.000001143 \end{bmatrix} \end{array}$$

Looking at the variance-covariance matrix relative to the Early Treatment era, $\underline{V}_e$, the standard errors for Λ, βc_2, a_{1978} and r1 are calculated to be 0.5834; 0.003976; 0.3937; and 0.00662 respectively, as shown in Table 4.2b overleaf. These are much better results for Λ and a_{1978}, with significantly less variability than seen for the Pre-treatment era, for which the standard errors are displayed in Table 4.2a. Consequently, the parameter values estimated within the year range 1987-1994 are considered to be more reliable. The standard error (S.E.) together with the parameter estimate (Λ = 1665; βc_1 =1.28; βc_2 = 0.5; a_{1978} = 405; and r1 = 1.23) can be employed to create a confidence interval (C.I.) for each MLE, for 95% confidence; these are listed in Tables 4.2a and 4.2b on the next page, with all figures to 4.s.f.. The same information is provided for the Combination Treatment era as for the Early Treatment era and the Pre-treatment era, as seen in Table 4.2c; for this time period the standard errors for each parameter estimate are even smaller than observed in the Early Treatment era, being calculated to 4.s.f. to be 0.2235 for Λ; 0.0007445 for βc_2; 0.2862 for a_{1978}; and 0.001069 for r2. In fact, referring back to the variance-covariance matrix for this time range, $\underline{V}_c$, it is apparent that many of the variances and co-variances are approximately zero; specifically, only the variances of Λ and a_{1978}, together with their co-variance, are greater than zero when rounded to 3.d.p. All of the standard errors in either the Early Treatment era or the Combination Treatment era are appreciably small in terms of their respective maximum likelihood estimates, as is confirmed looking at the extremely narrow ranges in the respective confidence intervals for each parameter estimate as listed in Tables 4.2b and 4.2c overleaf. In order to help explain the reasoning behind the tight scope of the C.I.'s witnessed overleaf, it is important to note that the confidence limits listed in Tables 4.2a, 4.2b and 4.2c are subject to changing parameter values affecting the minimization of the chi-square. That is to say that any alteration in parameter values outside of the range stated by the C.I.'s will result in an increased χ^2 value, calculated from AIDS incidence, HIV incidence and deaths from AIDS data. Thus, in order to maintain such a low chi-square value, and consequent good fit between expected and observed AIDS, HIV and deaths data, the parameters are confined within their respective exceptionally narrow limits.

As a final point, the determinant for each of the variance-covariance matrices can be calculated. Interestingly, all three computed determinants result in near zero values, with

Table 4.2a **Investigation of the Information Matrix extracted at end of Pre-Treatment era, in 1986.**

PARAMETER	MLE	S.E.	C.I.
Λ	1665	13.16	[1639, 1691]
βc_1	1.28	0.1381	[1.004, 1.556]
A_{1978}	405	13.15	[378.7, 431.3]

Table 4.2b **Investigation of the Information Matrix extracted at end of Early Treatment era, in 1994.**

PARAMETER	MLE	S.E.	C.I.
Λ	1665	0.5834	[1664, 1666]
βc_2	0.5	0.003976	[0.492, 0.508]
a_{1978}	405	0.3937	[404.2, 405.8]
r1	1.23	0.00662	[1.217, 1.243]

Table 4.2c **Investigation of the Information Matrix extracted at end of Combination Treatment era, in 2002.**

PARAMETER	MLE	S.E.	C.I.
Λ	1665	0.2235	[1665, 1665]
βc_2	0.5	0.0007445	[0.4985, 0.5015]
a_{1978}	405	0.2862	[404.4, 405.6]
r2	4.89	0.001069	[4.888, 4.892]

the determinant for $\underline{V}_p$ taking the largest value of 0.001988 (4.s.f.). The reason for these low determinants, however, is due to the extremely small values within the respective matrices, as opposed to the matrices being singular.

For each of the time eras a correlation matrix, $\underline{\rho}$, can be determined based on the respective variance-covariance matrix, $\underline{V}$. Again, the same subscript notation as used previously is applied to the correlation matrices shown overleaf which dictate the

correlation coefficients to 4.s.f. These correlation matrices are derived by dividing each variance-covariance coefficient within the matrix $\underline{V}$ by the product of the two relevant standard deviations, i.e. entry $V_{i,j}$, relating to the element in the i^{th} row and j^{th} column of matrix $\underline{V}$, is divided by the product of standard errors, as calculated previously, for the i^{th} and j^{th} parameter, hence all of the diagonal elements within the correlation matrix return a value of 1. From these matrices, relations between pairs of parameter estimates for each time era can be deduced and discussed. To begin with, the only coefficients reasonably close to zero (where a zero value coefficient shows independence between parameters) relate to the number of people living with HIV at the start of the epidemic, a_{1978}, in the Early Treatment era. This parameter produces a correlation value of 0.229 for its relationship with βc_2; -0.210 for its relationship with r1; and -0.479 for its relationship with Λ, all rounded to 3.d.p. A positive correlation coefficient means that the two associated parameters are positively allied, that is, if one increases then the other wants to increase also. For the Pre-treatment era the correlation between a_{1978} and βc_1 is valued at 0.920 (3.d.p.), this demonstrates a strong correspondence between the two parameters with its closeness to 1 suggesting a nearly linear association with positive gradient.

$$\underline{\rho}_p = \begin{array}{c} \\ \Lambda \\ \beta c_1 \\ a_{1978} \end{array} \begin{array}{c} \begin{array}{ccc} \Lambda & \beta c_1 & a_{1978} \end{array} \\ \begin{bmatrix} -1 & 0.987 & -0.844 \\ 0.987 & -1 & 0.920 \\ -0.844 & 0.920 & -1 \end{bmatrix} \end{array}$$

$$\underline{\rho}_e = \begin{array}{c} \\ \Lambda \\ \beta c_2 \\ a_{1978} \\ r1 \end{array} \begin{array}{c} \begin{array}{cccc} \Lambda & \beta c_2 & a_{1978} & r1 \end{array} \\ \begin{bmatrix} 1 & -0.958 & -0.479 & 0.941 \\ -0.958 & 1 & 0.229 & -0.996 \\ -0.479 & 0.229 & 1 & -0.210 \\ 0.941 & -0.996 & -0.210 & 1 \end{bmatrix} \end{array}$$

$$\underline{\rho}_c = \begin{array}{c} \\ \Lambda \\ \beta c_2 \\ a_{1978} \\ r2 \end{array} \begin{array}{c} \begin{array}{cccc} \Lambda & \beta c_2 & a_{1978} & r2 \end{array} \\ \begin{bmatrix} 1 & -0.967 & -0.865 & 0.830 \\ -0.967 & 1 & 0.796 & -0.897 \\ -0.865 & 0.796 & 1 & -0.839 \\ 0.830 & -0.897 & -0.839 & 1 \end{bmatrix} \end{array}$$

The connection between these two parameters has dropped to almost a quarter of its previous amount by the Early Treatment era (with correlation coefficient equal to approximately 0.229 between a_{1978} and βc_2 for the years 1987-1994) in accordance with the change in value of the infectivity rate, reducing from 1.28 to 0.5; the increased length of time since the start of the epidemic when a_{1978} played its most vital role; and the introduction of a fourth parameter into the estimation process, r1. The coefficient between a_{1978} and r1 seen in the Early Treatment era of -0.210 (3.d.p.), and that witnessed between a_{1978} and Λ of -0.479 (3.d.p.) for the same time period, demonstrate negative correlation between the two parameters in each set, i.e. as one increases the other wishes to decrease in value. By the Combination Treatment era this negative correspondence between a_{1978} and r2, and that between a_{1978} and Λ, has strengthened to -0.839 (3.d.p.) and -0.865 (3.d.p.) respectively, suggesting a nearly linear association between the two parameters in either pair with negative gradient. In addition, the relationship between a_{1978} and βc_2 in the Combination Treatment era has strengthened to take on a correlation coefficient of 0.796 (3.d.p.). All other elements, within the correlation matrices on the previous page, take on values close to $\pm$ 1, demonstrating the almost complete dependence the parameters have on one another. Of all the possible pairings of parameters, the sets that have strong negative correspondence (close to -1) include: $[\Lambda, \beta c_2]$; $[\Lambda, a_{1978}]$; $[\beta c, r]$; and $[a_{1978}, r]$, whilst those pairings that have strong positive associations (close to +1) only include: $[\beta c, a_{1978}]$; $[\Lambda, \beta c_1]$; and $[\Lambda, r]$. These relationships between the parameters being estimated seem sensible in terms of the compensatory effects on the fit between observed and expected AIDS data. For instance, if the entry rate, Λ, or the length of the incubation period of HIV, r, increases then, in order to compensate, the infectivity rate, βc, or the number of infected individuals at the start of the epidemic, a_{1978}, would need to decrease in value to keep the same numbers of new AIDS cases. Equally, if the length of the incubation period of HIV, r, increased then the entry rate would also need to increase, or if the infectivity rate, βc, rose then the number of infected individuals at the start of the epidemic, a_{1978}, would need to rise as well in order to keep the same fit for AIDS incidence.

4.3 Extrapolations

Now that a good-fitting, realistic, model has been formulated, it can be used to project the short-term future of the HIV/AIDS epidemic, with the assumption that all parameter values and conditions remain constant. Predicting HIV incidence, AIDS incidence and deaths from AIDS up until the year 2008 (with ω variable), as seen in Figure 4.6 overleaf, shows that levels of incidence are maintaining the stability witnessed in the last few years of the modelled epidemic. This means that, assuming no changes, approximately 1680 people will become infected with HIV each year whilst AIDS incidence and deaths from AIDS figures will remain at 200 new cases each year from now until the final year extrapolated, 2008. This may initially seem like a positive trend creating a hopeful insight of the epidemic to come. However, when investigated deeper there are further predictions that may be cause for concern. Figure 4.7 on the next page shows the prevalence of individuals within the sub-populations, X(t), Y(t), V(t), A(t) and Z(t), extrapolated to the year 2008. Whilst the number of individuals susceptible to HIV/AIDS, X(t), is relatively constant at just under 5000 susceptibles present each year, for the later years of the epidemic, and both High Risk and Low Risk AIDS prevalences, A(t) and Z(t) respectively, are maintaining low counts over the years leading up to 2008, the number of people living with HIV is increasing exponentially year on year. Coincident with the introduction of combination therapies in 1995, prevalence, in both High Risk and Low Risk HIV Infective categories, Y(t) and V(t) respectively, is rising to levels that may be deemed unsustainable in the near future, increasing to amounts never reached before. This is not surprising since treatments such as HAART have reportedly postponed the onset of AIDS, and/or death, to such an extent that it is now believed that virions in the blood can be virtually cleared, given that treatments are initiated early enough with the correct knowledge and expertise applied (Gulick *et al.* 1997; Hammer *et al.* 1997). Also, as seen in Figure 4.6, HIV incidence levels are constant, so more and more people are gathering in the infective stage of the epidemic. It can also be noted from Figure 4.7 that the prevalence of Low Risk Infectives actually overtakes that of the High Risk Infectives in 2002, due to the constant transition of individuals from High Risk to Low Risk behaviour.

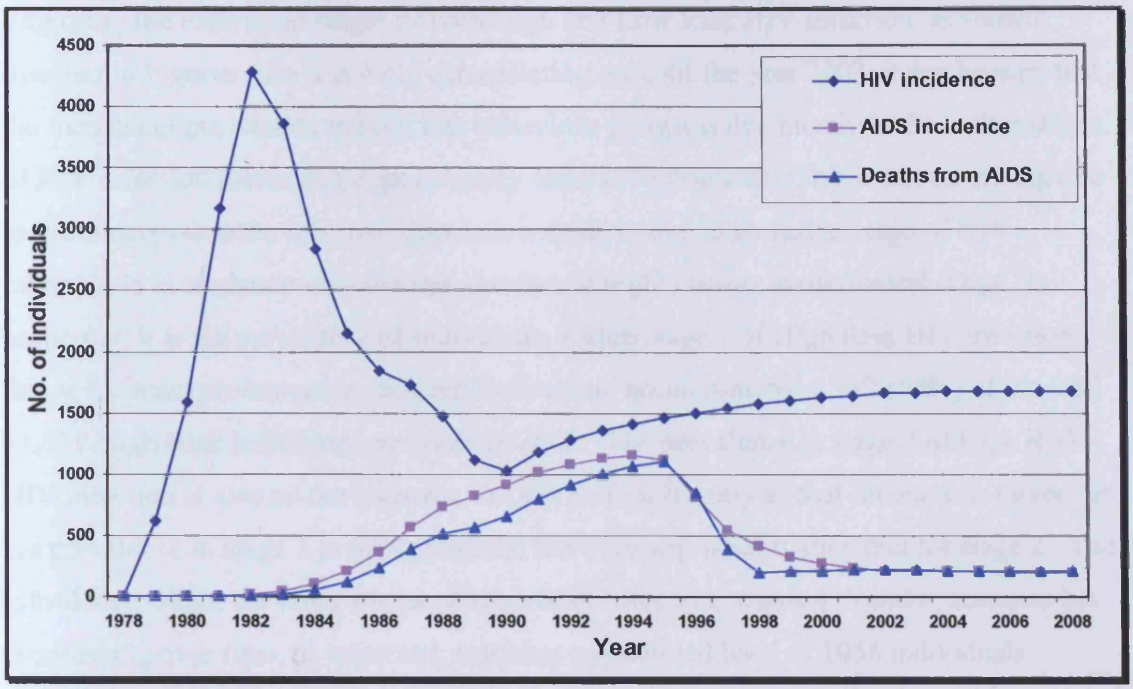

Figure 4.6 **HIV Incidence, AIDS Incidence and deaths from AIDS extrapolated up to 2008**

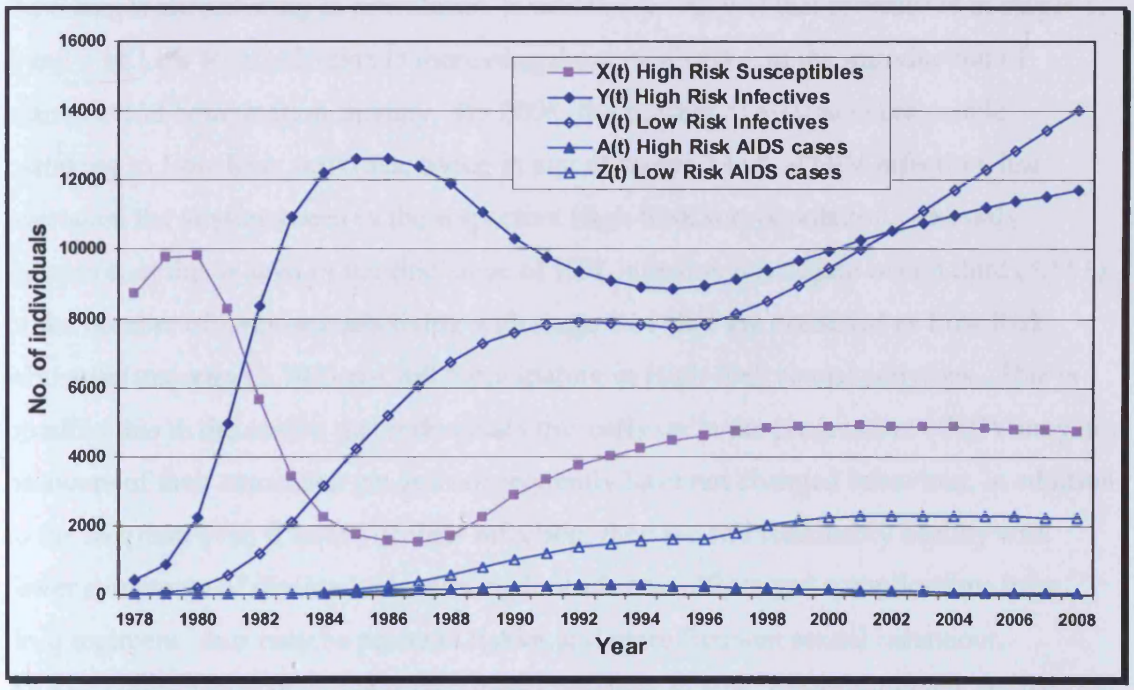

Figure 4.7 **Sub-populations extrapolated up to 2008**

Exploring the individual stages of both High and Low Risk HIV infection, as shown overleaf in Figures 4.8a and 4.8b, extrapolating up until the year 2008, it can be seen that the increasing prevalence in both risk behaviour groups is due mostly to the earlier stages of HIV infection increasing exponentially from 1995 onwards. This is not surprising due to the concept that the infective population shifts to one in an earlier stage of HIV infection in accordance with the introduction of highly active antiretroviral drugs. In particular, it is the prevalence of individuals within stage 1 of High Risk HIV infection that is the most prominent in its steep inclination, accounting for 6,742 (58%) of the total 11,677 High Risk Infections prevalent in 2008. The prevalence in stage 2 of High Risk HIV infection is also on the increase, but not as significantly as that for stage 1, moreover the prevalence in stage 3 is rising slightly, but even less notably than that for stage 2. The prevalence within the other stages of High Risk Infection, stages 4, 5 and 6, seems to be diminishing over time, as expected, reaching a combined level of 1058 individuals prevalent by 2008, only 9% of the total High Risk prevalence for this year. The Low Risk Infective stage prevalence figures, in Figure 4.8b, illustrate the explanations behind the exponential increase witnessed in the total Low Risk Infective prevalence. None of the 6 stages are reducing in prevalence, in addition to the fact that prevalence in stages 1, 2 and 3 of Low Risk Infection is increasing dramatically due to the introduction of antiretroviral combination therapy. By 2008, the number of HIV positive people partaking in Low Risk activities, living in any of stages 2 to 6 of HIV infection, has overtaken the amounts seen in the respective High Risk sub-population. The only exception of this is seen in the first stage of HIV infection where just over a third (3,551) of the number of homosexuals living with stage 1 of HIV are classified as Low Risk, whilst the majority (6,742) are still participating in High Risk sexual activities. This is possibly due to the notion that individuals this early on in the progression of HIV may not be aware of their serostatus yet and consequently have not changed behaviour, in addition to the fact that, even if aware of their infection, they are still reasonably healthy with fewer symptoms of disease and suffering less adverse effects and complications from drug regimens, thus may be prone to riskier and more frequent sexual behaviour.
As a consequence of the greater prevalence numbers of HIV, future estimates of HIV incidence might be set to increase since there are more people living with HIV in the

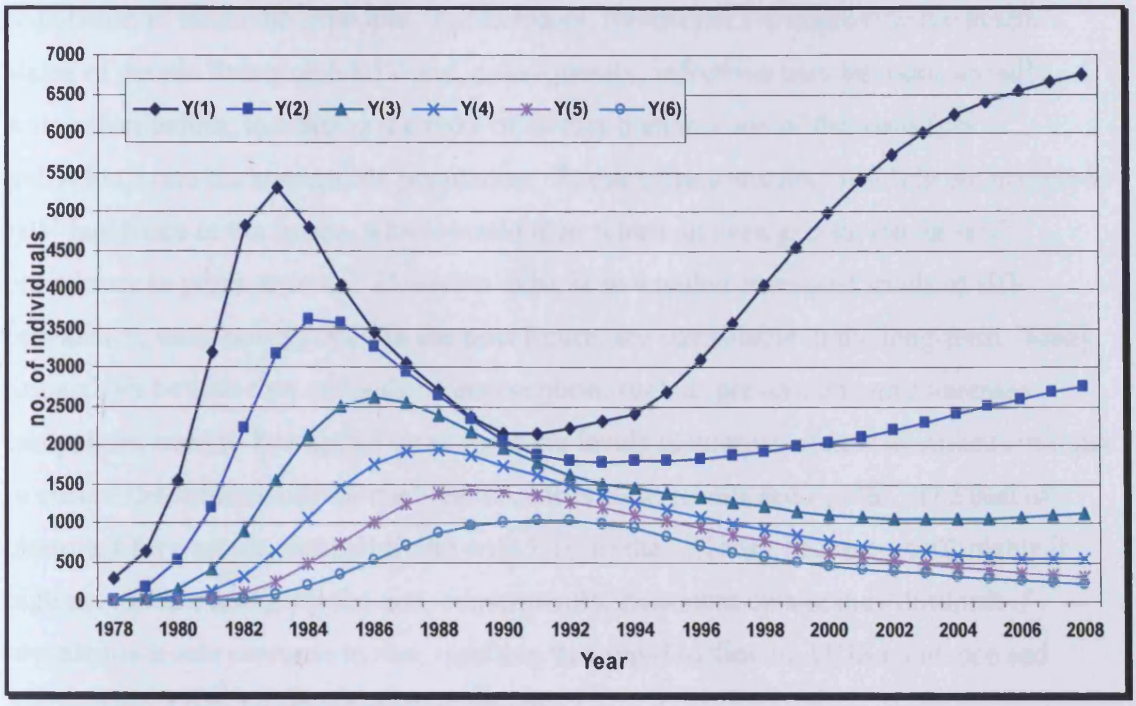

Figure 4.8a **Stage prevalence within the High Risk Infective category, extrapolated up until 2008.**

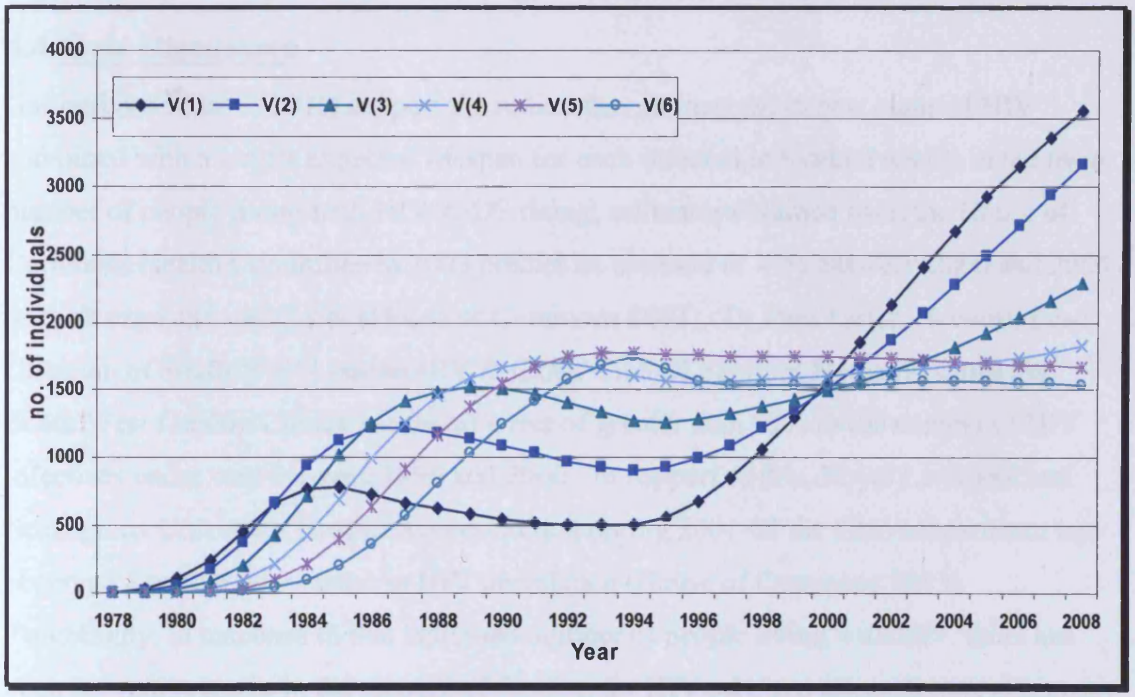

Figure 4.8b **Stage prevalence within the Low Risk Infective category, extrapolated up until 2008.**

population to infect other people. Furthermore, treatments are improving the health status of people living with HIV and, consequently, infectives may be more sexually active than before, increasing the risks of further transmission of the virus (per individual) into the susceptible population. These behaviours may result in an increase in HIV incidence in the future, which would then return an even greater rise in HIV prevalence in years to come. Concerns exist as to whether increased levels of HIV prevalence, such as suggested in the near future, are sustainable in the long-term. Many researchers believe that methods of intervention, such as prevention and awareness campaigns, need to be stepped up to meet the levels of success of new treatments in order to ensure the continuation of the beneficial treatment results seen so far. The cost of treatment for every individual living with HIV in the UK may become unaffordable if high prevalence levels persist and, consequently, treatment uptake may diminish if prevalence levels continue to rise, resulting in a rapid incline in AIDS incidence and deaths from AIDS to unprecedented amounts.

4.4 Cost Discussion

Gazzard & Johnson (2003) support the notion that an increase in new cases of HIV combined with a longer expected lifespan for each infected individual results in the mean number of people living with HIV/AIDS rising; estimates obtained from the House of Commons Health Committee in 2003 predict an increase of 47% between 2000 and 2005 over all exposure categories (House of Commons 2003). Dr Paul Lister, Network Lead Clinician of South West London HIV & GUM Clinical Services Network, states that South West London Clinics witnessed a rise of greater than 75% in the number of HIV infectives under care between 1996 and 2000. In support of this, Royal Liverpool and Broadgreen University Hospitals reported that during 2001-02 the GUM department had observed a continued increase in HIV prevalence (House of Commons 2003). Troublingly, in response to this increased number of people living with HIV, there has been no improvement in the amount of funding for HIV care and management, although funding did endeavour to meet the escalation of drug costs. In fact, concern as to the effects of under-funding is provided from Homerton University NHS Trust in Hackney

which testifies that some patients are now being refused access to HIV treatments and services on account of increased disease prevalence and demand.

In 2000, the average lifetime treatment cost for a HIV positive individual, which implies both spending on drugs and use of hospital resources (inpatient and outpatient), was evaluated to be in the range of £135,000 to £181,000 (DH 2001[b]). As maintained by the National Association of NHS Providers of AIDS Care and Treatment (PACT), the annual cost of managing a single patient with HIV in the UK is £15,000 (House of Commons 2003). The overall expenditure on HIV treatment and care in the UK, in 2002-03, was estimated to be £345 million, with the prospect of additional diagnoses costing a further £30 million (House of Commons 2003). Assessment of cumulative lifetime treatment costs by 2007, estimated by The Medical Foundation for AIDS and Sexual Health (MEDFASH), suggested that expenses will be greater than £5 billion for individuals known to be living with HIV. The cost/benefit of preventing a single case of HIV was estimated by MEDFESH to be approximately £0.5 million which agrees with the HPA who stated, in 2004, that each HIV infection prevented saves between £500,000 and £1 million (HPA 2004). MEDFASH then go on to conclude that averting half the annual number of existing new infections of HIV would bestow a cost/benefit of £1 billion (House of Commons 2003).

The House of Commons Health Committee reports that £165 million was appointed for treatment and care of HIV in 2001-02. In contrast to this seemingly large amount of money, present estimates are that suppliers of HIV services are under-funded each year by around £3,000-5,000 per patient. As the HIV incubation period is lengthened, and people are living with HIV for longer, the per-patient rate escalates. Additionally, as new increasingly expensive drugs are introduced, such rises in costs are likely to be steeper. Consequently, the financial burden caused by the HIV/AIDS epidemic on the NHS is increasing; HIV drug therapy is the largest burden on the allocation of funds for treatment and care. Continuous money shortages in HIV services, as well as the ever increasing price and choice of antiretroviral drugs, results not only in clinicians struggling to advise on apposite therapies, but also in necessary funds being redirected from other sexual health services (House of Commons 2003). The cost of antiretroviral regimens and the impact that this has on health finances has been a popular area of debate for many years

(Beck *et al.* 1994[a], 1994[b], 1996 and Beck & Mandalia 2003); recently, a pharmacoeconomic study suggested that the increase in expenditure on drugs experienced due to the introduction of HAART, has been compensated by the changing proportions of people using either inpatient or outpatient services (Beck & Mandalia 2003). Then again, the same article demonstrated that because the usage of new drugs and regimens are increasing (salvage therapy, for instance), drug costs may rise even further (Beck & Mandalia 2003, Youle 2001).

Increasing costs of HIV treatment and care in the UK are problematic for the NHS, which has limited resources available. Furthermore, ring-fenced funding for HIV treatment from the rest of a health authority's budget ended in 2002 and changes to the commissioning of HIV services were seen (All-Party Parliamentary Group on AIDS 2003, House of Commons 2003). The House of Commons Health Committee (2003) explains that Primary Care Trusts (PCTs) are now obliged to budget services for HIV positive individuals via mainstream allocations. The concern of many researchers in the field is the detrimental effect on HIV/AIDS service provision that the conclusion of ring-fenced funding will bring, even with assurances from the Department that investments in HIV treatment and prevention will be monitored (House of Commons 2003). Budget increases have been pledged to the NHS from 2002 to 2007, however, the sum of money that will be accessible for HIV services at this time is unsure, particularly as HIV treatment and care competes directly for funding with other services, possibly not being viewed compassionately as a result of the ongoing stigma linked with the disease (All-Party Parliamentary Group on AIDS 2003).

CHAPTER 5

WHAT-IF SCENARIOS

Within Chapter 4, the final Cardiff model was produced with parameter values either derived from previous literature, population statistics or maximum likelihood estimation. Within this chapter, the composed model is employed in order to predict the path of the HIV/AIDS epidemic over the near future given the occurrence of specific potential situations. For instance, the number of homo/bisexual men in the UK population could change or the behaviour of individuals might be modified as a result of future possible prevention campaigns. The most probable scenarios that may arise can be deduced by researching modern literature on the HIV/AIDS epidemic; looking at trends in other STI's; examining HIV/AIDS specific organizational web-sites and publications; surveying government policies and priorities towards HIV/AIDS, with specific regard to the availability of funding; and investigating changes in population statistics. The four most likely modifications that may be witnessed in the near future are: A change in the number of homosexuals living in the UK (either increasing or decreasing); an increase or a decrease in risky sexual behaviour; the introduction of a preventive vaccine; or the introduction of a therapeutic vaccine. Each of these situations is considered individually within this chapter to see the effect that alterations in the value of the relevant parameters will have on the epidemic's future path. All other parameters are assumed to maintain their previous values, as defined in Chapters 3 and 4. Forecasts will be made up until the year 2012, under the assumption that each change in the epidemic occurs in 2005, with a two year smoothing period from 2005 to 2007, giving a five year projection from 2007 to 2012, with the new constant parameter values in place.

The model derived in Chapter 4 was based upon AIDS incidence data relating to the year span 1979-2002, with base year 1978. Figures 5.1a, 5.1b and 5.1c show the extrapolated trajectories of the model up until the year 2012, assuming no change in parameter values. It is worth noting that the epidemic's course, seen in these Figures up until 2002, will not be affected by any future change in parameter values, thus, in order to illustrate only the time era when the epidemics path is influenced by changing parameter values, each 'what-if' scenario is displayed in Figure form relating to the 10 years 2002-2012 only.

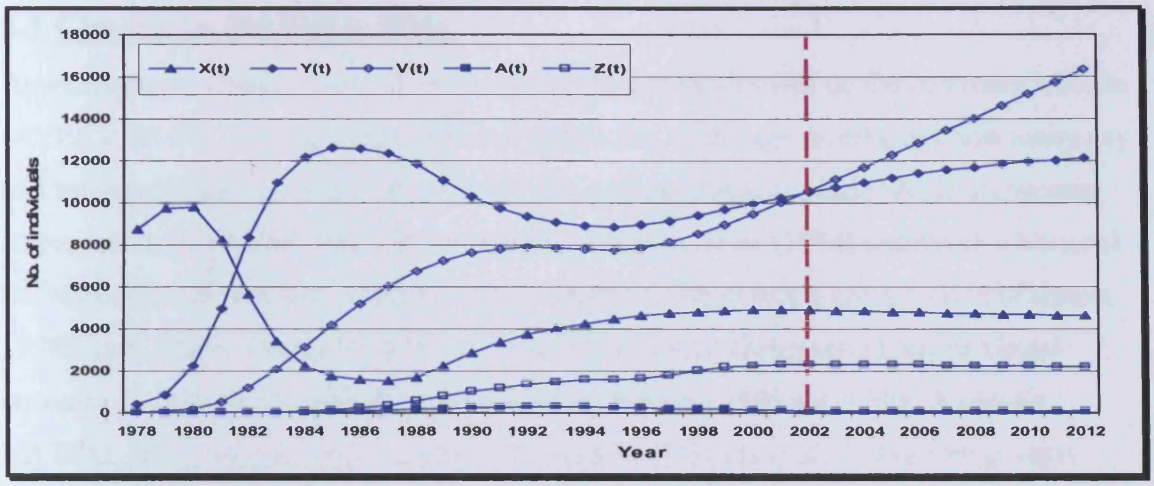

Figure 5.1a **Cardiff Model trajectories for prevalence in sub-populations, 1978-2012.**

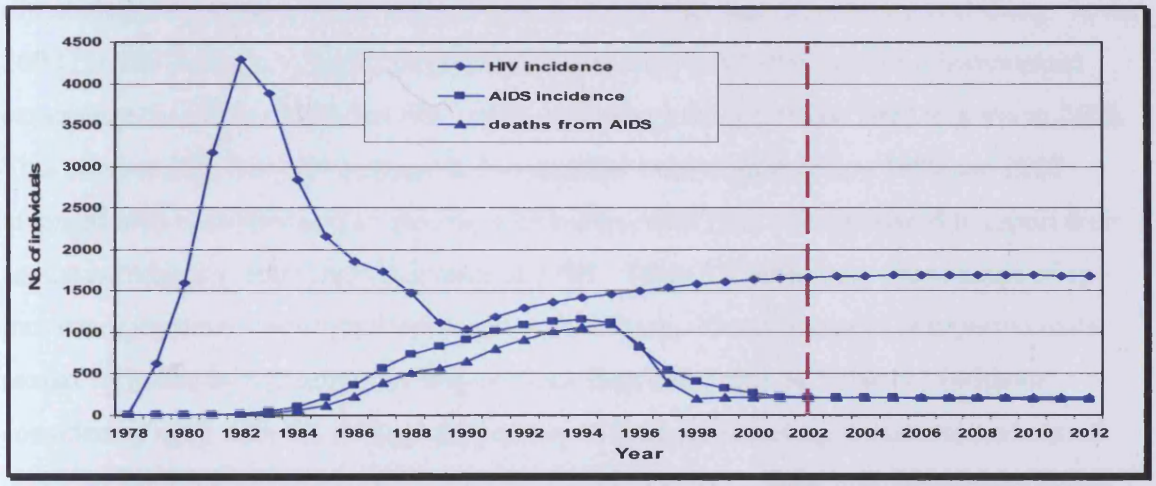

Figure 5.1b **Trajectories for HIV/AIDS incidence and deaths from AIDS, 1978-2012.**

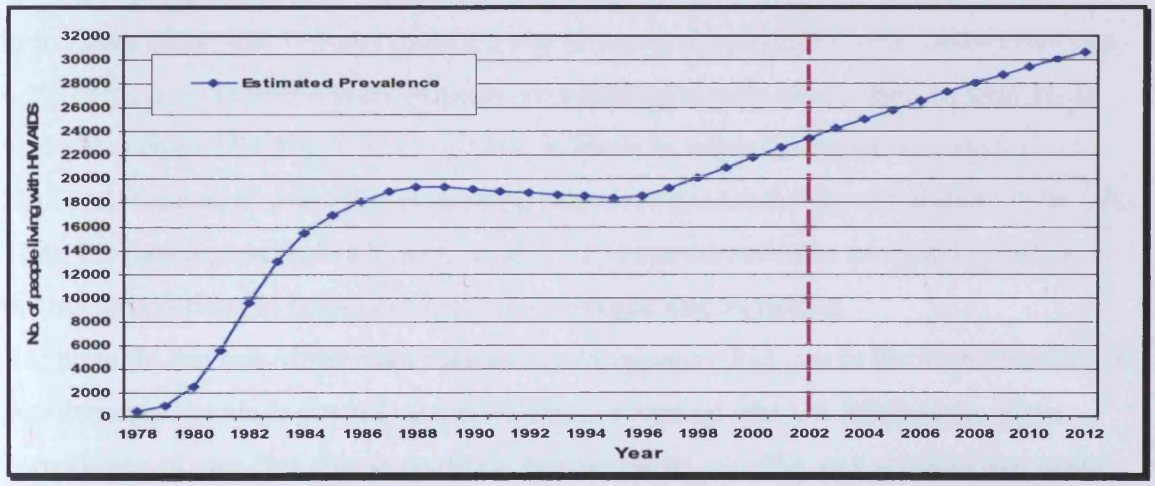

Figure 5.1c **Cardiff Model trajectory for total HIV/AIDS prevalence, 1978-2012.**

5.1 Change in the Entry Rate

Assessments on changing sexual behaviour in Britain are detailed on the Avert.org website (AVERT 2005[b]). The fact sheet provided within this web-page investigates how many gay and lesbian people live in the UK and how this sub-population of individuals is changing its proportion within the total UK population. Wellings *et al.* (1994) undertook a National Survey of Sexual Attitudes and Lifestyles (NATSAL) observing a cross section of almost 19,000 individuals throughout Britain in order to examine their perceptions on sexual encounters, including homosexual relationships, between 1989 and 1990. A second NATSAL study was repeated between 1999 and 2001 (Erens *et al.* 2003) with a subject group of just over 11,000 people. Table 5.1 overleaf compares the results of both studies, illustrating how same sex sexual behaviour in the British male population is shifting. In the 2000 NATSAL study, a larger proportion of men admitted to having had a homosexual experience than they did in the 1990 study, increasing from 5.3% in 1990 to 8.4% in 2000. This trend could reflect an increase in homosexual behaviour between 1990 and 2000 amongst men in Britain and/or that more homo/bisexual men were prepared to report their sexual activities in 2000 than they were in 1990. Table 5.2 introduces the concept of age into changing sexual behaviour among men in Britain. The differences in reported male sexual activities by age group are less obvious than those seen in Table 5.1 (without considering age), with the average proportion of men participating in homosexual sexual activities for 2000 being the same as it was in 1990 (4.3%). What one can construe from the male data seen in Table 5.2, is that homosexual encounters occur far more often for individuals older than 18 years of age; 5.6% of young men aged between 18-19 years and 6.3% of those aged between 20-24 years are both higher proportions than the total 16-24 year old average of 4.3%. Under reporting is likely to occur during surveys such as the NATSAL studies, possibly due to ongoing prejudice against the gay community in the UK. Thus, the data represented in Tables 5.1 and 5.2 is considered to be an underestimation of the true proportions of homosexual activity amongst men in Britain.

It is possible that one of the main reasons for the apparent increase in the male homosexual population in Britain is down to status acceptance amongst the UK inhabitants. More homo/bisexual men feel able to confront their sexuality, possibly as a result of two major changes which have taken place in the UK (and other parts of Europe and the United States

	NATSAL I (%) 1990	NATSAL II (%) 2000
Ever had a sexual experience, not necessarily including genital contact, with a partner of the same sex?	*5.3*	*8.4*
Ever had sex with a same sex partner, including genital contact?	*3.7*	*6.3*
Have you had a same sex partner in the last five years?	*1.4*	*2.6*

Table 5.1 **Findings of NATSAL surveys among men in Britain.**

	NATSAL I (%) 1990	NATSAL II (%) 2000			
		16-17yrs	18-19yrs	20-24yrs	Average, 16-24 yrs
Ever had a sexual experience with a same sex partner?	*4.3*	*1.2*	*5.6*	*6.3*	*4.3*
Ever had sexual intercourse/genital contact with a same sex partner?	*2.4*	*1.2*	*2.3*	*4.2*	*2.6*

Table 5.2 **Findings of NATSAL surveys among 16-24 year old men in Britain.**

of America) over recent years, these are (AVERT 2005[b]):

- More frequent imagery of gay and lesbian people (e.g. popular gay musicians and gay characters in mainstream television shows)
- More gay and lesbian strives for equality which attracts public, political and legal attention (e.g. the demand for parenting and marital rights).

Within this section the focus is on a change in the entry rate to the epidemic model due to the idea that the homosexual population in the UK has either grown or reduced in size, as discussed in the previous literature. These same concepts can be applied to changing sexual behaviour of homosexual men, however may not be directly linked to greater or lesser risk-taking. The notion of more or fewer homo/bisexual men partaking in high risk sexual activities is considered in the next section, specifically looking at the effect of a change in the infectivity rate, βc. In order to model the possibility of an increasing (or decreasing) homosexual population in the UK, the entry rate into the High Risk Susceptible category, Λ, can be enlarged or reduced accordingly. The change in value of the entry rate occurs in 2005, assuming the homo/bisexual population increases or decreases at this time, and takes two years of weekly linear increments before reaching its final value of either $\pm 10\%$ on its original value, by 2007. More specifically, Λ will take the value of 1665 up until 2005 (since this is the value it was estimated to be in Chapter 4, using MLE) at which point it will begin its transformation over two years, 2005-2006, to form its new value of $1665 \pm (0.1 \times 1665) = 1498.5$ or 1831.5, by 2007. The two year transition represents the idea that changes in the population do not occur within a single time increment of 1 week, but more likely as a steady progression over time, thus avoiding abrupt changes in parameter values and smoothing out 'kinks'. The weekly increment is taken as a linear amount, as in Chapter 4, and is calculated for this particular change in parameter value as follows:

$$|\Lambda_{old} - \Lambda_{new}|/104$$

Figures 5.2a, 5.2b and 5.2c, incorporated over the next few pages, show the effect on the epidemics path when altering the entry rate into the High Risk Susceptibles in this way.

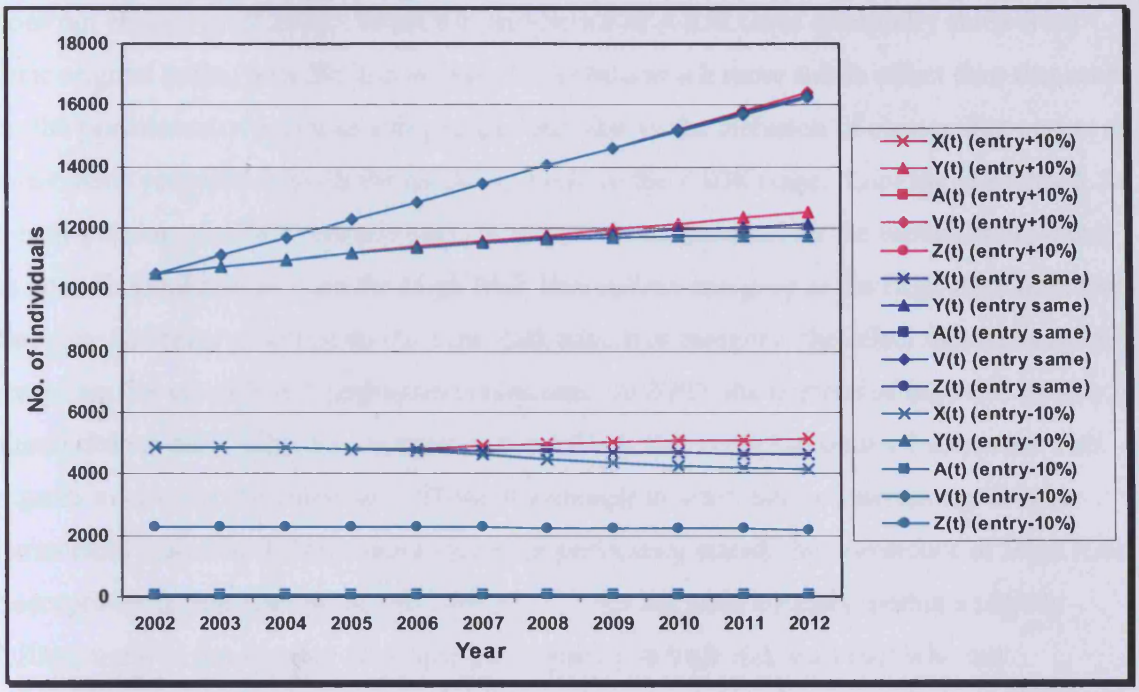

Figure 5.2a **Sub-populations within the Cardiff model with the Entry Rate, Λ, varying from 2005, reaching ±10% by 2007.**

Note that up until 2005 all scenarios follow the same path due to the fact that, as yet, there have been no modifications performed within the model. It is post 2005 that the effect of changing the value of the entry rate, Λ, by ±10%, or not at all, can be observed.

From Figure 5.2a, it is noticeable that a change in the entry rate from 2005 onwards, of ±10%, specifically affects the susceptible and infective sub-populations, X(t), Y(t) and V(t). However, extrapolating up until the year 2012, there is no apparent effect on the AIDS case sub-populations, A(t) or Z(t). This is because different sub-populations within the model have different reaction times to a change in parameter value; in particular, a change in entry rate will affect the High Risk Susceptible sub-population first and the AIDS case sub-populations last. The fact that A(t) or Z(t) do not change prior to 2012 is dependent on the length of the HIV stages within Y(t) and V(t); if projected over a longer period of time A(t) would change, however, it is not wise to extrapolate beyond 2012 for reliability of predictions. Figure 5.2a shows this difference in reaction times, with the prevalence of High Risk Susceptibles, X(t), and the prevalence of High Risk Infectives, Y(t), reacting in 2006, slightly before the prevalence of Low Risk Infectives ,V(t), which

does not change until 2010. When the prevalence of AIDS cases eventually shifts from their original paths, post 2012, it is expected to be a much more subtle effect than that seen on the prevalence of previous sub-populations, due to the diffusion of change that occurs as individuals progress through the model en route to the AIDS stage. Looking at Figure 5.2a, this dispersion of effect, that a change in entry rate has incurred on the model, is apparent; as an individual moves from the High Risk Susceptible category to the High Risk Infective category and then, possibly, to the Low Risk Infective category, the effect that a change in entry rate has on each sub-population decreases. In 2005, the number of high risk people susceptible to HIV, X(t), was estimated to be 4801; this is the same for all scenarios with regards to altering the entry rate. Without a change in entry rate and assuming all other parameters maintain their constant values as previously stated, the prevalence of High Risk Susceptibles is predicted to be 4617 by 2012. This suggests a steady, perhaps slightly falling, trend in the number of people participating in high risk activities who are susceptible to HIV/AIDS. In comparison to this, the number of High Risk Susceptibles, with a change in entry rate, by 2012, is either greater than (if Λ increased by 10%) or less than (if Λ decreased by 10%) the 4617 prevalence by nearly 500 homosexuals (this is a change in prevalence of X(t) of just over 10%). This rise, or fall, in the number of Susceptibles has had a consequent effect on the number of High Risk Infectives, Y(t), which by 2012 has either increased (if Λ increased by 10%) or decreased (if Λ decreased by 10%) by approximately 400 people (roughly $\pm$ 3%) on its predicted original value of 12,104 people when no change in entry rate is considered. Furthermore, this change in prevalence of High Risk Infectives, Y(t), has affected the prevalence of Low Risk Infectives, V(t), which by 2012 is about $\pm$ 90 individuals ($\pm$ 0.55%) on its original prediction (assuming no change in entry rate occurs) of 16,308 people.

Figure 5.2b shows the trajectories of HIV incidence, AIDS incidence and deaths from AIDS, over the years 2002-2012, considering a change in the entry rate of either $\pm$10%, or not at all, in 2005. Similar to Figure 5.2a, AIDS incidence and deaths from AIDS numbers do not seem to be affected by a change in entry rate, prior to 2012. This can be explained by the delayed and reduced effect that a change in entry rate has on these later stages within the model, as with the prevalence of AIDS cases, A(t) and Z(t). HIV incidence, however, has significantly altered its course due to a change in entry rate value. The variation begins

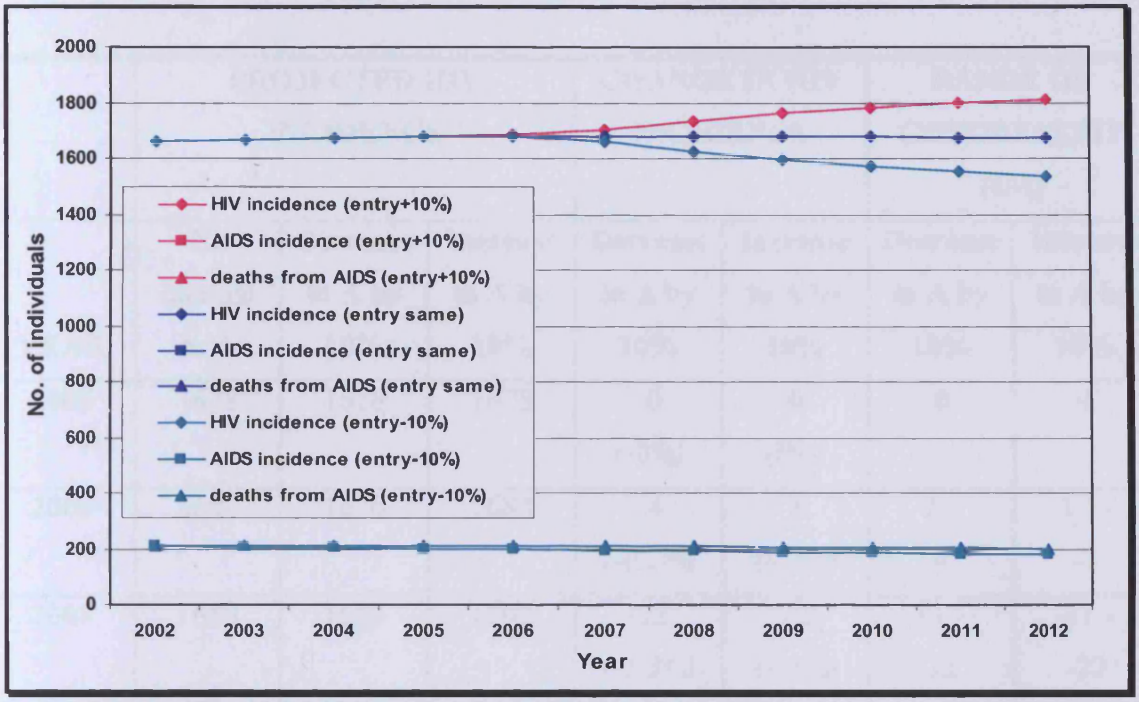

Figure 5.2b **HIV, AIDS and deaths cases with the Entry Rate, Λ, varying from 2005, reaching ±10% by 2007.**

almost immediately, in 2006, with HIV incidence rising if the entry rate increases by 10% in 2005, and falling if the entry rate decreases by 10%. In 2005, the annual number of homosexuals predicted to contract HIV is 1678. Assuming no change in entry rate, the number of new infections each year is projected to maintain a reasonably stable level, up until 2012. In comparison to this, if a 10% rise in entry rate takes place in 2005, then for each year after this point (2006 through to 2012) an increase in the annual number of new infections is predicted to occur. Similarly, if a 10% fall in entry rate takes place in 2005, then HIV incidence is expected to reduce each year. Table 5.3, overleaf, illustrates this difference in projected HIV incidence for each year, in terms of the number of HIV infections gained or lost subject to a change in entry rate, in addition to the implication in terms of costs saved or spent which is provided using knowledge that the cost/benefit per single case of HIV infection prevented is estimated to be in the range of £0.5 million to £1 million (HPA 2004). The table shows that 523 individuals less than the 13,418 predicted to contract HIV in the years 2005 to 2012, will become infected with the virus if the entry rate reduces by 10% in 2005-2006, equivalent to a reduction in HIV incidence of 3.9%. In

	PROJECTED HIV INCIDENCE			CHANGE IN HIV INCIDENCE		RANGE OF COST/BENEFIT (£M)	
YEAR	No change in Λ	Decrease in Λ by 10%	Increase in Λ by 10%	Decrease in Λ by 10%	Increase in Λ by 10%	Decrease in Λ by 10%	Increase in Λ by 10%
2005	1678	1678	1678	-0 *(-0%)*	0 *(0%)*	0	0
2006	1680	1676	1683	-4 *(-0.2%)*	3 *(0.2%)*	2 – 4	-1.5 – -3
2007	1680	1658	1702	-22 *(-1.3%)*	22 *(1.3%)*	11 – 22	-11 – -22
2008	1680	1626	1732	-54 *(-3.2%)*	52 *(3.1%)*	27 – 54	-26 – -52
2009	1678	1596	1758	-82 *(-4.9%)*	80 *(4.8%)*	41 – 82	-40 – -80
2010	1676	1572	1779	-104 *(-6.2%)*	103 *(6.1%)*	52 – 104	-51.5 – -103
2011	1674	1552	1794	-122 *(-7.3%)*	120 *(7.2%)*	61 – 122	-60 – -120
2012	1672	1537	1806	-135 *(-8.1%)*	134 *(8%)*	67.5 – 135	-67 – -134
TOTAL	**13418**	**12895**	**13932**	**-523 (-3.9%)**	**514 (3.8%)**	**261.5 – 523**	**-257 – -514**

Table 5.3 **Projected HIV incidence and consequent cost implications, resultant from a change in entry rate, for the years 2005 – 2012.**

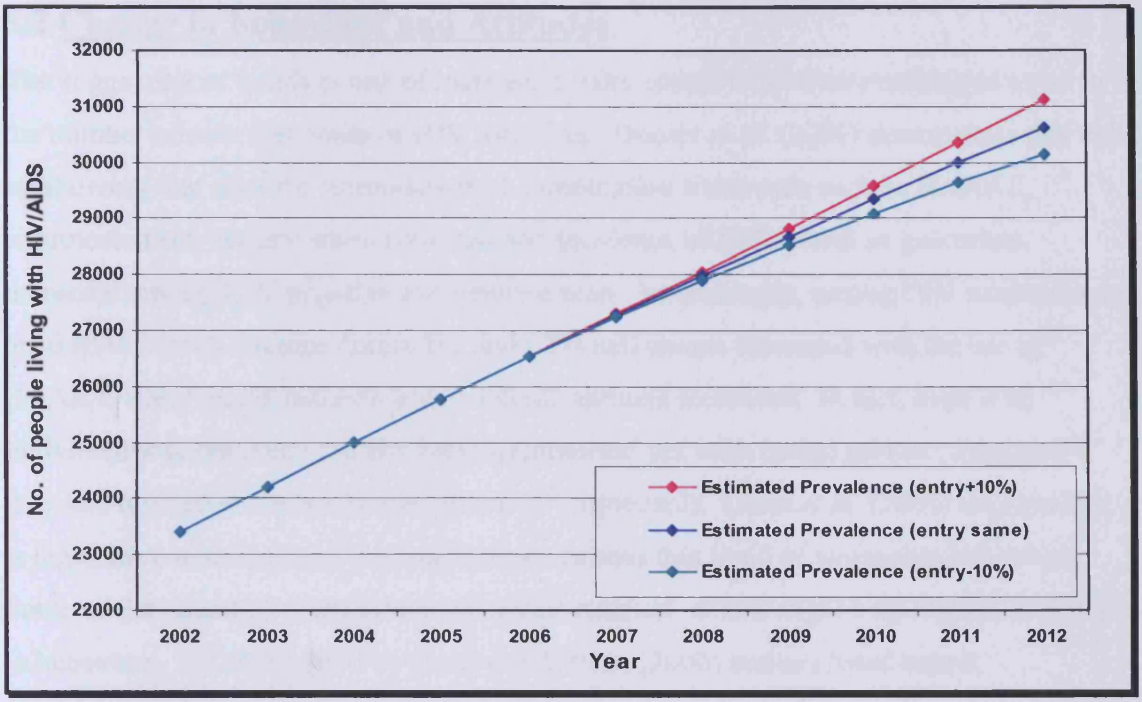

Figure 5.2c **HIV/AIDS Prevalence with the Entry Rate, Λ, varying from 2005, reaching ±10% by 2007.**

terms of the financial costs avoided as a result of these 523 people not contracting HIV, a potential £261.5 - £523 million could be saved in 8 years. Correspondingly, however, if the entry rate increases by 10%, then an additional 514 infections are predicted to occur over the years 2005 - 2012, equating costs of £257 - £514 million.

Projected HIV/AIDS prevalence is illustrated in Figure 5.2c, with or without a change in entry rate in 2005. A significant change in prevalence is not witnessed until 2007, when, as expected, an increase in the entry rate results in HIV/AIDS prevalence enlarging to amounts greater than it would have reached otherwise, and, similarly, a decrease in the entry rate results in HIV/AIDS prevalence shrinking below its otherwise expected trajectory. By 2012, dependent upon whether the entry rate has risen; not changed; or fallen, extrapolated HIV/AIDS prevalence reaches values of 31,099; 30,617; or 30,126, respectively. This means that an increase in entry rate by 10% in 2005 results in the number of people living with HIV/AIDS rising by nearly 500 people (1.57%) by the year 2012. Similarly, a decrease in entry rate by 10% in 2005 results in the number of people living with HIV/AIDS falling by nearly 500 (1.6%) by the year 2012.

5.2 Change in Behaviour and Attitudes

The suggestion of trends is one of increasing risky sexual behaviour resulting in a rise in the number of new diagnoses of HIV infection. Dukers *et al.* (2001) demonstrate this trend by showing that after the introduction of combination treatments such as HAART, unprotected sex became more common and incidence of STI's, such as gonorrhea, increased among HIV negative and positive men. Interestingly, among HIV infected men, once HIV-1 RNA became detectable and CD4 cell counts increased with the use of HAART, risky sexual behaviour with casual partners increased. In fact, even if an individual was not receiving HAART, unprotected sex with casual partners increased if they had high HIV-1 RNA levels (above 10^5 copies/ml). Glass *et al.* (2004) confirm that it is imperative to understand the mechanisms behind this trend of worsening behaviour. Some of the potential determinants of sexual conduct, which might help explain a change in behaviour, are highlighted by Donovan & Ross (2000) and are listed below:

- Psychosocial factors (procreation/desire/curiosity etc.),
- Evolutionary factors (selective advantage/disadvantage),
- History & Culture (perception of peer behaviour),
- Individual developmental and physiological factors (neurological/hormonal factors),
- Intoxicants (alcohol/drugs),
- Particular situation and opportunity,
- Education and knowledge of partners' (real or potential) infection status.

HIV optimism, as a consequence of new HIV drug therapies such as HAART, has been theorised as one possible explanation behind the recent incline in high-risk sexual behaviour. In 2002, Elford *et al.* examined the effect of HIV optimism on sexual behaviour among London Gay men between 1998 and 2001 and found that the percentage of men declaring high-risk unprotected anal intercourse (UAI) increased from 15.3% to 38.8% for HIV-positive men; from 6.8% to 12.1% for HIV-negative men; and from 2.1% to 7.7% for men who had not been tested before. Of these participants, less than one in three claimed to be optimistic about new HIV therapies. Elford *et al.* (2002) concluded that there was no

significant difference in the rate of increase of high-risk sexual behaviour, between 1998 and 2001, for gay men in London, whether optimistic or not. A further aspect of HIV optimism, in addition to new drug therapies, is the availability of post exposure prevention (PEP), which, too, needs to be considered as a contributable factor to escalating levels of risk behaviour among homosexuals. However, Waldo *et al.* (2000) conclude that, among gay men in San Francisco, there is little evidence to suggest that the availability of PEP for sexual exposures might be linked to increased sexual risk taking. Perceived viral load, but not actual load, is another possible factor related with increasing unprotected sex with stable partners of negative (or unknown) HIV status (Stolte *et al.* 2004), as well as seeking sex on the internet being associated with recent increasing STD incidences and high-risk sexual behaviour among gay men, both HIV positive and negative, in London (Elford *et al.* 2001). In addition to these associations with increasing risky behaviour, HIV testing, in particular the voluntary confidential HIV test (VCT), remains strongly related to sub-populations at high risk (McGarrigle *et al.* 2005). In a survey produced by Leaity *et al.* (2000), no significant dissimilarities were discovered in the frequency of unprotected penetrative sex (UPS) between repeat and first-time testers, except for gay men with a history of three or more previous HIV tests, who reported raised levels of risky behaviour. Furthermore, an increase in self-testing methods (serving populations who either do not have access to, or do not use, facility-based standard VCT services) could additionally encourage high-risk behaviour in these sub-populations (Spielberg *et al.* 2004).

On a more positive side, Leaity *et al.* (2000) suggest that, repeat HIV testing enables: the foundation of seroconcordance with a regular partner (i.e. identical HIV status), thus forming an important role in terms of risk reduction; the opportunity to provide HIV test counselling to address high-risk behaviour issues and reinforce personal risk-reduction approaches; and strategies to reduce undiagnosed prevalent HIV infection (McGarrigle *et al.* 2005). HIV counselling and testing has been shown to improve sexual behaviour among people who are HIV positive (Weinhardt *et al.* 1999 and CDC 2000), whilst for HIV negative people, the results on the benefits of counselling are a little more varied. Counselling methods need to be modernized in order to maximize effectiveness in reducing high-risk sexual behaviour and, consequently, prevention of increasing numbers of new infections. As well as counselling, HIV testing can provide the opportunity to encourage

gay men to participate in negotiated safety (NS). NS refers to a HIV risk reduction strategy (Kippax *et al.* 1993 and 1997) based on two main ethics (Elford *et al.* 1999):

1. An acknowledgment to only have unprotected anal intercourse (UAI) with their regular partner and not with casual partners,
2. Verification that both men in a (regular) relationship are HIV seroconcordant.

Davidovich *et al.* (2000) investigated the concept that steady relationships provide a situation that permits sexual risk-taking, finding that elevated rates of risky UAI were coincident with steady partners, even after correcting for NS. Elford *et al.* (1999) surveyed gay men in London gyms, revealing that most homo/bisexual men have adopted the first notion of NS (as listed above), but not the second. As a result, greater than 1 in 10 men testified to participating in high-risk UAI with their main partner. Thus, Elford *et al.* (1999) conclude that HIV prevention strategies should continue to promote NS for gay men in a relationship. This notion is supported by most researchers, including: Dukers *et al.* (2001) who confirm the need for readdressing prevention programmes to the requirements of HIV infected homosexuals, as well as promoting safe sex prevention messages among uninfected men; and Stolte *et al.* (2004) whom also reinforce the call for pioneering prevention activities.

According to a study released on May 13th 2003, by the Global HIV Prevention Working Group, HIV/AIDS prevention programmes are reaching fewer than 1 in 5 people at risk of HIV infection worldwide (McCarthy 2003). McCarthy (2003) goes on to say that 29-45 million of HIV incidences predicted between 2003 and 2010 could be avoided if key prevention strategies are initiated. For instance: activities that control sexually transmitted infections; voluntary counselling and testing; encouragement of harm reduction programmes; and promotion of delaying sexual activity, reducing the number of sexual partners, and using condoms. Whenever a fully researched behavioural intervention is put in place, assuming substantial funding is available, HIV incidence and/or prevalence decline (Donovan & Ross 2000); studies by Kegeles *et al.* (1999), Meda *et al.* (1999) and Celentano *et al.* (1998) are just a few examples of successful prevention programmes in action. For details of specific interventions and preventions that are currently

recommended for widespread distribution, refer to the CDC's Division of HIV/AIDS Prevention which has produced a Compendium of HIV Prevention Interventions with Evidence of Effectiveness (CDC 1999[b]); most of these, however, are resource exhaustive and complex to adapt to the real world (Rietmeijer 2003).

Building on the above information, four 'what-if' scenarios are modelled within this section, based upon changing sexual behaviours within the homo/bisexual population in the UK, altering the value of the infectivity rate, βc. More specifically, it is the mean number of sexual partners, c, that is expected to be influenced by changing behaviours, rather than the rate of transmission of HIV per contact, β. In Chapter 4, βc was estimated, using maximum likelihood techniques, to take a value of 1.28 over the years 1978-1986 and a value of 0.5 thereafter (with a two year linear smoothing process from 1987-1988). Within this chapter, a further change in behaviour is modelled, assuming occurrence in 2005, with two year linear smoothing. As at 2005, the value of the infectivity parameter, βc, will begin to either increase by 10%; stay the same value as it was previously (0.5); decrease by 10%; or reduce to a value of zero. These changes in value of βc model the following situations respectively: increased risky sexual behaviour as a result of HIV optimism or perceived viral load, for instance; non-changing sexual behaviour; decreased risky sexual behaviour due to a possible intervention of prevention programmes; or an end to all risky sexual behaviour attributable to a highly successful prevention strategy being implemented. Since $\beta c = 0.5$ prior to these 'what-if' scenarios taking place in 2005, the resultant change in value of βc will either be: +0.05; 0; -0.05; or -0.5, respectively. These changes in value will occur over two years of linear smoothing (2005-2006) adhering to the weekly incremental technique as used in Chapter 4 and in the previous section of this Chapter. For this specific case, the weekly increments are as follows:

$$|\beta c_{old} - \beta c_{new}|/104$$

Thus, βc results in a new constant value from 2007 onwards of either: 0.55; 0.5; 0.45; or 0, respectively. Figures 5.3a, 5.3b and 5.3c, illustrated within the following pages, show the resultant trajectories for each 'what-if' scenario regarding a change in behaviour. The prevalence within each sub-population, as seen in Figure 5.3a overleaf, shows many of the

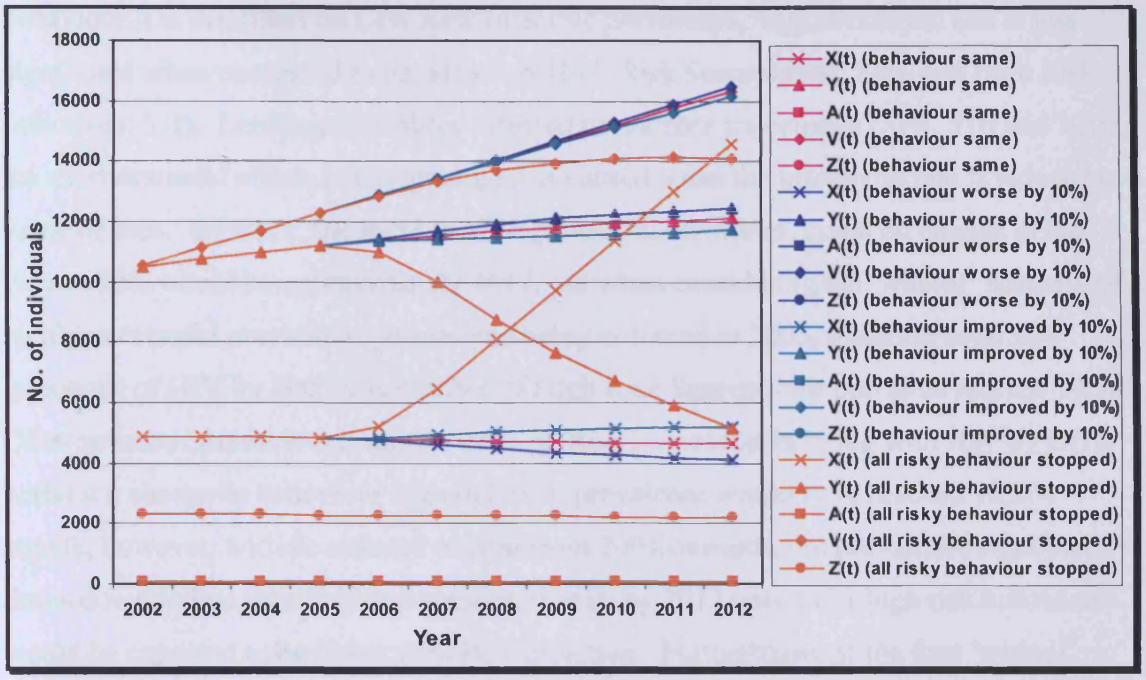

Figure 5.3a **Sub-populations within the Cardiff model with the Infectivity Rate, βc, varying from 2005, reaching ±10%, or 0, by 2007.**

same reactions to a change in infectivity rate, as they did in Figure 5.2a to a change in entry rate. Only the High Risk Susceptible sub-population, X(t), and the Infective (High Risk and Low Risk) sub-populations, Y(t) and V(t) respectively, appear to be affected prior to, and including, the year 2012. Both the High Risk and Low Risk AIDS case sub-populations, A(t) and Z(t) respectively, do not alter from their original path, which they would follow given no change in parameter values. This lack of effect on AIDS prevalence could be resultant of two main contributing factors: firstly, a change in infectivity rate in 2005 might affect the AIDS prevalence estimates (high risk and low risk), but not prior to 2012; and secondly, the amount of effect that a change in value of the infectivity rate causes is concentrated on the sub-populations closest to it, i.e. High Risk Susceptibles and Infectives, with the effect becoming increasingly less the further away a population is from the respective parameter, with Low Risk Infectives showing a lesser effect than either High Risk Susceptibles or High Risk Infectives, and AIDS cases (High Risk and Low Risk) displaying an even slighter effect than Low Risk Infectives. Figure 5.3a illustrates that these two principles hold true in terms of the sub-populations affected by a change in

behaviour, i.e. the effect on Low Risk Infective prevalence, V(t), is delayed and is less significant when compared to the effect on High Risk Susceptibles, X(t), and High Risk Infectives, Y(t). Looking at all three affected prevalence trajectories (X(t), Y(t) and V(t)), the most dramatic effect, not surprisingly, is caused when the infectivity rate is reduced to a value of zero. By 2012, the number of High Risk Susceptibles, given no change in the value of βc, would be approximately 4617, yet when considering the 'what-if' scenario of a highly successful prevention programme being enforced in 2005, resulting in no new infections of HIV by 2007, the number of High Risk Susceptibles prevalent reaches 14,585. Of even more interest is the number of High Risk homosexuals living with HIV by 2012; without a change in behaviour high risk HIV prevalence would have reached 12,104 people, however, with βc reduced to zero from 2007 onwards, the prevalence significantly drops down to less than half that number, that is, by 2012 only 5133 high risk individuals would be expected to be living with HIV infection. Furthermore, of the four 'what-if' scenarios modelled in this section, only the case where HIV incidence is equivalently stopped (that is, βc drops to zero) reduces the exponential increase that would otherwise occur in the Low Risk Infective category; improving the value of the infectivity rate noticeably diminishes the incline of low risk HIV prevalence, as seen by the reduction in value of βc by 10% in Figure 5.3a, however, it is not until βc is dropped to zero that this prevalence stops increasing altogether and even starts to fall by 2012. The suggestion here is that new infections of HIV need to be permanently stopped in order to bring the HIV/AIDS epidemic under restraint and prevent further escalating prevalence figures. When considering a slight increase or decrease in value of βc, of 10%, caused by either an increase in risky sexual behaviours or a decrease in risky sexual behaviours respectively, the trajectories of prevalence in the High Risk Susceptible sub-population, High Risk Infective sub-population and Low Risk Infective sub-population are affected as one might expect. An increase in high risk behaviour of homosexual men results in a decrease in the number of high risk susceptibles present in 2012 (4116 people compared to 4617) and an increase in the number of homosexual men living with HIV in 2012, for both high risk and low risk sub-populations, (12,418 compared to 12,104 and 16,446 compared to 16,308, respectively) when evaluated against the prevalence in these sub-populations if no change in behaviour occurs. Similarly, a decrease in high risk behaviour of homosexual men

results in an increase in the number of high risk susceptibles present in 2012 (5205 people compared to 4617) and a decrease in the number of homosexual men living with HIV in 2012, for both high risk and low risk sub-populations, (11,724 compared to 12,104 and 16,155 compared to 16,308, respectively) when contrasted to the prevalence in these sub-populations if there was no change in behaviour.

The effect that a change in behaviour has on HIV incidence is seen in Figure 5.3b. Similar to the work performed in the previous section, referring to a change in value of the entry rate, when the value of the infectivity rate is altered projected AIDS incidence and deaths from AIDS estimates are not affected prior to 2012. When βc begins its transition, in 2005, to take on a value of zero, by 2007, HIV incidence immediately drops to zero due to the very nature of the infectivity rate parameter. When βc takes on a slightly larger or smaller value, of $\pm 10\%$, the number of new HIV infections reacts by either jumping to a peak of 1797 new infections in 2008, or falling to a trough of 1552 new infections in 2008, respectively, compared to 1680 new infections predicted given no change in behaviour. After the extreme count of new cases of HIV in either case, the path of HIV incidence gradually begins to curve back to the steady level witnessed if no change in infectivity rate occurs. The point where all three trajectories rejoin is not seen prior to the year 2012, but the trends of both scenarios (a slight increase in risky behaviour and a slight decrease in risky behaviour) suggest that all paths will eventually converge back to the one original path, or at least, each scenario will ultimately result in a similar number of HIV incidences once the initial impact of the change in value of the infectivity rate has occurred and recovery from this impact has taken place. The annual number of new HIV infections with regards to each scenario (+10%, no change or -10%) in 2012 are 1707, 1672 or 1617 new incidences of HIV, respectively. This trend for HIV incidence to revert back to approximately 1675 new HIV infections each year, despite a change in behaviour, is cause for concern as well as being beneficial. Considering an uptake in high risk behaviour, for such reasons as HIV optimism, perceived viral load or reinforcement through testing methods (i.e. repeated negative test results adversely encouraging high-risk individuals to maintain, or increase, their risky sexual behaviour), the tendency of HIV incidence numbers to maintain their stability is one of a positive nature. However, when considering the intervention of prevention programmes having an incomplete effect on HIV

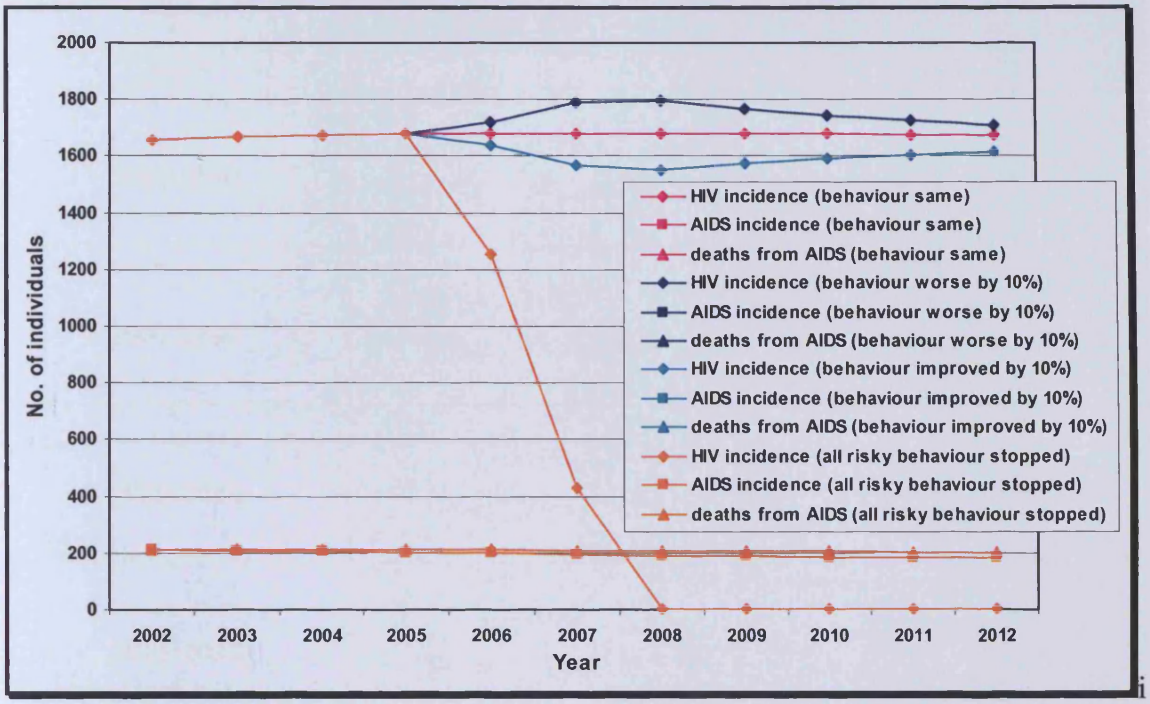

Figure 5.3b **HIV incidence, AIDS incidence and deaths cases with the Infectivity Rate, βc, varying from 2005, reaching ±10%, or 0, by 2007.**

incidence figures, that is, prevention strategies not being entirely successful and new HIV infections still occurring as a consequence, the movement of HIV incidence figures back to the steady levels that would have been seen without any such intervention questions the effectiveness of prevention tactics when not well-defined or sufficiently funded. On the contrary, when a prevention strategy is 100% successful, as modelled by the scenario where βc reaches a permanent value of 0 from 2007 onwards, there is no such apparent recovery of HIV incidence. This, however, may be deemed as unrealistic, thus the scenario where a number of semi-successful prevention programmes being put into action is considered, as demonstrated in Table 5.4 overleaf, with the results imposed onto Figure 5.3b(2). This idea has been implemented by assuming that every two years, another prevention programme, with resultant 10% reduction in the infectivity rate, βc, is introduced. It is also assumed that each prevention strategy takes two years to fully instigate, hence a two year linear smoothing process is employed for each change in value of βc. As seen in Figure 5.3b(2), the continuous intervention of prevention programmes

Year	Change in βc	Value of βc
2004	0	0.5
2005-2006	-10% $\lvert \beta c_{old} - \beta c_{new} \rvert / 104$	0.45
2007-2008	-10% $\lvert \beta c_{old} - \beta c_{new} \rvert / 104$	0.405
2009-2010	-10% $\lvert \beta c_{old} - \beta c_{new} \rvert / 104$	0.3645
2011-2012	-10% $\lvert \beta c_{old} - \beta c_{new} \rvert / 104$	0.32805

Table 5.4 **Changing βc subject to continuous semi-effective prevention programmes.**

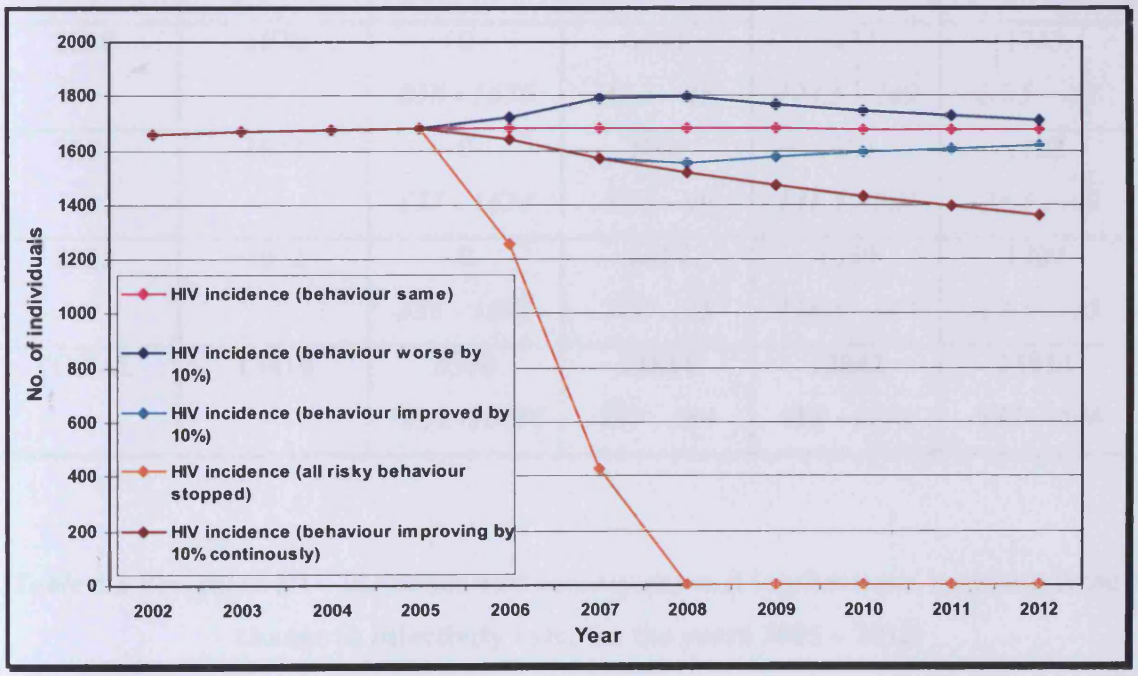

Figure 5.3b(2) **HIV incidence with the Infectivity Rate, βc, varying from 2005, reaching ±10%, 0, or with continuous semi-effective prevention methods.**

PROJECTED HIV INCIDENCE *RANGE OF COST/BENEFIT (£M)*					
YEAR	**No change in βc**	**Decrease in βc by 100%**	**Decrease in βc by 10%**	**Continual Decrease in βc by 10%**	**Increase in βc by 10%**
2005	1678 *0*	1678 *0*	1678 *0*	1678 *0*	1678 *0*
2006	1680	1253 *213.5 - 427*	1638 *21 - 42*	1638 *21 - 42*	1721 -20.5 - -41
2007	1680	429 *625.5 - 1251*	1569 *55.5 - 111*	1569 *55.5 - 111*	1788 -54 - -104
2008	1680	0 *840 - 1680*	1552 *64 - 128*	1513 *83.5 - 167*	1797 *-58.5 - -117*
2009	1678	0 *839 - 1678*	1574 *52 - 104*	1467 *105.5 - 211*	1767 *-44.5 - -89*
2010	1676	0 *838 - 1676*	1591 *42.5 - 85*	1427 *124.5 - 249*	1743 *-33.5 - -67*
2011	1674	0 *837 - 1674*	1605 *34.5 - 69*	1391 *141.5 - 283*	1723 *-24.5 - -49*
2012	1672	0 *836 - 1672*	1617 *27.5 - 55*	1359 *156.5 - 313*	1707 *-17.5 - -35*
TOTAL	**13418**	**3360** ***5029 -10058***	**12824** ***297 - 594***	**12042** ***688 - 1376***	**13924** ***-253 - -506***

Table 5.5 **Projected HIV incidence and consequent cost implications, resultant from a change in infectivity rate, for the years 2005 – 2012.**

inhibit the HIV incidence curve from returning to its previous elevated levels, demonstrating that even semi-effective prevention strategies can have a significant effect on the number of new HIV infections occurring when considered within a larger intervention programme, i.e. a multi-staged prevention programme consisting of numerous prevention activities. However, the concern still remains that if the continual prevention strategy were to end, or be interrupted for some reason, HIV incidence levels would begin to rise again. Table 5.5, on the previous page, illustrates the effect on extrapolated HIV incidence over the years 2005 to 2012, resultant from a change in the infectivity rate. Also within Table 5.5, a summary of the potential costs in relation to the differing number of new HIV cases each year is provided, formulated by multiplying each single case of HIV infection prevented by its relevant cost/benefit, estimated to be in the range of £0.5 million to £1 million (HPA 2004). Over the time period 2005-2012, a total of 13,418 new HIV infections are predicted, if no change in behaviour occurs; if a slight decrease or increase in risky behaviour takes place (i.e. βc decreases or increases by 10% respectively) then this total number of new infections either falls to 12,824 (-4.4%) or rises to 13,924 (+3.8%). The financial costs associated with such changes in behaviour equate to a potential £297 - £594 million saved in 8 years if behaviour becomes less risky (that is, assuming the scenario of a prevention programme being enforced which not only stops the trends of increasing risk taking but also reduces the present amount of high-risk sexual activities by 10%) or £253 - £506 million spent, that may be saved if the increase in high-risk sexual behaviour is stopped. Even further sums of money could possibly be conserved if a series of prevention programmes are introduced, reducing risk taking by 10% every two years. For this scenario, extrapolations suggest a total ranging between £688 and £1,376 million saved, over the seven years 2005-2012. Furthermore, if new HIV infections are stopped altogether by 2007, then an incredible £5,029 - £10,058 million could potentially be saved. However, these amounts are calculated with no consideration for the costs involved in implementing such a prevention programme. Consequently, they represent gross, not net, benefit incurred and are thus greatly over estimated.

As suggested by the investigation so far into the effect a change in behaviour has on projected populations, when looking at total HIV/AIDS prevalence figures, as seen in Figure 5.3c, overleaf, each scenario follows its expected altered course: an increase in

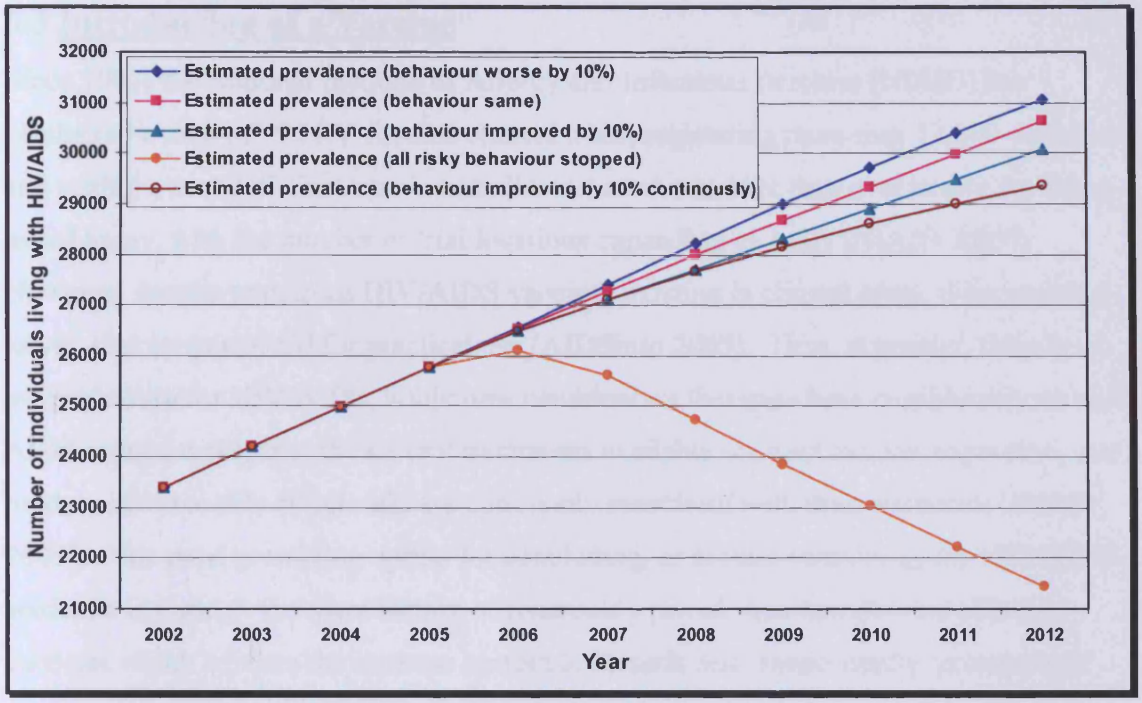

Figure 5.3c **HIV/AIDS Prevalence with the Infectivity Rate, βc, varying from 2005, reaching ±10%, 0, or with continuous semi-effective prevention methods.**

high-risk behaviour results in higher HIV/AIDS prevalence (31,068 people estimated to be living with HIV/AIDS by 2012); a slight decrease in risky behaviour results in HIV/AIDS prevalence increasing at a slower rate (30,083 people estimated to be living with HIV/AIDS by 2012); and an end to all high-risk sexual behaviour amongst homo/bisexual men results in HIV/AIDS prevalence dropping dramatically down to an estimated 21,416 homosexual men living with HIV/AIDS by 2012, compared to 30,617 individuals if there is no change in behaviour. When the scenario of continuous prevention methods implemented every 2 years is considered, each resulting in a reduction in the value of βc by 10%, total HIV/AIDS prevalence stops increasing at the same speed as it would otherwise. In fact, the curve of the prevalence path for this scenario of continuous intervention distinctly gives the impression that each prevention activity that is employed slows the rate of incline of the total HIV/AIDS prevalence further and further, suggesting that beyond 2012, prevalence figures can be restrained and possibly even reduced with the utilization of semi-effective, but numerous, prevention strategies.

5.3 Introduction of a Vaccine

Since 1987, the National Institute of Allergy and Infectious Diseases (NIAID) has conducted a total of 79 HIV vaccine clinical trials, registering more than 12,000 volunteers and testing over 52 distinct vaccine candidates; more vaccines than ever before are being tested today, with the number of trial locations expanding globally (NIAID 2005[a]). However, despite numerous HIV/AIDS vaccines existing in clinical trials, there are none, as yet, that are permitted for practical use (AIDSinfo 2005). Thus, at present, there is no available cure for HIV/AIDS; while new combination therapies have considerably reduced AIDS-related morbidity, the current treatments available are multifarious, expensive, can produce adverse side effects and are commonly associated with drug resistance (NIAID 2005[a]). The most promising option for concluding, or at least restraining, the HIV/AIDS epidemic is through the manufacture of reasonably priced, non-harmful and effective vaccines which educate the immune system to identify and, consequently, protect itself against viruses such as HIV (NIAID 2005[a]). Vaccines, such as these, are known as preventive vaccines and are targeted at HIV-negative individuals with the aim of preventing HIV infection (AIDSinfo 2005). Other types of HIV vaccines are also being tested, and may be advantageous for HIV-positive individuals by postponing the establishment of AIDS or by decelerating the progression of HIV (NIAID 2005[a]); these types of vaccine are known as therapeutic vaccines and their objective is to improve the immune system (AIDSinfo 2005).

It is widely believed, by scientists and researchers alike, that a successful vaccine is achievable. In fact, main objectives throughout the world are to restrain, or even end, the HIV/AIDS epidemic by developing an effective vaccine to protect individuals against contraction of HIV, against illness once infected with HIV, or to decrease viral load post infection with the virus (NIAID 2005[b]). However, designing such a vaccine will inevitably be problematic: it will necessitate numerous trials, each trial drawing closer to an effective vaccine; vaccines for other communicable diseases are prone to be more effective than an early HIV vaccine candidate; and a HIV vaccine is doubtful to be valuable against all HIV strains (CDC 2001). The ideal vaccine would be 100% effective against HIV infection, inexpensive, easy to store and administer, capable of protecting against all strains of HIV and accessible to defend every person from infection (NIAID 2005[a], 2005[b]). Even if a

vaccine only partially protects the total target population, it could still significantly affect transmission rates of HIV and help manage the HIV/AIDS epidemic (NIAID 2005[a]). In 2004, the National Institute of Allergy and Infectious Diseases listed some types of experimental vaccine presently under investigation, these included (NIAID 2004):

"

- Component (or Subunit) vaccine: a structural piece of HIV, such as the outer surface components ... or a regulatory protein, produced by genetic engineering
- Live vector vaccine: a live bacterium or virus such as vaccinia (used in the smallpox vaccine) modified so it can not cause disease but can transport into the body a gene or genes that makes one or more HIV proteins
- Vaccine combination: for example, use of a recombinant vector vaccine to induce cellular immune responses followed by booster shots of a component vaccine to stimulate antibody production, referred to as a prime-boost strategy
- Peptide vaccine: chemically synthesized pieces of HIV proteins (peptides) known to stimulate HIV-specific immunity
- Virus-like particle vaccine (pseudovirion vaccine): a non-infectious HIV look-alike that has one or more, but not all, HIV proteins
- DNA vaccine: direct injection of genes coding for HIV proteins
- Whole-killed virus vaccine: HIV that has been inactivated by chemicals, irradiation, or other means so it is not infectious
- Live-attenuated virus vaccine: live HIV from which one or more disease-promoting genes of the virus have been deleted. Due to safety considerations, live-attenuated HIV vaccines have not been tested in humans. "

NIAID are founding the Center for HIV/AIDS Vaccine Immunology (CHAVI), in 2005, in order to hasten the forthcoming development of a safe and effective HIV vaccine. This is in response to optimism for more hopeful vaccine candidates to go under development in the near future; standardized lab assays around the world; greater capacities for clinical trial programmes; and better resourced animal facilities (NIAID 2005[b]).

In view of the above literature appraisal on current vaccine capabilities and the optimistic progression to the development of a future HIV vaccine, this section considers two case scenarios: the introduction of a preventive vaccine and the introduction of a therapeutic vaccine. For both scenarios, a new parameter is invented which represents the coverage of a 100% effective vaccine within its respective population, that is, the proportion of the population that the vaccine is administered to, after a period of initiation for that vaccine (i.e. a smoothing process lasting two years, as performed previously). These new parameters, denoted vac_p and vac_t, symbolizing the coverage of the preventive vaccine and therapeutic vaccine respectively, are initially given a value of 0 at the start of the epidemic (1978), i.e. 0% of the population is vaccinated. In 2005, vac_p and vac_t will begin to increase from this value of zero, over a linear smoothing period of two years, to eventually take on their final proportion of coverage, from 2007 onwards, of either: 50%; 70%; or 90%, of the population vaccinated (i.e. $vac_p = vac_t = 0.5$, 0.7 or 0.9 respectively).

5.3.1 The Introduction of a Preventive Vaccine

As mentioned above, in order to represent the introduction of a preventive vaccine, vac_p is established within the model corresponding to coverage of the vaccine in the population. The vaccine within this scenario is assumed to be 100% safe and effective, thus, when an individual is administered with the preventive vaccine, they are assumed to no longer be susceptible to the HIV virus. The nature of a preventive vaccine is that it is administered to non-infectives in an attempt to prevent contraction of HIV, hence, within this scenario it is the transition from the High Risk Susceptible sub-population, X(t), to the High Risk Infective sub-population, Y(t), that is relevant for the incorporation of the new parameter, vac_p. Previously, the parameter associated with this movement between compartments, within the Cardiff Model, was α, the rate at which High Risk Susceptibles become infected, which was calculated as follows:

$$\alpha = \beta c \frac{Y(t) + A(t)}{X(t) + Y(t) + A(t)}$$

To incorporate vac_p within this transition from the X(t) category to the Y(t) category, α is multiplied by (1 - vac_p) to get the new rate at which Susceptibles become infected of:

$$\alpha(1-vac_p) = (1-vac_p)\beta c\frac{Y(t)+A(t)}{X(t)+Y(t)+A(t)}$$

Three situations are modelled allowing for different final coverage levels of the vaccine, these are 50%, 70% or 90% vaccine coverage (i.e. 50%, 70% or 90% of the High-Risk Susceptible population will be treated with the preventive vaccine by 2007). For each case, vac_p goes through a smoothing period, from 2005 to 2007, where it increases from its original value of 0 (0% coverage) to its new value of 0.5, 0.7 or 0.9 respectively. The linear smoothing process is the same as used previously and incorporates the following linear weekly increments:

$$\left|vac_{p\,new} - vac_{p\,old}\right|/104$$

Figure 5.4a shows the sub-population prevalences, where, as noticed in prior 'what-if' scenarios, both of the AIDS case prevalence paths (High Risk and Low Risk) are not affected by a change in parameter value this early on in the stages of the epidemic. As with a change in value of the entry rate and a change in value of the infectivity rate, the introduction of a preventive vaccine, affecting the incidence of HIV from the High Risk Susceptible category, is not directly linked to the AIDS case sub-populations and, hence, any effect that may be witnessed in either the High Risk or Low Risk AIDS case categories, A(t) or Z(t) respectively, will happen later and lesser than for the other sub-populations. This trend is witnessed in the prevalence of the High Risk Susceptibles, X(t), and the High-Risk Infectives, Y(t), which react much quicker, changing course immediately in 2005, to the introduction of a preventive vaccine than the prevalence of Low Risk Infectives, V(t), which does not change its path until 2007. Also, the amount by which each prevalence changes is worthy of note; for the High Risk Susceptibles the prevalence for each scenario, 0%; 50%; 70%; and 90%, by 2012, is 4617; 8594 (an increase of 86%); 10,883 (an increase of 136%); and 13,360 (an increase of 189%),

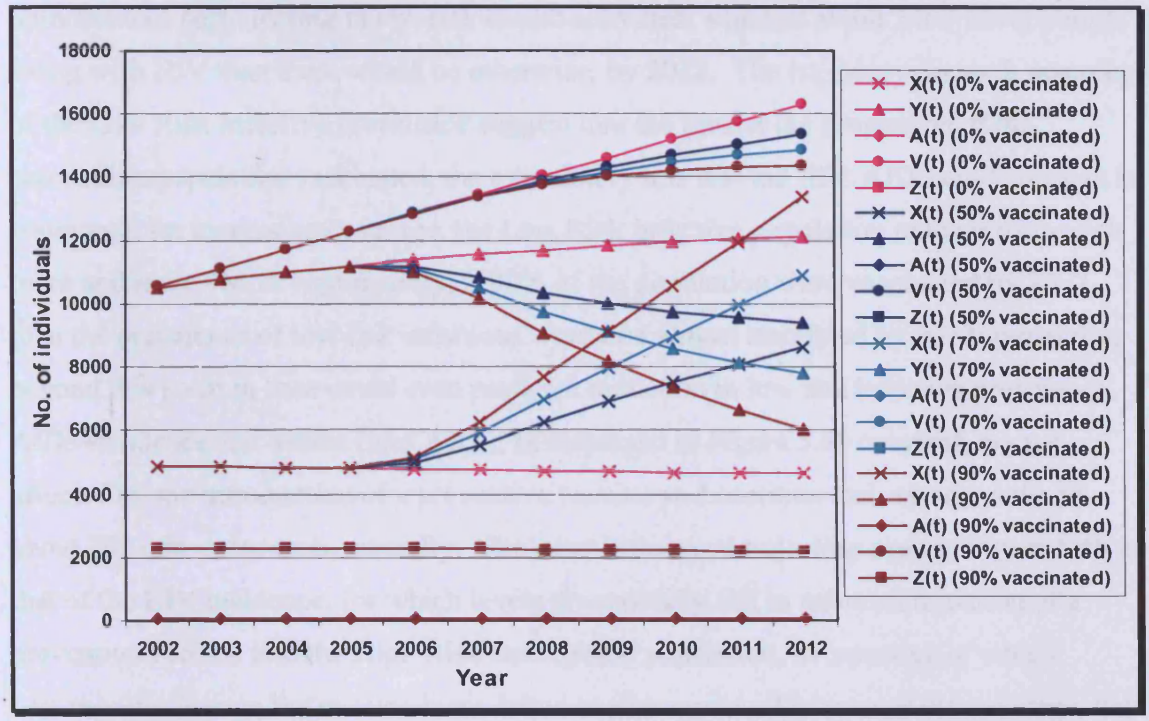

Figure 5.4a **Sub-populations within the Cardiff model with coverage of Preventive Vaccine, vac_p, introduced in 2005, reaching 50%, 70% or 90% by 2007.**

respectively, and for the High Risk Infectives the prevalence for each scenario is 12,104; 9395 (a decrease of 22%); 7766 (a decrease of 36%); and 5999 (a decrease of 50%) high risk people living with HIV by 2012, respectively. This implies that given the introduction of an 100% safe and effective preventive vaccine in 2005, even without full coverage, the HIV/AIDS epidemic is significantly altered: with only 50% coverage the number of high risk individuals living with HIV is reduced by more than a fifth by 2012; with 70% coverage, less than two-thirds of the original number of high risk individuals are expected to be living with HIV by 2012; and with 90% coverage, more than half of the high risk individuals expected to be living with HIV in 2012, if no vaccine is introduced, are now expected to be HIV negative. For all three measures of vaccine coverage, the prevalence of Low Risk Infectives, V(t), is reduced: 50% coverage relates to 15,367 low risk individuals living with HIV in 2012, compared to 16,308 without the introduction of a vaccine, approximately 1000 people less; 70% coverage corresponds to 14,876 low risk people living with HIV, roughly 1500 less; and 90% coverage refers to 14,347 HIV-positive

homosexuals participating in low risk sexual activities, which is about 2000 fewer people living with HIV than there would be otherwise, by 2012. The trajectory for each mapping of the Low Risk Infective prevalence suggest that the greater the proportion of the susceptible population vaccinated, the more likely it is that the HIV/AIDS epidemic can be restrained; for increasing coverage, the Low Risk Infective population reduces its growth more and more. Most significantly, if 90% of the population were vaccinated by 2007, then the prevalence of low risk infections would be almost stabilized by 2012; projecting beyond this point in time could even predict a reduction in low risk infective prevalence. AIDS incidence and deaths from AIDS, as displayed in Figure 5.4b overleaf, are not affected by the introduction of a preventive vaccine and continue their steady paths of about 200 new cases each, annually. The most influenced trajectory seen in Figure 5.4b is that of the HIV incidence, for which levels dramatically fall in value on initiation of a preventive vaccine into the High Risk Susceptible population, irrespective of which coverage percentage the vaccine is modelled to encompass. The greater the coverage, the steeper the decline in HIV incidence; by 2008, 50% coverage accomplishes levels lower than 1000 infections annually, 70% coverage incurs a fall in HIV incidence to below 600 individuals annually, and 90% coverage attains readings nearly as low as 200 new HIV infections occurring annually. However, it is noteworthy that despite these impressive declines in HIV incidence, post 2008 each path slowly begins to escalate again. Between 2008 and 2012, HIV incidence has increased from 945 to 1107 for 50% coverage, from 587 to 676 for 70% coverage, and from 206 to 210 for 90% coverage. This could either suggest that HIV incidence will, eventually, return to its previous high levels, despite the introduction of a 100% effective vaccine, or that HIV incidence levels will stabilize at a new quantity, dependent upon the proportion of the population vaccinated. Inspecting the curves for each scenario of coverage, in Figure 5.4b, one could speculate that for 50% coverage HIV incidence will settle at about 1200 new infections annually, for 70% coverage HIV incidence will converge to about 700 new infections annually, and for 90% coverage HIV incidence will maintain its levels of about 200 new infections annually. Another noticeable trend, when looking at Figure 5.4b, is that the greater the coverage, the less the HIV incidence increases post 2008. In fact, for 90% coverage, it could be argued that HIV incidence has already stabilized at new levels of 200 new infections each year.

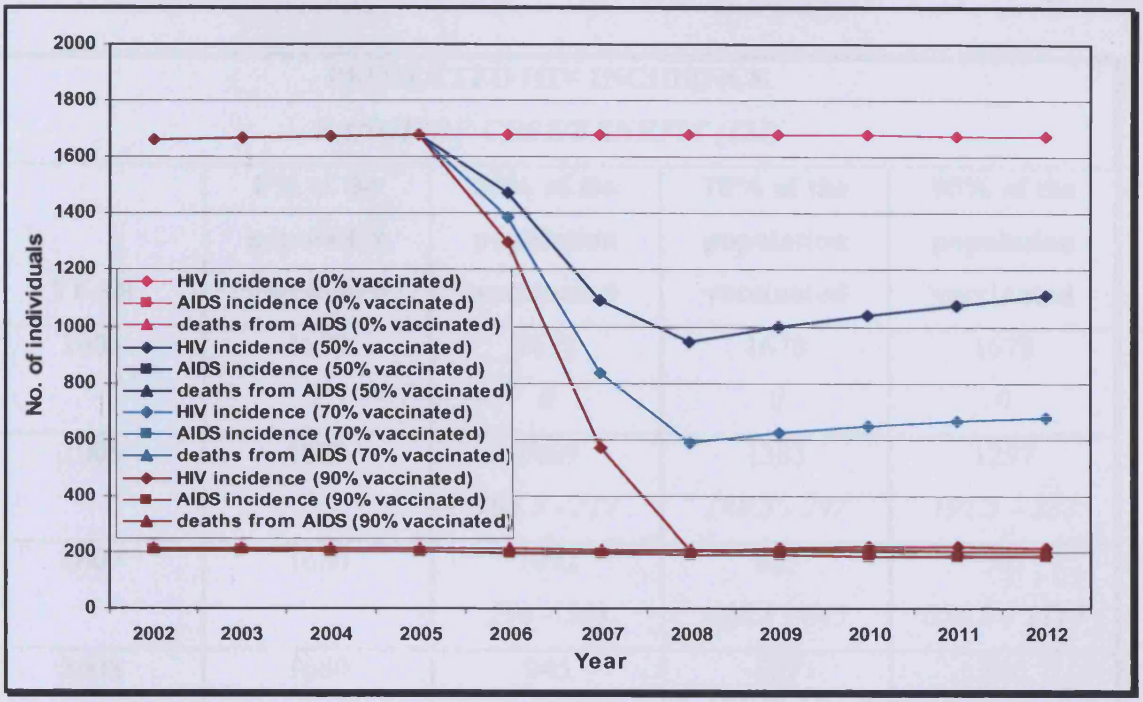

Figure 5.4b **HIV, AIDS and deaths cases with coverage of Preventive Vaccine, vac_p, introduced in 2005, reaching 50%, 70% or 90% by 2007.**

Table 5.6, on the following page, illustrates the effect on extrapolated HIV incidence over the years 2005 to 2012, resultant from the introduction of a preventive vaccine. Also within Table 5.6, a summary of the potential costs in relation to the differing number of new HIV cases each year is provided, as in the previous sections of this Chapter. The total extrapolated number of new HIV infections occurring between the years 2005–2012 differs depending on the percentage of the population treated with the preventive vaccine. With 0% vaccinated, HIV incidence over the 7 years totals 13,418 new infections, this diminishes rapidly with the introduction of a vaccine, returning total HIV incidences of 9402 (-29.9%), 7094 (-47.1%) and 4588 (-65.8%), for 50%, 70% and 90% coverage rates, respectively. The associated financial costs equate to a potential £2,008 - £4,016 million saved in 7 years if 50% of the population are vaccinated; £3,162 - £6,324 million saved if 70% of the population are vaccinated; and £4,415 - £8,830 million saved if 90% of the population are vaccinated. As for the costs involved with implementing prevention programmes however, the cost/benefits here do not take into account the expenses involved in producing and distributing such a vaccine, thus, over estimate the true savings.

PROJECTED HIV INCIDENCE *RANGE OF COST/BENEFIT (£M)*				
YEAR	**0% of the population vaccinated**	**50% of the population vaccinated**	**70% of the population vaccinated**	**90% of the population vaccinated**
2005	1678	1678 *0*	1678 *0*	1678 *0*
2006	1680	1469 *105.5 - 211*	1383 *148.5 - 297*	1297 *191.5 – 383*
2007	1680	1092 *294 - 588*	835 *422.5 - 845*	567 *556.5 – 1113*
2008	1680	945 *367.5 - 735*	587 *546.5 - 1093*	206 *737 – 1474*
2009	1678	997 *340.5 - 681*	623 *527.5 - 1055*	212 *733 – 1466*
2010	1676	1039 *318.5 - 637*	648 *524 - 1028*	203 *736.5 – 1473*
2011	1674	1075 *299.5 - 599*	664 *505 - 1010*	215 *729.5 – 1459*
2012	1672	1107 *282.5 - 565*	676 *498 – 996*	210 *731 – 1462*
TOTAL	**13418**	**9402** ***2008 - 4016***	**7094** ***3162 - 6324***	**4588** ***4415 – 8830***

Table 5.6 **Projected HIV incidence and consequent cost implications, resultant from the introduction of a preventive vaccine, for the years 2005 – 2012.**

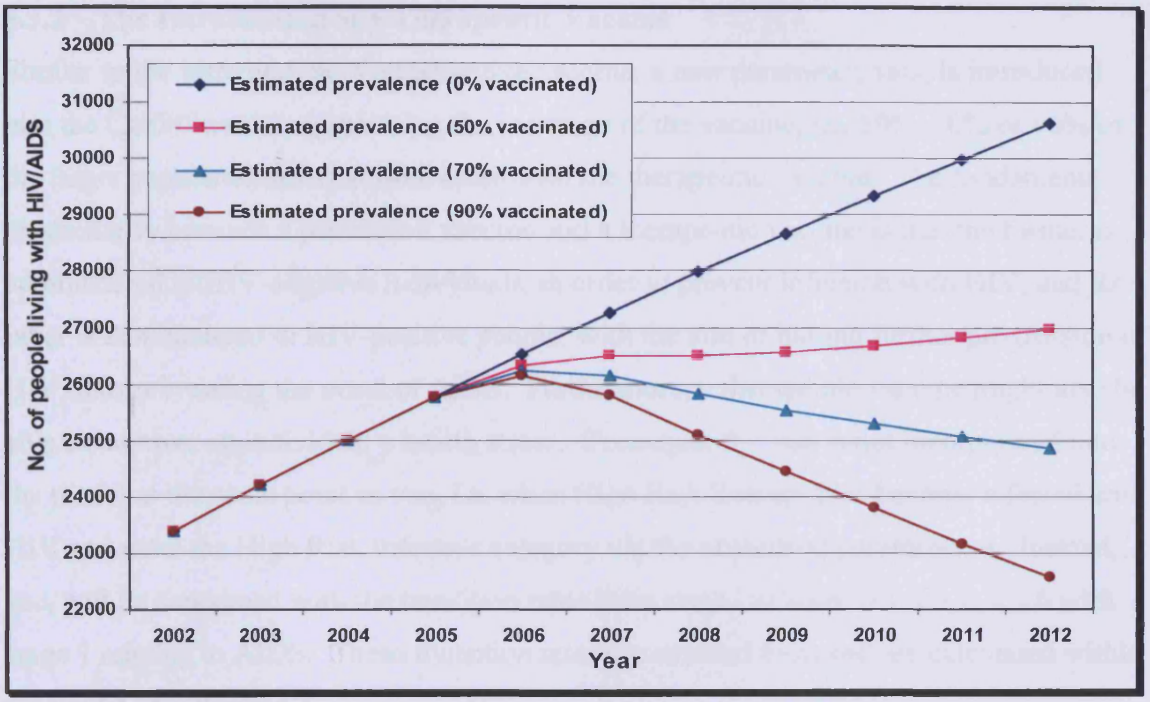

Figure 5.4c **HIV/AIDS Prevalence with coverage of Preventive Vaccine, vac_p, introduced in 2005, reaching 50%, 70% or 90% by 2007.**

Figure 5.4c shows total HIV/AIDS prevalence for each scenario regarding the establishment of a preventive vaccine, i.e. for each coverage level of 0%, 50%, 70% and 90%. Almost immediately after the introduction of a preventive vaccine, in 2005, the HIV/AIDS prevalence curve changes its path dramatically for each coverage level, dropping radically away from its otherwise linear increase if a vaccine is not introduced. The greater the coverage the greater the effect on HIV/AIDS prevalence, although even 50% coverage brings the HIV/AIDS prevalence, predicted for 2012, down to 27,000 from 30,600. For both 70% and 90% coverage, not only has the growth of HIV/AIDS prevalence been restrained, the introduction of a 100% effective preventive vaccine at these levels has caused a severe decline in HIV/AIDS prevalence from 2006 onwards; 70% coverage reaching prevalence levels of less than 25,000 by 2012, and 90% coverage reaching amounts as low as an estimated 22,600 people living with HIV/AIDS in 2012.

5.3.2 The Introduction of a Therapeutic Vaccine

Similar to the introduction of a preventive vaccine, a new parameter, vac_t, is introduced into the Cardiff model representing the coverage of the vaccine, i.e. 50%, 70% or 90% of the target population being administered with the therapeutic vaccine. The fundamental dissimilarity between a preventive vaccine and a therapeutic vaccine is that the former is administered to HIV-negative individuals, in order to prevent infection with HIV, and the latter is administered to HIV-positive people, with the aim of halting further progression of HIV, thus preventing the onset of AIDS. Furthermore, a therapeutic vaccine might also be able to improve an individual's health status. Consequently, vac_t is not incorporated into the model at the same point as vac_p i.e. when High Risk Susceptibles become infected with HIV and enter the High Risk Infective category via the associated parameter, α. Instead, vac_t will be concerned with the transition rates from stage i to stage i+1, i = 1, ..., 6 with stage 7 relating to AIDS. These transition rates are denoted by γ_i and are calculated within the model as follows:

$$\gamma_i = {}^{m}\!/_{r \times IP}, \qquad i = 1,\ldots,6.$$

where m = 6 is the number of stages in the HIV infective category, IP is the incubation period of HIV, which is assumed to be 11.4 years (derived from work by Snary 2000), and r is a measure of treatment effect on the incubation period. Chapter 4 investigates the parameter r in much detail, estimating its value for different time eras within the model in addition to allocating various smoothing methods employing longer transitions of change in parameter value as well as unequal transition rates. The value of r by 2002, with equal transition rates back in force, was estimated to be 4.89, thus $\gamma_i \approx 0.108$, i = 1, ..., 6.
With the notion that the therapeutic vaccine being introduced is 100% safe and effective, the γ_i are assumed to reduce to a value of zero for those that the vaccine is administered to, reflecting no more progression through the stages of HIV once an individual has been vaccinated. The new transition rates to allow for the introduction of a therapeutic vaccine are thus calculated as follows:

$$(1 - vac_t)\gamma_i = {}^{(1 - vac_t)m}\!/_{r \times IP}, \qquad i = 1,\ldots,6.$$

vac_t initiates at a value of zero (representing 0% of the infective population vaccinated with the therapeutic vaccine) at the start of the epidemic and increases in 2005, over two years of smoothing, to take on its new value of either: 0.5; 0.7; or 0.9, by 2007. For this case, the linear weekly increments added to vac_t over the 2 years, 2005-2006, are:

$$\left|vac_{t\,new} - vac_{t\,old}\right| / 104$$

As well as preventing further progression of HIV, the introduction of a therapeutic vaccine could also improve the health status of an HIV-positive individual. The concept of improving health can be modelled by evaluating backward movements through the stages of HIV disease progression, i.e. an increase in CD4 cell count. Thus, we introduce the parameter γ_{bi} to represent the backward transition rates from stage i to stage i-1, where i = 2, ..., 6, assuming all transition rates are equal i.e. $\gamma_{b2} = \gamma_{b3} = \ldots = \gamma_{b6}$. As for the forward transition rates, γ_i, the supposition is of '1-step' directional movements only, that is to say an individual can progress to the next consecutive stage of HIV disease, or digress back to the previous stage of HIV disease, but can not 'jump' or 'skip' stages. It is assumed that, since a therapeutic vaccine is not a cure for HIV, once an individual is infected with HIV there is no full recovery back to the susceptible category, thus there is no backward transition from stage 1 of infection to stage 0 (where stage 0 represents the High Risk Susceptible sub-population). Also, once an individual has progressed to AIDS there is no reversion to being HIV only, hence no backward transition from stage 7 to stage 6. These backward transition rates create additional paths within the model, thus the differential-difference equations need to be revised to incorporate the new movements (equations (5.1a)-(5.1e) overleaf). Note that the backward transition rates (representing improvements in health) are only applicable to those people whom have been vaccinated with the therapeutic vaccine. Thus, γ_{bi} is multiplied by the proportion of vaccine coverage within the infective population, vac_t, as seen in the differential-difference equations (5.1a)-(5.1e). Since, prior to 2005, no therapeutic vaccine is assumed to exist (i.e. vac_t is designated a value of zero up until this point in time), the $vac_t\gamma_{bi}$ terms, seen in equations (5.1b) and (5.1d), equate to zero previous to 2005, resulting in the set of original differential-difference equations, without considering the introduction of a therapeutic vaccine.

$$X(t+\delta t) = X(t) + [\Lambda - \mu_1 X(t) - \alpha X(t)]\delta t \qquad \ldots(5.1a)$$

$$\left.\begin{aligned} Y(t+\delta t) &= \sum_{i=1}^{m} Y_i(t+\delta t) \\ Y_1(t+\delta t) &= Y_1(t) + [\alpha X(t) + vac_t \gamma_{b2} Y_2(t) - (\gamma_1 + \nu_2 + \mu_2) Y_1(t)]\delta t \\ Y_i(t+\delta t) &= Y_i(t) + [\gamma_{i-1} Y_{i-1}(t) + vac_t \gamma_{b(i+1)} Y_{i+1}(t) - (vac_t \gamma_{bi} + \gamma_i + \mu_2 + \nu_2) Y_i(t)]\delta t \\ & \qquad\qquad i = 2, \ldots, m-1 \\ Y_m(t+\delta t) &= Y_m(t) + [\gamma_{m-1} Y_{m-1}(t) - (vac_t \gamma_{bm} + \gamma_m + \mu_2 + \nu_2) Y_m(t)]\delta t \end{aligned}\right\} \ldots(5.1b)$$

$$A(t+\delta t) = A(t) + [\gamma_m b Y_m(t) + \gamma_m g V_m(t) - (\omega + \nu_3) A(t)]\delta t \qquad \ldots(5.1c)$$

$$\left.\begin{aligned} V(t+\delta t) &= \sum_{i=1}^{m} V_i(t+\delta t) \\ V_1(t+\delta t) &= V_1(t) + [\nu_2 Y_1(t) + vac_t \gamma_{b2} V_2(t) - (\gamma_1 + \mu_2) V_1(t)]\delta t \\ V_i(t+\delta t) &= V_i(t) + [\gamma_{i-1} V_{i-1}(t) + \nu_2 Y_i(t) + vac_t \gamma_{b(i+1)} V_{i+1}(t) - (vac_t \gamma_{bi} + \gamma_i + \mu_2) V_i(t)]\delta t \\ & \qquad\qquad i = 2, \ldots, m-1 \\ V_m(t+\delta t) &= V_m(t) + [\gamma_{m-1} V_{m-1}(t) + \nu_2 Y_m(t) - (vac_t \gamma_{bm} + \gamma_m + \mu_2) V_m(t)]\delta t \end{aligned}\right\} \ldots(5.1d)$$

$$Z(t+\delta t) = Z(t) + [\gamma_m (1-b) Y_m(t) + \gamma_m (1-g) V_m(t) + \nu_3 A(t) - \omega Z(t)]\delta t \qquad \ldots(5.1e)$$

Additionally, the backward transition rates, γ_{bi}, can be set to zero before 2005 to illustrate the notion that there is no vaccine before this time, hence no improvements in health are present, however, vac_t is already designated this role, therefore altering the value of γ_{bi}, from zero to its new value, is inconsequential. Once the vaccine is instigated in 2005 and vac_t begins its increase from 0 to 0.5, 0.7 or 0.9, by 2007, the backward transition rates, γ_{bi}, are introduced into the calculation of the differential-difference equations as the $vac_t\gamma_{bi}$

terms begin to take on positive values. Three situations of improving health, for those individuals administered with the vaccine after 2005, are modelled within this section: firstly, the case where $\gamma_{bi} = 0$ is considered, representing no improvements in health with the treatment of a therapeutic vaccine, however progression of HIV disease is halted; secondly, $\gamma_{bi} = 0.5$ is modelled, reflecting a backward movement at a rate of 0.5 (signifying an average of 2 years per stage before moving back to a previous stage of HIV infection), plus the conclusion of further HIV disease progression; and finally, the case where $\gamma_{bi} = 1$ is contemplated, demonstrating a backward movement at a rate of 1 (implying an average time of 1 year spent in each stage of HIV before improving to the previous stage), as well as no further forward movements through the HIV stages. Each scenario of improving health ($\gamma_{bi} = 0$, 0.5 or 1) is examined for each of the coverage levels that the therapeutic vaccine reaches ($vac_t = 0$, 0.5, 0.7 or 0.9), with the model projections up until the year 2012 illustrated in Figures 5.5a(1), 5.5a(2) and 5.5a(3), with regards to the number of people living in each sub-population of the HIV/AIDS epidemic; Figures 5.5b(1), 5.5b(2) and 5.5b(3), relating to the number of new HIV and AIDS cases as well as deaths from AIDS; and Figures 5.5c(1), 5.5c(2) and 5.5c(3), with respect to total HIV/AIDS prevalence. Firstly, looking at the effect the introduction of a 100% safe and effective therapeutic vaccine has on the sub-populations within the model, assuming only a prevention in disease progression is resultant, with no improvements in health (illustrated in Figure 5.5a(1)), the two most affected sub-populations are the Low Risk Infectives, V(t), and the Low Risk AIDS cases, Z(t). The prevalence of High Risk Susceptibles, X(t), is not affected since it is assumed that the therapeutic vaccine is not a cure for HIV, thus, once an individual is infected with HIV they have the virus for life i.e. there is no possible return back to susceptible status. For the High Risk Infective sub-population, Y(t), there is no change in course since the rate at which High Risk Infectives, in the last stage of HIV, progress to AIDS, γ_6, is insignificant in comparison to the rate at which High Risk Infectives, from all stages of HIV, become low risk, ν_2. Similarly, the High Risk AIDS cases, A(t), are not affected due to the fact that combination therapies have already reduced High Risk AIDS prevalence down to zero with the reduction in the transition rate, γ_6, together with the concept that there are fewer people in stage 6 of HIV infection for this transition rate to be applicable to, as the majority of infectives, by 2005, remain in the earlier stages of the

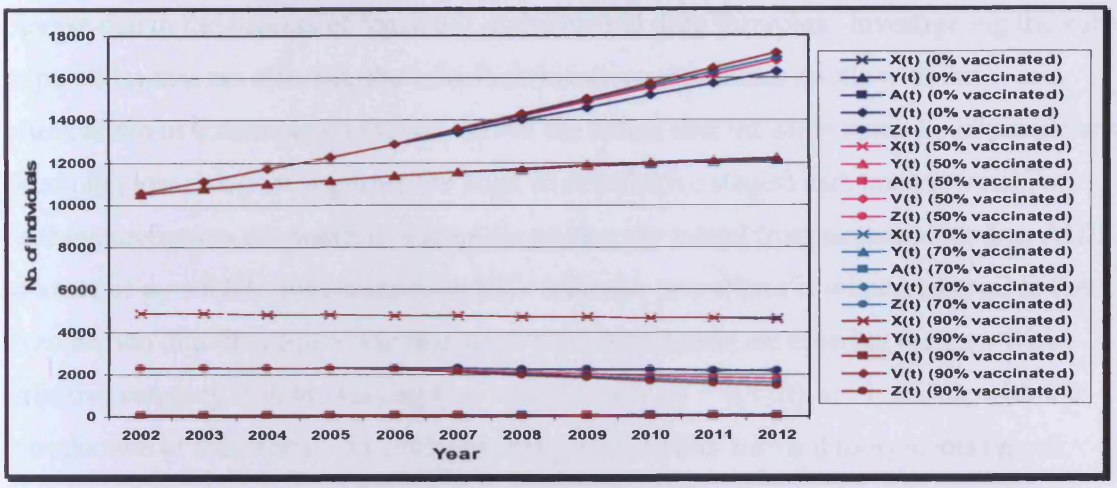

Figure 5.5a(1) **Sub-populations with Therapeutic Vaccine, vac_t, and $\gamma_{bi} = 0$.**

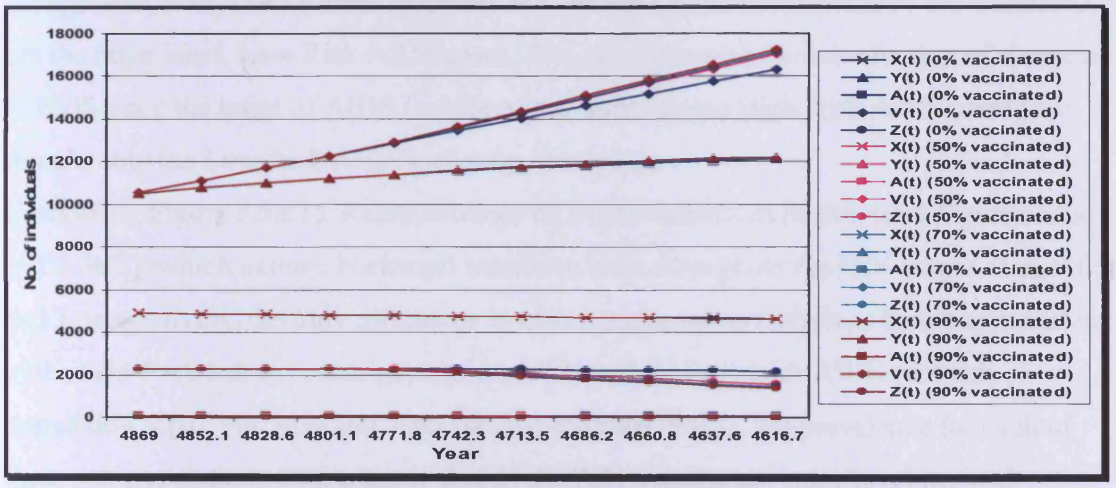

Figure 5.5a(2) **Sub-populations with Therapeutic Vaccine, vac_t, and $\gamma_{bi} = 0.5$.**

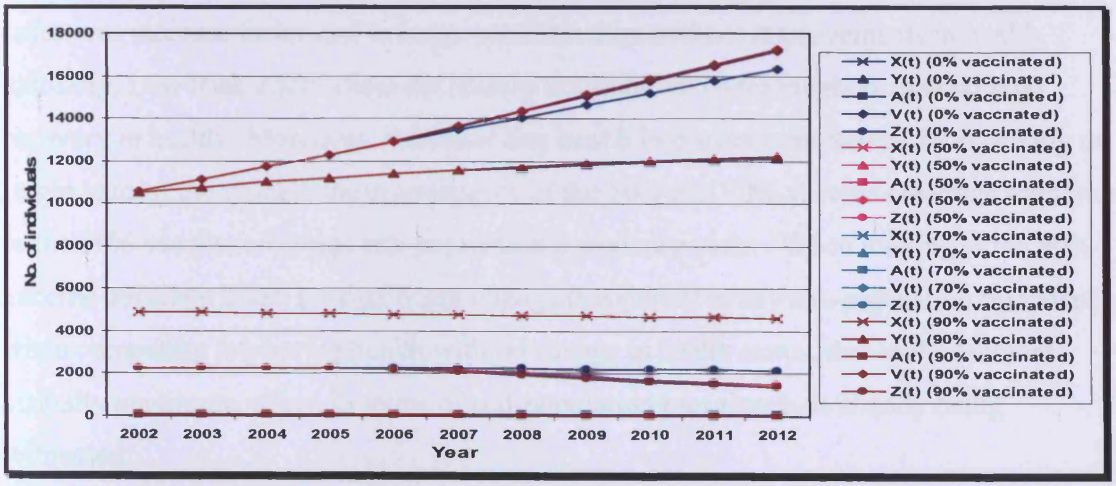

Figure 5.5a(3) **Sub-populations with Therapeutic Vaccine, vac_t, and $\gamma_{bi} = 1$.**

disease due to the success of 'cocktail' antiretroviral drug therapies. Investigating the sub-populations that are affected, the Low Risk Infective prevalence swells with the introduction of a therapeutic vaccine due to the notion that the same numbers of people are becoming low risk (moving from the High Risk Infective stages) and, once low risk, no further movements are possible, except for exiting the model from causes other than AIDS at a rate of $\mu_2 = 0.03$. Escalating Low Risk Infective prevalence is witnessed prior to the introduction of a therapeutic vaccine since more individuals are entering the Low Risk Infective category than are leaving (i.e. $\nu_2 Y_i(t) > \mu_2 V_i(t) + \gamma_6 V_6(t)$, i = 1, ..., 6); with the introduction of the vaccine, in 2005, resulting in no further forward movements ($\gamma_i = 0$, i = 1, ..., 6), the inequality of new low risk HIV infection and exits from this category is exaggerated, thus, even further increases in Low Risk Infective prevalence are witnessed. On the other hand, Low Risk AIDS cases, Z(t), decrease with the introduction of a vaccine in 2005 since the onset of AIDS is stopped and there are no High Risk AIDS cases to transfer into the Low Risk AIDS category, via rate ν_3.

Comparing Figure 5.5a(1), which assumes no improvements in health, with Figures 5.5a(2) and 5.5a(3), which assume backward transition rates throughout the HIV stages of $\gamma_{bi} = 0.5$ and 1, respectively, the only difference in effect on the sub-populations that is apparent is in the Low Risk Infective sub-population, V(t), and the Low Risk AIDS case sub-population, Z(t). For 50% and 70% vaccine coverage levels, the prevalence for each of these sub-populations converges to that of the 90% vaccine coverage level i.e. with improvements in health for lower vaccine coverage levels (50% and 70%), Low Risk Infectives increase faster and to larger numbers than without improvements in health, similarly, Low Risk AIDS cases decrease quicker and to lesser numbers than with no recovery in health. Moreover, the faster that health improves (represented by γ_{bi} taking on larger values) the quicker the convergence of the 50% and 70% vaccine coverage scenarios to the 90% vaccine coverage sub-population prevalence paths. When looking at the 90% vaccine coverage level, no significant change is apparent in any sub-population prevalence, when comparing improving health with no change in health status, due to the fact that virtually maximum effect, in terms of sub-population prevalence, is already being witnessed.

Figure 5.5b(1), overleaf, shows HIV incidence, AIDS incidence and deaths from AIDS for

the years 2002-2012 with the introduction of a therapeutic vaccine that prevents further progression of the virus once administered, but does not improve an individual's health. No matter how many infectives (50%, 70% or 90%) the new therapeutic vaccine is administered to, the number of new cases of HIV infection is not affected; it is only AIDS incidence and deaths from AIDS that change course. This is due to the fact that a therapeutic vaccine is provided for the infective populations to aid individuals living with HIV/AIDS, thus the susceptible category or, more specifically, the rate at which HIV is contracted, is not influenced. AIDS incidence falls to new steady levels of about 90 new cases for 50% vaccine coverage; 50 new cases for 70% vaccine coverage; and 10 new cases for 90% vaccine coverage, by 2012, compared to the alternate annual AIDS incidence of approximately 200 new cases of AIDS, for no vaccine coverage. This resultant change in AIDS incidence is not unexpected due to the very nature of the new therapeutic vaccine preventing the onset of AIDS. Consequently, the more infectives vaccinated, the fewer people that progress to AIDS, hence AIDS incidence reduces further for higher coverage levels of the vaccine. Comparing AIDS incidence for all scenarios of improving health, i.e. $\gamma_{bi} = 0$, 0.5 or 1, the greater the rate of improvement in health, the quicker AIDS incidence falls to new lower levels. For the case where $\gamma_{bi} = 1$, as seen in Figure 5.5b(3), AIDS incidence reduces to zero by 2012 for all coverage levels considered (50%, 70% and 90%). Accordingly, deaths from AIDS also fall with the introduction of a therapeutic vaccine, since fewer individuals are living with AIDS, hence, less people are present to die from the disease. Note that the death rate from AIDS, ω, maintains its estimated value of 0.09 throughout the extrapolated years, 2002-2012, and has not changed value as a result of the introduction of a therapeutic vaccine due to the assumption that once an individual contracts AIDS, their immune system is too weak for a therapeutic vaccine to be effective. Similar to the effect on AIDS incidence, the greater the rate of improvement in health, γ_{bi}, the quicker the number of people dying from AIDS declines. However, for 90% coverage the number of deaths from AIDS is not significantly affected by any suggested improvements in health since nearly complete maximum affect is already being observed. Thus, as the rate for improving health increases the trajectory of deaths from AIDS for both 50% and 70% vaccine coverage levels converge to that for 90% vaccine coverage. It would be expected in future years for deaths from AIDS to eventually reduce to zero if

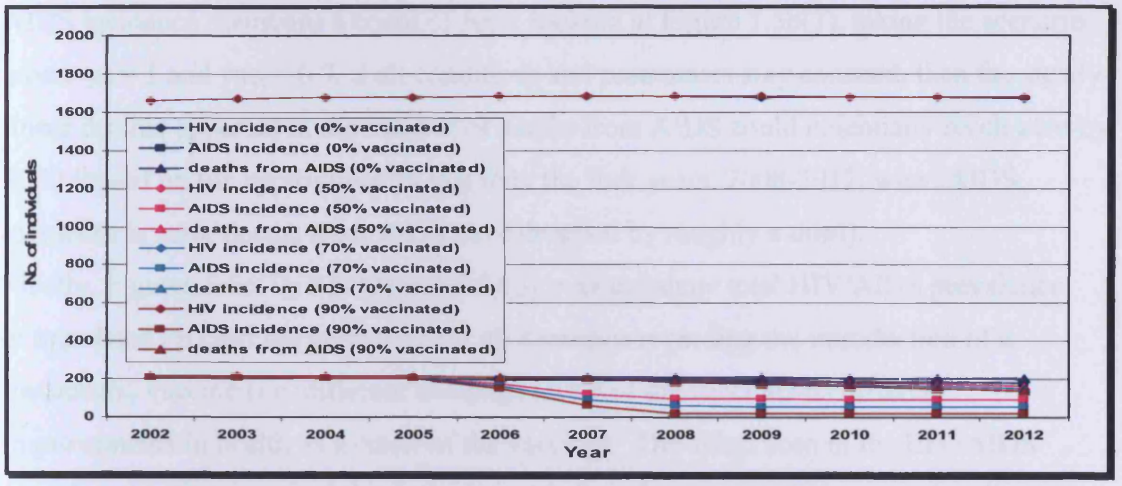

Figure 5.5b(1) **HIV, AIDS and deaths with Therapeutic Vaccine, vac_t, and $\gamma_{bi} = 0$.**

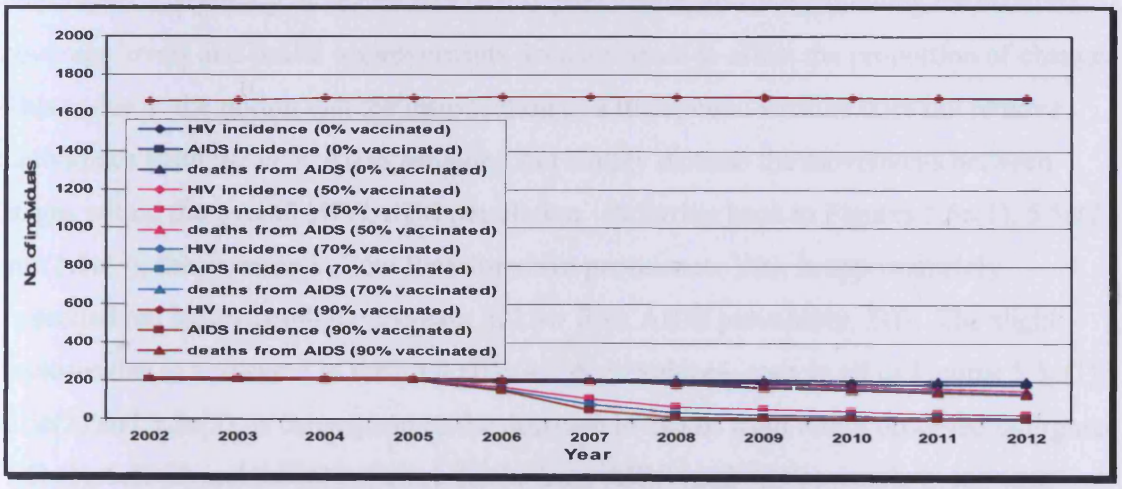

Figure 5.5b(2) **HIV, AIDS and deaths with Therapeutic Vaccine, vac_t, and $\gamma_{bi} = 0.5$.**

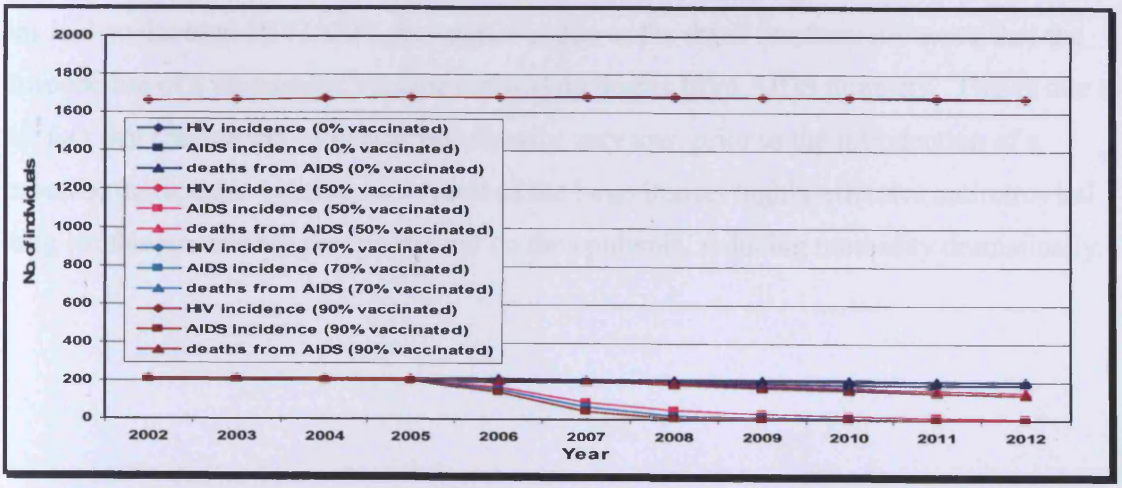

Figure 5.5b(3) **HIV, AIDS and deaths with Therapeutic Vaccine, vac_t, and $\gamma_{bi} = 1$.**

AIDS incidence maintains a count of zero; looking at Figure 5.5b(3), taking the scenario where $\gamma_{bi} = 1$ and $vac_t = 0.9$, if all conditions and parameters stay constant, then the steady linear decline apparent in the number of deaths from AIDS could potentially reach zero by 2020 (based on the approximation that over the four years, 2008-2012, when AIDS incidence is zero, deaths from AIDS have dropped by roughly a third).

Finally, Figures 5.5c(1), 5.5c(2) and 5.5c(3) overleaf show total HIV/AIDS prevalence extrapolated up until the year 2012 for all scenarios regarding the introduction of a therapeutic vaccine (i.e. different coverage levels of the vaccine and different improvements in health as a result of the vaccine). The effect seen in the HIV/AIDS prevalence projection is minimal; the introduction of a therapeutic vaccine, for all cases considered, marginally increases HIV/AIDS prevalence, however, allowing for different coverage levels and health improvements does not seem to affect the proportion of change. This is due to the notion that the introduction of a therapeutic vaccine does not remove individuals from the HIV/AIDS category, but simply dictates the movements between stages within the overall HIV/AIDS population. Referring back to Figures 5.5a(1), 5.5a(2) and 5.5a(3), the increase in Low Risk Infective prevalence, V(t), is approximately cancelled out by the resultant decrease in Low Risk AIDS prevalence, Z(t). The slight increase that is witnessed in the total HIV/AIDS prevalence, seen in all of Figures 5.5c(1), 5.5c(2) and 5.5c(3), is consequent to the decrease in deaths from AIDS observed in Figures 5.5b(1), 5.5b(2) and 5.5b(3). Fewer deaths from AIDS imply more people living with HIV/AIDS, i.e. greater HIV/AIDS prevalence. The lack of effect that a reduction in deaths has had on the total HIV/AIDS prevalence is due to the small resultant influence that the introduction of a therapeutic vaccine has had on deaths from AIDS numbers. This is due to the fact that the number of deaths was already very low, prior to the introduction of a potential therapeutic vaccine, as a result of the large impact highly effective antiretroviral drug combinations have previously had on the epidemic, reducing morbidity dramatically.

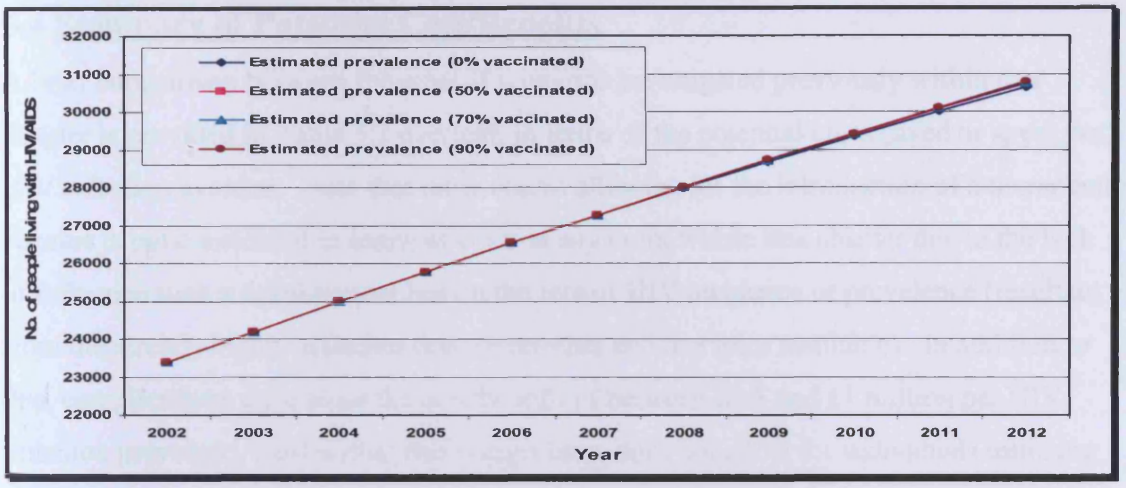

Figure 5.5c(1) **HIV/AIDS prevalence with Therapeutic Vaccine, vac_t, and $\gamma_{bi} = 0$.**

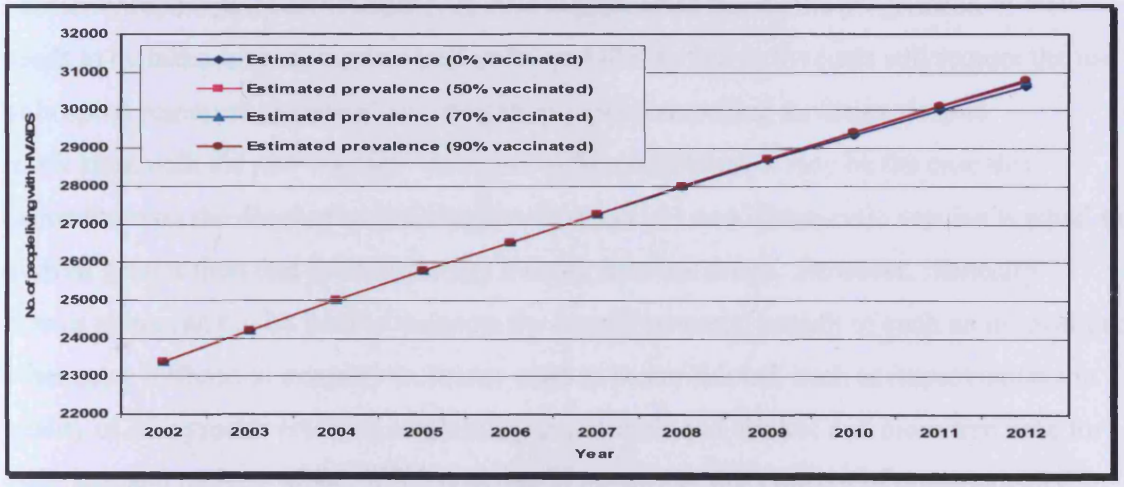

Figure 5.5c(2) **HIV/AIDS prevalence with Therapeutic Vaccine, vac_t, and $\gamma_{bi} = 0.5$.**

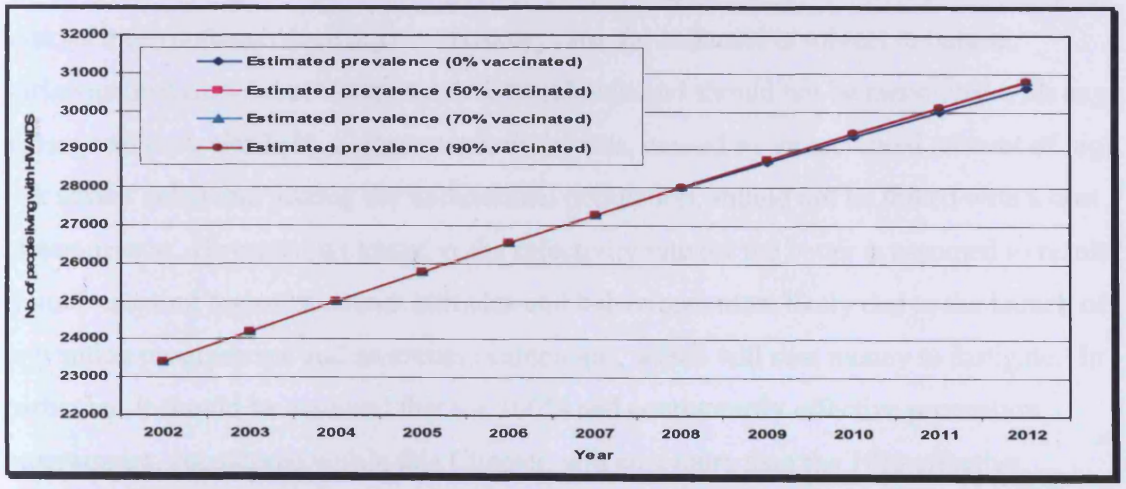

Figure 5.5c(3) **HIV/AIDS prevalence with Therapeutic Vaccine, vac_t, and $\gamma_{bi} = 1$.**

5.4 Summary of Potential Cost/Benefits

A brief comparison between the what-if scenarios investigated previously within this chapter is provided in Table 5.7 overleaf, in terms of the potential costs saved or spent per HIV infection avoided. Note that the scenario allowing for the introduction of a therapeutic vaccine is not considered in terms of costs at any point within this chapter due to the lack of influence such a development has on the rate of HIV incidence or prevalence (resultant from the already highly effective drug treatments and therapies available). In addition to this, complications arise since the cost/benefit of between £0.5 and £1 million per HIV infection prevented, used within this comparison, does not allow for individuals initiating therapy but not needing it to continue due to the initiation of a therapeutic vaccine. Furthermore, the point at which the vaccine is prescribed during the progression of HIV needs to be taken into account as well as the possibility that individuals still require the use of hospital resources (inpatient and outpatient) and counselling facilities, despite medication with the new vaccine. In terms of financial costs, it may be the case that expenditure on the development and administration of a new therapeutic vaccine is equal to or even greater than that spent presently on antiretroviral drugs. However, monetary figures alone can not be used to measure the overall potential benefit of such an innovation; other more difficult to quantify measures need to be considered, such as improvements in quality of life; greater resource availability at hospitals and clinics; and more free time for clinicians and patients alike. It is important to remember this concept of non-monetary value when looking at Table 5.7, as well as considering the costs behind implementing the various interventions. A change in the entry rate, for instance, is subject to natural variations that may occur within the UK population and should not be associated with any subsequent cost, similarly, a greater infectivity rate, caused by an increased amount of high risk sexual behaviour among the homosexual population, should not be linked with a cost of occurrence. However, a change in the infectivity rate for the better is assumed to result from decreasing high-risk sexual attitudes and behaviours most likely due to the launch of prevention programmes and awareness campaigns, which will cost money to instigate. In particular, it should be assumed that the 100% and continuously effective prevention programmes, considered within this Chapter, will cost more than the 10% effective intervention. The greatest cost associated with the occurrence of any of the scenarios

SCENARIO	TOTAL HIV INCIDENCE 2005-2012	COST/BENEFIT (£M) 2005-2012
Change in Entry Rate +10%	13932	-257 - -514
Change in Entry Rate -10%	12895	261.5 – 523
Change in Infectivity Rate +10%	13924	-253 - -506
Change in Infectivity Rate -10%	12824	297 – 594
Change in Infectivity Rate -10% continuously	12042	688 – 1376
Change in Infectivity Rate -100%	3360	5029 – 10058
Preventive Vaccine with 50% coverage	9402	2008 – 4016
Preventive Vaccine with 70% coverage	7064	3162 – 6324
Preventive Vaccine with 90% coverage	4588	4415 – 8830

Table 5.7 **Cost/Benefit comparisons for 'what-if' scenarios over the years 2005-2012.**

discussed is expected to be related to the introduction of a preventive vaccine, its invention, distribution and administration. Moreover, the greater the coverage of the preventive vaccine the greater the costs are expected to be. However, for this work, since no information on expenses associated with the occurrence of any such 'what-if' scenario is available, further investigation into the net cost/benefits is halted and focus is brought back to the gross cost/benefits seen in Table 5.7, above. That is, the total amount of money that could potentially be saved if prevention programmes are introduced, or a preventive

vaccine invented, without accounting for the price of implementing either form of intervention. For comparison, with no intervention a total of 13,418 new HIV infections are predicted to occur during the years 2005-2012. The best case scenario, from Table 5.7, is the situation where a 100% effective prevention programme is put into place, completely halting all new infections of HIV from 2007 onwards. This reduces total HIV incidence over the years 2005-2012 down to 3,360 (a reduction of about 75%) and could potentially save £5,029 - £10,058 million. However, the idea of preventing all possible new HIV infections completely can be deemed as an unrealistic success. Second best is the scenario where a preventive vaccine is introduced; for all three coverage levels (50%, 70% and 90%) the total number of new HIV cases over the years 2005-2012 has dropped dramatically to 9,402 (-30%), 7,064 (-47%) and 4,588 (-66%), respectively, resulting in possible costs saved of between £2,008 - £8,830 million, dependent on the coverage level. As mentioned previously, this scenario may be viewed as the most expensive to implement, however, these expenses may be outweighed by the substantial costs saved as a result. Failing the introduction of a preventive vaccine, the next best scenario, and possibly the most realistic of all the scenarios considered, is that of the intervention of continuous prevention programmes which can moderate total HIV incidence, during the years 2005-2012, down to 12,042 (-10%) and save costs amounting to a prospective £688 - £1,376 million.

CHAPTER 6

SUGGESTIONS FOR FUTURE WORK AND SUMMARY

6.1 Suggestions for Future Work

The main outcome of the HIV/AIDS epidemic model created within this thesis is the excellent fit produced between observed and expected HIV incidence, AIDS incidence and deaths from AIDS data, providing a basis for more in-depth investigation into specific sub-topics. For instance, clinical stages of HIV infection, normally defined by a measure of CD4 count, can be mapped onto the 6 mathematical stages of HIV infection incorporated into this model, which are assumed to be of equal length. This develops a specified version of the model capable of helping policy makers, clinicians and health officials make better, more informed decisions due to the ability to measure, or estimate: costs of treatments; treatment uptake; treatment effectiveness (possibly linked to adherence); cost-effectiveness of prevention programmes; and the development of drug resistance. For reference, Rauner & Brandeau (2000) discuss key issues of AIDS policy modelling.

The datasets used as the source of observed AIDS incidence, HIV incidence (ENAADS) and deaths from AIDS (CDSC) throughout this thesis are based on homosexual men in the UK. In order to investigate other transmission modes within the UK, the same datasets can be employed as the foundation of observed figures. In particular, heterosexual transmission has overtaken homosexual transmission over recent years, in terms of new HIV incidences, and will potentially be the future main mode of HIV transmission within the UK. The Cardiff HIV/AIDS Model produced within this thesis can be utilised to model the heterosexual population within the UK simply by implementing the observed data for heterosexual infections (ENAADS and CDSC) and re-estimating the entry rate into the High Risk Susceptibles; the infectivity rate (or, the mean number of sexual contacts per individual); the number of heterosexuals living with

HIV/AIDS at the start of the epidemic; and the effect of treatments on the length of the incubation period. All other parameters and model assumptions could be presumed to remain as originally designated when modelling the homosexual population. Other geographical regions can also be modelled by applying the relevant observed data for those regions and re-estimating the parameters (Λ, βc, a_{1978} and r), however, care needs to be taken when doing so due to the concept that a number of parameter values within the model are based on UK population statistics, research or epidemiological studies, i.e. the exit rate, μ, from the model from causes other than AIDS; the rate, ν, at which an individual changes behaviour from high to low risk; and the death rate, ω, may all take on different values for other regions within Europe or elsewhere in the world.

Many more adaptations and extensions can be investigated within the Cardiff HIV/AIDS Epidemic Model due to its flexibility. Further ideas can mostly be based upon the main assumptions employed in the creation of the model within this thesis, as explored in the following sections of this chapter.

6.1.1 Further work involving the Entry Rate

The first assumption within the Cardiff Model to examine is the entry rate, Λ, into the model. Throughout this work it has been assumed that entry into the model is via the High Risk Suscepible category only. Extended work could look at the possibilities of entry into both the High Risk and Low Risk Susceptible categories. Furthermore, a proportion of entry, say q, into either risk group can be set, see Figure 6.1.

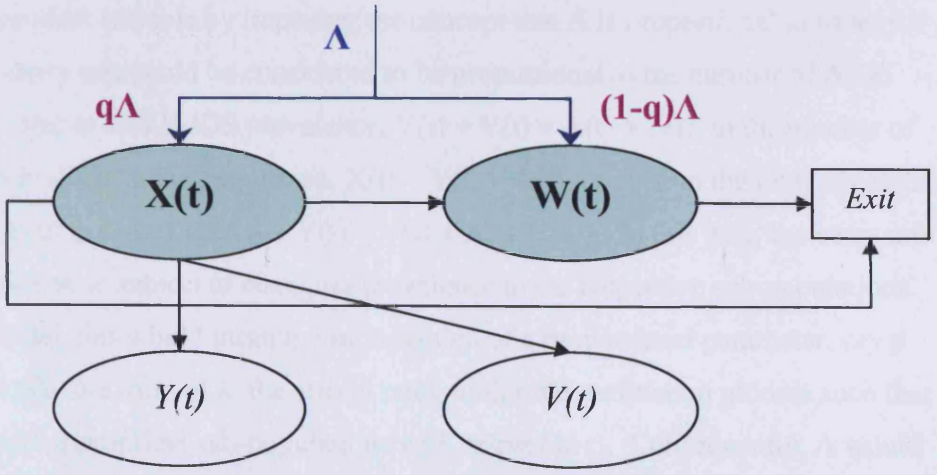

Figure 6.1 **Entry rate into both High Risk and Low Risk Susceptible categories.**

Note that if q = 1 the model is the same as proposed throughout this thesis, with all individuals entering the model via the High Risk Susceptible category, at an entry rate of Λ. The proportion of entry split between high and low risk behaviour sub-populations, q, can be investigated in more detail, allowing q to take various values between the range $0 \leq q \leq 1$. This new consideration for the entry rate would specifically affect the differential-difference equations associated with the sub-populations X(t) and W(t). The modified formulae for these sub-populations are shown in equations (6.1a) and (6.1b) below.

$$X(t+\delta t) = X(t) + [q\Lambda - (\mu_1 + \nu_1)X(t) - \alpha X(t)]\delta t \qquad \ldots(6.1a)$$

$$W(t+\delta t) = W(t) + [(1-q)\Lambda + \nu_1 X(t) - \mu_1 W(t)]\delta t \qquad \ldots(6.1b)$$

The adapted equations, as seen above, would replace the original equations in the Cardiff HIV/AIDS model and, consequently, the differential-difference equations within the VB script, relating to the High Risk and Low Risk Susceptibles, would require reprogramming. Then, the MLE techniques can be reproduced for this modified model involving the new concept of insertion of the entry rate, with q and Λ being estimated. In addition to this broadened exploration of the point of entry into the model, is the investigation of the assumption that the entry rate, Λ, is estimated as a single independent parameter, with N_{1978} fixed. The entry rate is subsequently constant over time as a result of this assumption and consequent estimation process. However, Λ could be represented as a time-dependant variable by imposing the concept that Λ is proportional to time; for instance, the entry rate could be considered to be proportional to the number of AIDS cases, A(t) + Z(t); to HIV/AIDS prevalence, Y(t) + V(t) + A(t) + Z(t); to the number of High Risk individuals in the population, X(t) + Y(t) + A(t); or even to the total population in the model at time t, X(t) + W(t) + Y(t) + V(t) + A(t) + Z(t). In this way, the entry rate would vary over time subject to changing prevalence in the respective sub-populations. Within the model, this would mean the introduction of a proportional parameter, say p (which could take the form of λ, the arrival rate), within the estimation process such that Λ = p x (sum of appropriate sub-populations with respect to t). Consequently, Λ would be removed from the estimation process and calculated as shown above.

6.1.2 Further work involving the Infectivity Rate

Another consideration for future work involves the infectiousness of HIV/AIDS, β, which is assumed to be constant throughout this thesis. Studies by Anderson (1988); Blythe & Anderson (1989[b]); Roberts & Dangerfield (1990[b]); Dangerfield & Roberts (1994); Jacquez *et al.* (1994); Garnett & Anderson (1996); and Dangerfield (1999), however, employ the notion of greater infectiousness in the earlier stages of the HIV infection, which decreases before rising again just prior to progression to AIDS. This concept of variable infectiousness can be introduced into the model by defining a different infectivity rate for each stage of HIV infection. When doing so, since the infectivity rate, βc, takes into consideration the rate of transmission per contact (infectiousness of HIV/AIDS), β, as well as the mean number of sexual contacts per individual, c, the change in behaviour noticeable, relative to different levels of perceived viral load, also needs to be considered. That is, the healthier an individual believes he is, the riskier his sexual behaviour tends to be, i.e. c might be expected to be greater in the earlier and middle stages of HIV infection. Thus, an exaggerated greater infectivity rate at the start of HIV disease progression could be investigated, with falling infectivity as the disease develops, perhaps with a slight rise just before the onset of AIDS in accordance with the literature references listed above, although this rise in infectiousness might be cancelled out by a decrease in sexual activity associated with poor health. Another consideration with respect to the infectivity rate, βc, is the assumption of constant value over time for the Pre-treatment era, 1979-1986, and for the Early Treatment and Combination Treatment eras, 1987-2002, post smoothing. Investigation could be made into the effect of a time-dependant βc profile on the fit to the ENAADS AIDS incidence data. Since HIV incidence is problematic to estimate, due to a long incubation period and lack of acute symptoms prior to severe immunosuppression, and, even though numbers of diagnosed infections are deemed more accurate records, diagnosis may take place years after initial contraction with HIV, other sexually transmitted disease (STD) data is the best option for monitoring levels of high risk behaviour. Thus, a time-dependent βc term can be created which enlists the profile of the incidence of a STD with a short incubation period. Snary (2000) inspects this suggestion within her PhD thesis and employs rectal gonorrhoea data in order to directly obtain a time-dependent profile for parameter βc.

Equation (6.2) below is the initial, simple, formula utilised for the work undertaken by Snary (2000), before considering other more complicated formats for the make-up of a time-dependant infectivity rate.

$$\beta c_t = \frac{RG_t}{RG} \times \beta c \qquad \ldots(6.2)$$

Where βc_t is the value of the parameter βc at time t,

RG_t is the number of rectal gonorrhoea cases in year t,

RG is the mean number of rectal gonorrhoea cases over the years 1979-1994 and,

βc is the mean value of the infectivity parameter for the same period 1979-1994.

Within this extension, the mean value of the infectivity parameter, βc, can still be estimated using maximum likelihood techniques, as performed previously.

6.1.3 Further work involving changing behaviours

The Cardiff Model within this thesis assumes a change in behaviour from High Risk to Low Risk at the rate of ν_1 for the Susceptible category, ν_2 for the Infective categories and ν_3 for the AIDS case category. However, the assumption is that an individual will not, once converted to their respective Low Risk category, return back to their previous High Risk category. That is to say that so far within this work, the transition between risk groups has been one-way in direction. Further work could contemplate a two-way movement between respective behaviour sub-populations, as illustrated in Figure 6.2 overleaf. The idea that an individual may revert back to their previous high risk behaviour is supported by data from other STD's, such as rectal gonorrhoea, that suggest a significant increase in UK reported cases due to such factors as complacency; HIV optimism as a result of new combination drug therapies; and a reduction in media coverage and publicity. As shown in Figure 6.2, the parameters ν_{b1}, ν_{b2} and ν_{b3} can be introduced into the model to represent the rates at which individuals revert from the Low Risk categories back to the respective High Risk categories. This would result in the

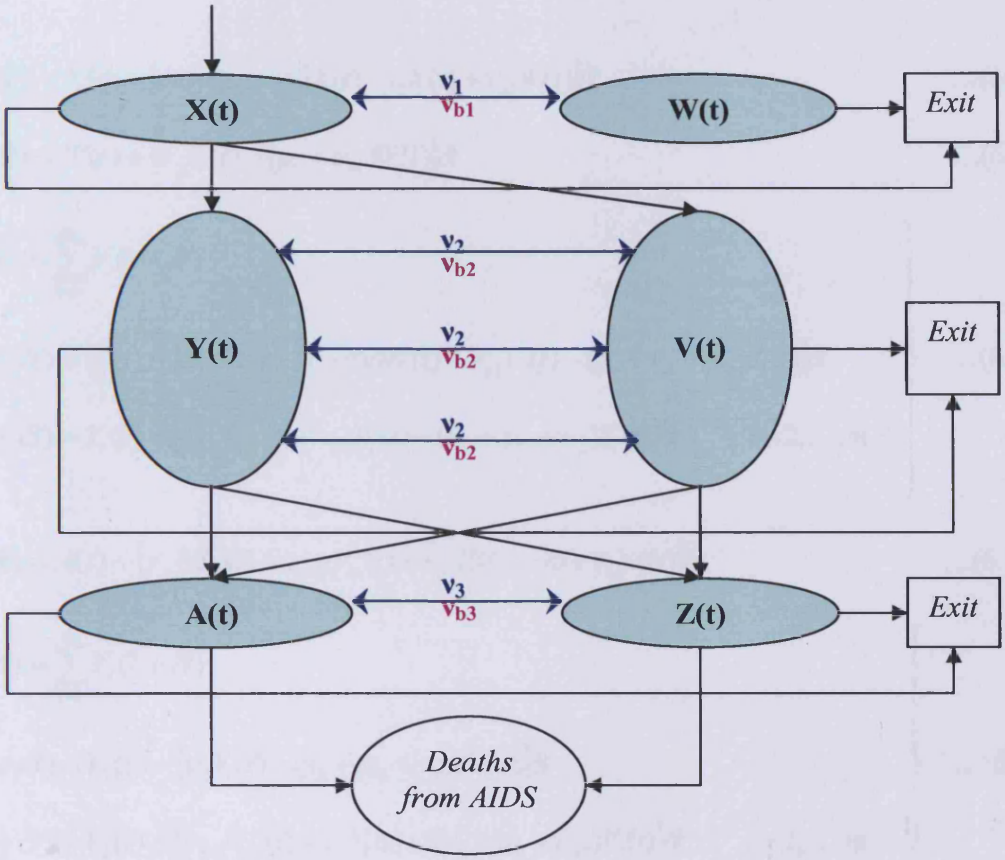

Figure 6.2 **Two-way directional movements between High Risk and Low Risk sub-populations.**

alteration of differential-difference equations in order to include the aforementioned backward transitions, from Low Risk to High Risk. The Cardiff HIV/AIDS model would need re-evaluating with the adapted equations, as shown overleaf in equations (6.3a)-(6.3f), replacing those already programmed into the VB script. Once the modified model is set-up, the new backward transition rates of behaviour change need to be assessed and quantified to permit the program to perform the formulation of the model and subsequent estimation of the specified parameter values using maximum likelihood techniques.

$$X(t+\delta t)=X(t)+\left[\Lambda-(\mu_1+\nu_1)X(t)-\alpha X(t)+\nu_{b1}W(t)\right]\delta t \qquad \ldots(6.3a)$$

$$W(t+\delta t)=W(t)+\left[\nu_i X(t)-(\mu_1+\nu_{b1})W(t)\right]\delta t \qquad \ldots(6.3b)$$

$$\left.\begin{aligned} Y(t+\delta t)&=\sum_{i=1}^{m}Y_i(t+\delta t)\\ Y_1(t+\delta t)&=Y_1(t)+\left[a\alpha X(t)+(1-a)\alpha W(t)+\nu_{b2}V_1(t)-(\gamma_1+\nu_2+\mu_2)Y_1(t)\right]\delta t\\ Y_i(t+\delta t)&=Y_i(t)+\left[\gamma_{i-1}Y_{i-1}(t)+\nu_{b2}V_i(t)-(\gamma_i+\mu_2+\nu_2)Y_i(t)\right]\delta t \qquad i=2,\ldots,m \end{aligned}\right\} \ldots(6.3c)$$

$$A(t+\delta t)=A(t)+\left[\gamma_m bY_m(t)+\gamma_m gV_m(t)+\nu_{b3}Z(t)-(\omega+\nu_3)A(t)\right]\delta t \qquad \ldots(6.3d)$$

$$\left.\begin{aligned} V(t+\delta t)&=\sum_{i=1}^{m}V_i(t+\delta t)\\ V_1(t+\delta t)&=V_1(t)+\left[\nu_2 Y_1(t)-(\gamma_1+\mu_2+\nu_{b2})V_1(t)\right]\delta t\\ V_i(t+\delta t)&=V_i(t)+\left[\gamma_{i-1}V_{i-1}(t)+\nu_2 Y_i(t)-(\gamma_i+\mu_2+\nu_{b2})V_i(t)\right]\delta t \qquad i=2,\ldots,m \end{aligned}\right\} \ldots(6.3e)$$

$$Z(t+\delta t)=Z(t)+\left[\gamma_m(1-b)Y_m(t)+\gamma_m(1-g)V_m(t)+\nu_3 A(t)-(\omega+\nu_{b3})Z(t)\right]\delta t \qquad \ldots(6.3f)$$

6.1.4 Further work involving treatment uptake considerations

Another area for deliberation is the conjecture that treatment uptake is assumed equal for all stages of HIV infection in the formation of the Cardiff model within this work; the parameter r applies to all stages of HIV infection at the same rate, with the exception of stage 6 when highly effective combination treatments are introduced since a slower and dulled reaction to the new therapies is expected for this sub-population of people with a weaker immune system and possible development of drug resistance. The model can be re-evaluated to look at the concept of when best to initiate treatment. For instance,

Longini assumes the initiation of treatment once CD4 levels drop to below 500 cells/μl (that is, treatment uptake commences from stage 3 onwards) in line with US guidelines, whilst current UK guidelines suggest that treatment should be initiated once CD4 count falls below 350 cells/μl (BHIVA 1999), which is concurrent with stage 4 of HIV infection onwards within Longini's classification of stages. This would imply a re-estimation of the parameter r, relevant only to those beyond a certain point in HIV disease progression. For example, if the scenario where treatment is initiated for individuals with a CD4 cell count less than 500 cells/μl is employed, then the transition rates would be calculated as follows:

$$\gamma_i = {}^{m}\!/_{IP}, \qquad i = 1,2.$$

$$\gamma_i = {}^{m}\!/_{r \times IP}, \qquad i = 3,\ldots,6.$$

This concept of treatment initiation and uptake can easily be introduced into the Cardiff HIV/AIDS model simply by restating the initial calculation of the transition rates within the model, to that shown above, and then re-performing maximum likelihood estimation on all relevant parameters, not just on r, since changing the foundation of the model may also affect the rest of the parameters subject to estimation. Note that the formulation of the transition rates could be kept the same as it was previously within the model but with the added constraint that if i = 1 or 2, then r = 1.

6.1.5 Further work involving the Incubation Period

Finally, and perhaps most importantly, we consider the assumption placed on the incubation period; that a patient follows a '1-step' forward-movement-only transition path through the 6 stages of HIV infection, with the added notions that an individual can only enter the infective category via stage 1 and can not advance to AIDS unless in the final stage of disease progression. This section considers a variety of different concepts involving numerous possible transition paths through the incubation period and how these assorted paths can be introduced into the Cardiff HIV/AIDS model. A combination of '1-step' or 'multi-step' models are explored, with either forward movement only or

with the additional inclusion of backward transition through the HIV stages of infection. Figure 6.3a represents this interpretation of the incubation period as it has been implemented throughout this thesis, where each numbered box represents that specific stage of HIV infection.

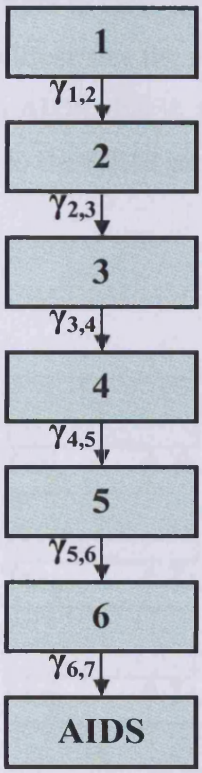

Figure 6.3a **Incubation Period with '1-step' forward movements only**

For this exploration into different transition routes through the incubation period, it is important to set up a clear and understandable notation. Thus, $\gamma_{i,j}$ will represent the transition rate from stage i to stage j, where i,j = 1,2, …, 7 with stage 7 equivalent to AIDS. Hence, throughout the work within this thesis, $\gamma_{i,j}$ could also be denoted as $\gamma_{i,i+1}$. Extending from the original '1-step' forward movement transition, as seen in Figure 6.3a, '1-step' backward transition can be incorporated into the incubation period, as well as '2-step' forward and backward movements. These '2-step' actions allow an individual to 'skip' or 'jump' a stage of HIV infection and progress to the next-but-one stage of HIV infection, thus broadening the model to allow for fast progressors of HIV disease, whose health deteriorates severely in a short period of time, or the impact of highly effective

treatments on an individual's CD4 count. For both the incorporation of '1-step' and '2-step' backward progression through HIV infective stages, the assumption that once AIDS is contracted an individual can not then return to being HIV only holds. Thus, as seen in Figure 6.3b, there is no backward transition from the AIDS stage (that is, stage 7) to any of the HIV infective stages. In addition to these new 1- and 2- step, forward and backward, movements, Figure 6.3b illustrates the possible transition from the later stages of HIV infection to jump straight to AIDS, that is, the model illustrated in Figure 6.3b enables individuals to leap directly to the AIDS stage from any of the HIV stages 3, 4, 5 or 6.

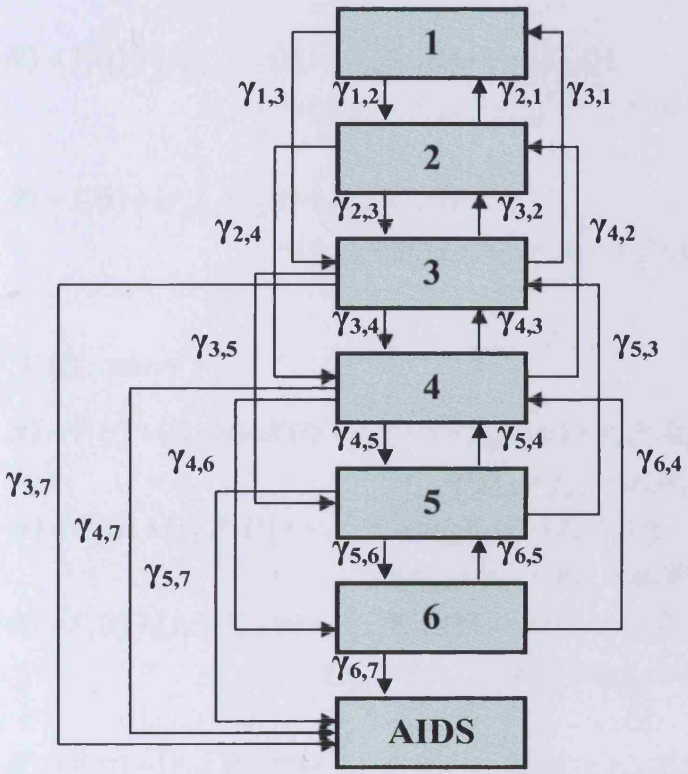

Figure 6.3b **Incubation Period with '1-step', '2-step' and 'multi-step to AIDS' forward and backward movements**

Equations (6.4a)-(6.4e) demonstrate the relevant alterations that would need to be made to the infective differential-difference sub-population equations, Y(t) and V(t), as well as the AIDS case sub-population equations, A(t) and Z(t), and the formulation of AIDS incidence, if all of the transitional routes illustrated in Figure 6.3b were incorporated.

$$
\left.
\begin{aligned}
&Y(t)=\sum_{i=1}^{m} Y_i(t) \quad \textit{where}\\
&Y_1(t+\delta t)=\boldsymbol{Y_1(t)}+[a\alpha X(t)+\gamma_{2,1}Y_2(t)+\gamma_{3,1}Y_3(t)\\
&\qquad -(\gamma_{1,2}+\gamma_{1,3}+\mu_2+\nu_2)Y_1(t)]\delta t\\
&Y_2(t+\delta t)=\boldsymbol{Y_2(t)}+[\gamma_{1,2}Y_1(t)+\gamma_{3,2}Y_3(t)+\gamma_{4,2}Y_4(t)\\
&\qquad -(\gamma_{2,1}+\gamma_{2,3}+\gamma_{2,4}+\mu_2+\nu_2)Y_2(t)]\delta t\\
&Y_i(t+\delta t)=\boldsymbol{Y_i(t)}+[\gamma_{i-2,i}Y_{i-2}(t)+\gamma_{i-1,i}Y_{i-1}(t)+\gamma_{i+1,i}Y_{i+1}(t)+\gamma_{i+2,i}Y_{i+2}(t)\\
&\qquad -(\gamma_{i,i-2}+\gamma_{i,i-1}+\gamma_{i,i+1}+\gamma_{i,i+2}+\gamma_{i,7}+\mu_2+\nu_2)Y_i(t)]\delta t\\
&\qquad\qquad i=3,\ldots,m-2\\
&Y_i(t+\delta t)=\boldsymbol{Y_i(t)}+[\gamma_{i-2,i}Y_{i-2}(t)+\gamma_{i-1,i}Y_{i-1}(t)+\gamma_{i+1,i}Y_{i+1}(t)\\
&\qquad -(\gamma_{i,i-2}+\gamma_{i,i-1}+\gamma_{i,i+1}+\gamma_{i,7}+\mu_2+\nu_2)Y_i(t)]\delta t\\
&\qquad\qquad i=m-1\\
&Y_i(t+\delta t)=\boldsymbol{Y_i(t)}+[\gamma_{i-2,i}Y_{i-2}(t)+\gamma_{i-1,i}Y_{i-1}(t)\\
&\qquad -(\gamma_{i,i-2}+\gamma_{i,i-1}+\gamma_{i,7}+\mu_2+\nu_2)Y_i(t)]\delta t\\
&\qquad\qquad i=m
\end{aligned}
\right\}\cdots(6.4a)
$$

$$
\left.
\begin{aligned}
&V(t)=\sum_{i=1}^{m} V_i(t) \quad \textit{where}\\
&V_1(t+\delta t)=\boldsymbol{V_1(t)}+[(1-a)\alpha X(t)+\nu_2Y_1(t)+\gamma_{2,1}V_2(t)+\gamma_{3,1}V_3(t)\\
&\qquad -(\gamma_{1,2}+\gamma_{1,3}+\mu_2)V_1(t)]\delta t\\
&V_2(t+\delta t)=\boldsymbol{V_2(t)}+[\gamma_{1,2}V_1(t)+\nu_2Y_1(t)+\gamma_{3,2}V_3(t)+\gamma_{4,2}V_4(t)\\
&\qquad -(\gamma_{2,1}+\gamma_{2,3}+\gamma_{2,4}+\mu_2)V_1(t)]\delta t\\
&V_i(t+\delta t)=\boldsymbol{V_i(t)}+[\gamma_{i-2,i}V_{i-2}(t)+\gamma_{i-1,i}V_{i-1}(t)+\nu_2Y_i(t)+\gamma_{i+1,i}V_{i+1}(t)+\gamma_{i+2,i}V_{i+2}(t)\\
&\qquad -(\gamma_{i,i-2}+\gamma_{i,i-1}+\gamma_{i,i+1}+\gamma_{i,i+2}+\gamma_{i,7}+\mu_2)V_i(t)]\delta t\\
&\qquad\qquad i=3,\ldots,m-2\\
&V_i(t+\delta t)=\boldsymbol{V_i(t)}+[\gamma_{i-2,i}V_{i-2}(t)+\gamma_{i-1,i}V_{i-1}(t)+\nu_2Y_i(t)+\gamma_{i+1,i}V_{i+1}(t)\\
&\qquad -(\gamma_{i,i-2}+\gamma_{i,i-1}+\gamma_{i,i+1}+\gamma_{i,7}+\mu_2)V_i(t)]\delta t\\
&\qquad\qquad i=m-1\\
&V_i(t+\delta t)=\boldsymbol{V_i(t)}+[\gamma_{i-2,i}V_{i-2}(t)+\gamma_{i-1,i}V_{i-1}(t)+\nu_2Y_i(t)\\
&\qquad -(\gamma_{i,i-2}+\gamma_{i,i-1}+\gamma_{i,7}+\mu_2)V_i(t)]\delta t\\
&\qquad\qquad i=m
\end{aligned}
\right\}\cdots(6.4b)
$$

$$A(t+\delta t) = A(t) + [b(\gamma_{6,7}Y_6(t) + \gamma_{5,7}Y_5(t) + \gamma_{4,7}Y_4(t) + \gamma_{3,7}Y_3(t)) + g(\gamma_{6,7}V_6(t) + \gamma_{5,7}V_5(t) + \gamma_{4,7}V_4(t) + \gamma_{3,7}V_3(t)) - (\nu_3 + \mu_3 + \omega)A(t)]\delta t \quad \cdots(6.4c)$$

$$Z(t+\delta t) = Z(t) + [(1-b)(\gamma_{6,7}Y_6(t) + \gamma_{5,7}Y_5(t) + \gamma_{4,7}Y_4(t) + \gamma_{3,7}Y_3(t)) + (1-g)(\gamma_{6,7}V_6(t) + \gamma_{5,7}V_5(t) + \gamma_{4,7}V_4(t) + \gamma_{3,7}V_3(t)) + \nu_3 A(t) - (\mu_3 + \omega)Z(t)]\delta t \quad \cdots(6.4d)$$

$$\textit{AIDS Incidence} = \gamma_{6,7}\left[\sum_{i=1}^{52} Y_6(i) + \sum_{i=1}^{52} V_6(i)\right] + \gamma_{5,7}\left[\sum_{i=1}^{52} Y_5(i) + \sum_{i=1}^{52} V_5(i)\right] + \gamma_{4,7}\left[\sum_{i=1}^{52} Y_4(i) + \sum_{i=1}^{52} V_4(i)\right] + \gamma_{3,7}\left[\sum_{i=1}^{52} Y_3(i) + \sum_{i=1}^{52} V_3(i)\right] \quad \ldots(6.4e)$$

The full set of modified differential-difference equations are as seen in equations (6.4a)-(6.4e); the other sub-population equations are not affected by changes made within the incubation period, i.e. X(t), W(t), HIV incidence and HIV/AIDS prevalence are all calculated as previously.

All of the aforementioned possible movements within a staged incubation period are illustrated in Figure 6.3b and allowed for in the amendments of the differential-difference equations (6.4a)-(6.4e). Of course, in the development of future work, not all of these possible paths of progression through the incubation period of HIV need to be considered simultaneously, in fact, more in depth investigation, and consequent understanding, can occur if each scenario is considered individually. For instance, the investigation into backward transition rates alone is a multifaceted process with numerous possibilities requiring a large amount of research and analysis on a number of different scenarios. In order to study the individual aspects included within Figure 6.3b and equations (6.4a)-(6.4e) separately, the irrelevant transition rates need not be considered, and thus can be set to zero to give the interpretation required. For example, to focus on '1-step' forward

or backward movements only, the model for the incubation period as seen in Figure 6.3b is employed with $\gamma_{i,i+2} = 0$, i = 1, …,5; $\gamma_{i,7} = 0$, i = 3, 4; and $\gamma_{i+2,i} = 0$, i = 1, …, 4. Thus, the model illustrated in Figure 6.3c below is utilised, with the paths highlighted in blue being the active routes, with associated transition rates, and the dashed paths being inactive, corresponding to the transition rates that have been set to zero.

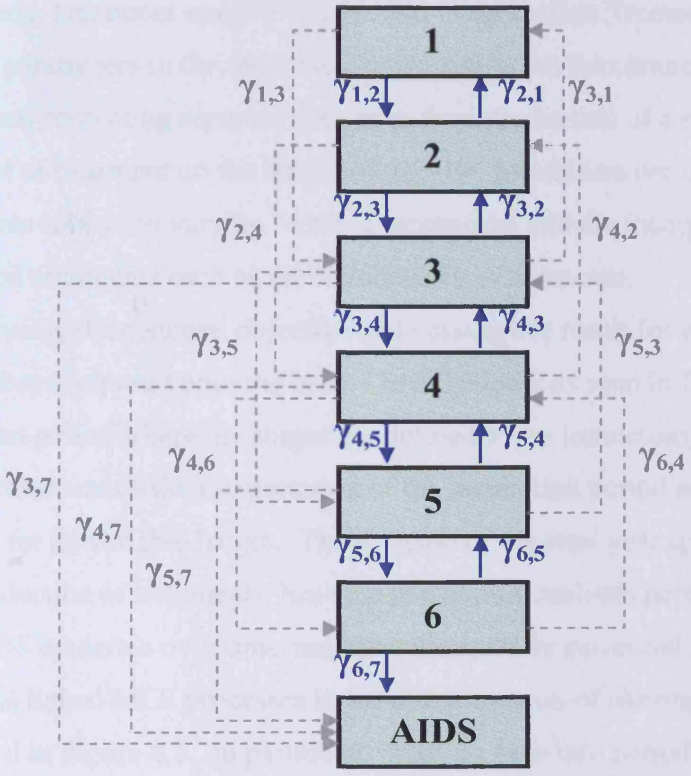

Figure 6.3c **Incubation Period with '1-step' forward and backward movements only**

Accordingly, equations (6.4a)-(6.4e) are utilised within the formation of the Cardiff HIV/AIDS model with the relevant transition rates set to zero (as listed above).
Any situation of transition through the incubation period can be examined in this manner, by considering the model equations (6.4a)-(6.4e) to represent the parent model encasing all other sub-models and possible paths through the HIV incubation period.

6.2 Summary

The Cardiff HIV/AIDS Epidemic Model implemented throughout this thesis has proven to be a flexible and invaluable tool, demonstrating the potential and adaptability of a deterministic compartmental transmission model. The versatility of the model has allowed: the introduction of stages within the incubation period of HIV; the splitting of time into periods relating to the introduction of treatments (i.e. Pre-treatment era 1979-1986; Early Treatment era 1987-1994; and Combination Treatment era 1995-2002); the value of parameters in the model to change subject to maximum likelihood estimation techniques, respecting separate time eras; the introduction of a new parameter signifying the effect of treatment on the length of the HIV incubation period; the modelling of future projections subject to varying 'what-if' scenarios; and the incorporation of even further developed treatments such as the introduction of a vaccine.

Summarising, the concept, objective and consequent result for each of the modifications named above imposed onto the basic Cardiff Model as seen in Figure 2.3, a staged incubation period where the stages are defined by an immunological marker, CD4 count, has provided a realistic interpretation of the incubation period as well as a reliable estimate for its variable length. The division of the total year span 1979-2002, subject to the introduction of treatments, has engaged a more realistic perspective on the changing HIV/AIDS epidemic over time and has subsequently permitted the incorporation of numerous linked MLE processes in the determination of altering parameter values, as illustrated in Figure 4.1. In particular, splitting time into periods has encouraged investigation into changing behaviours and attitudes as reflected within the re-estimation of the infectivity parameter, βc, from 1987 onwards. Also, in order to represent a longer survival time as a result of improving therapies and treatments, the parameter r was introduced which was evaluated in some detail for each time era, taking on a value of 1 in the Pre-treatment era and being re-estimated for both the Early treatment and Combination Treatment eras. Furthermore, this parameter is directly proportional to the length of the incubation period, and during its second transition, from the Early Treatment era to the Combination Treatment era, the value of the parameter r took on a multifaceted smoothing process to reflect the complex and continuous effect of new combination drug therapies on the incubation period and, consequently, the transition

rates between the HIV infective stages. Overall, the result has been highly successful, with an excellent fit between observed and expected AIDS incidence, HIV incidence and deaths from AIDS being created. Thus, a reliable, realistic and accurate model of the HIV/AIDS Epidemic has been formed and instigated to predict the path of the epidemic over future years, as explored in Chapter 4, highlighting concern for the escalating prevalence of HIV infection. Also, various what-if scenarios have been modelled using the Cardiff HIV/AIDS model; for instance, scenarios of changing future sexual behaviours or the introduction of a potential new preventive or therapeutic vaccine have been investigated, as detailed in Chapter 5.

In conclusion, the work presented within this thesis has achieved the initial objectives set i.e. an excellent fitting model of the HIV/AIDS epidemic has been created, allowing confidence in projecting short-term forecasts modelling various 'what-if' scenarios. An important finding drawn from the model extrapolations is the rapidly growing prevalence of HIV infections. This worrying observation needs to brought to the attention of government officials and relevant decision-makers in order for corrective initiatives to be implemented, thus reducing the currently unsustainable prevalence of HIV in the UK male homosexual population.

BIBLIOGRAPHY

Abdool Karim S S, Abdool Karim Q, Friedland G, Lalloo U and El Sadr WM on behalf of the START project (2004). Implementing antiretroviral therapy in resource-constrained settings: opportunities and challenges in integrating HIV and tuberculosis care. *AIDS* **18:** 975-979.

Abrams EJ, Kuhn L (2003). Should treatment be started among all HIV-infected children and then stopped? *Lancet* **362:** 1595-96; 15 November.

AIDS Knowledge Base (1999). *A Textbook on HIV Disease from the University of California, San Francisco and San Francisco General Hospital.* In: Cohen PT, Sande MA, Volberding PA (eds). Third Edition (HIV InSite Version). URL: http://hivinsite.uscf.edu/akb/1997/index.html

AIDSInfo (2005). *AIDSinfo – HIV/AIDS vaccines.* A service of the US Department of Health and Human Services. URL: aidsinfo.nih.gov/vaccines/ (Last Accessed 12th April 2005).

AIDS Weekly (2003). First UK National Database Measures Levels of HIV Drug Resistance. *AIDS Weekly* 11.17.03.

All-Party Parliamentary Group on AIDS (2003). *Migration and HIV: improving lives in Britain.* London: All-Party Parliamentary Group on AIDS, 2003.

Ancelle-Park RA (1992). European AIDS definition. *Lancet* **339:** 671.

Ancelle-Park RA (1993). Expanded European AIDS case definition. *Lancet* **341:** 441.

Anderson RM (1982). *The Population Dynamics of Infectious Diseases: Theory and Applications.* Chapman & Hall, London, UK.

Anderson R M (1988). The epidemiology of HIV infection: variable incubation plus infectious periods and heterogeneity in sexual activity. *Journal of Royal Statistical Society Series A* **151:** 66-98.

Anderson RM (1989). Editorial Review: Mathematical and statistical studies of the epidemiology of HIV. *AIDS* **3:** 333-346.

Anderson RM, Blythe SP, Gupta S, Konings E (1989). The transmission dynamics of the human immunodeficiency virus type 1 in the male homosexual community in the United Kingdom: the influence of changes in sexual behaviour. *Phil. Trans. Roy. Soc. Lond. B* **325:** 45-98.

Anderson RM, May RM (1992). Understanding the AIDS pandemic. *Scientific American* **266**(5): 20-26.

ATHENA cohort study group (2003). Mortality and Progression to AIDS after starting highly active antiretroviral therapy. *AIDS* **17:** 2227-2236.

AVERT (2005[a]). *UK HIV/AIDS FAQs: A.11.*
URL: www.avert.org (Last Accessed 7th April 2005).

AVERT (2005[b]). *Gay & Lesbian Information. How many Gay people are there? Numbers of Gay people.*
URL: www.avert.org/hsexul.htm (Last Accessed 15th April 2005).

AVERT (2005[c]). *Introduction to HIV/AIDS Treatment. The names of antiretroviral drugs.*
URL: www.avert.org/introtrt.htm (Last Accessed 3rd October 2005).

Bacchetti P, Segal MR, Jewell NP (1993). Backcalculation of HIV infection rates. *Statistical Science* **8:** 82-119.

Bailey NTJ (1964). Some Stochastic Models for small epidemics in large populations. *Applied Statistics* **13:** 9-19.

Bailey NTJ (Ed.) (1975). *The Mathematical Theory of Infectious Diseases and its Applications*. Charles Griffin & Company Ltd., London and High Wycombe.

Bailey NTJ (1991). The use of operational modelling of HIV/AIDS in a systems approach to public health decision making. *Mathematical Biosciences* **107:** 413-430.

Bailey NTJ (1992[a]). Operational modelling of HIV/AIDS to assist public health policy-making and control. In: Jager JC and Ruitenberg EJ (eds). *AIDS impact assessment: modelling and scenario analysis.* Amsterdam, Elsevier, pp 27-36.

Bailey NTJ (1992[b]). *Modelling HIV/AIDS for public health decision making using only public health data.* VIII International Conference on AIDS/III STD World Congress, Amsterdam July [PoC 4475].

Bailey NTJ (1992[c]). Parameter estimation in the operational modelling of HIV/AIDS. In: Mardia KV (ed). *Art of Statistical Science.* John Wiley & Sons Ltd, Ch. 19, pp 277-298.

Bailey NTJ (1993). An improved hybrid HIV/AIDS model geared to specific public health data and decision making. *Mathematical Biosciences* **117:** 221-237.

Bailey NTJ (1994[a]). HIV/AIDS: core group dynamics and public health action. In: Kaplan EH and Brandeau ML (eds). *Modelling the AIDS Epidemic: Planning, Policy and Prediction.* Raven Press Ltd., New York, pp 29-52.

Bailey NTJ (1994[b]). Estimating HIV incidence and AIDS projections: prediction and validation in the public health modelling of HIV/AIDS. *Statistics in Medicine* **13:** 1933-1943.

Bailey NTJ (1997). A revised assessment of the HIV/AIDS incubation period, assuming a very short early period of high infectivity and using only San Francisco public health data on prevalence and incidence. *Statistics in Medicine* **16:** 2447-2458.

Baragona S (2003). *UN Unveils New AIDS Strategy*. VOANews; Washington; 1 December.

Barouch D H, Letvin N L (2004). HIV escape from cytotoxic T lymphocytes: a potential hurdle for vaccines? Beth Israel Deaconess Medical Centre, Harvard Medical School. *Lancet* **364:** 10-11, 3 July.

Beck EJ, Kennelly J, McKevitt C, Whitaker L, Wadsworth J, Miller DL, Easmon C, Pinching AJ, Harris JR (1994[a]). Changing use of hospital services and costs at a London AIDS referral centre, 1983-1989. *AIDS* **8:** 367-377.

Beck EJ, Whitaker L, Kennelly J, McKevitt C, Wadsworth J, Miller DL, Easmon C, Pinching AJ, Harris JRW (1994[b]). Changing presentation and survival, service utilization and costs for AIDS patients: insights from a London referral centre. *AIDS* **8:** 379-384.

Beck EJ, Kupek EJ, Petrou S, Wadsworth J, Miller DL, Pinching AJ, Harris JAR, Academic Department of Public Health, St Mary's Hospital and Medical School, London, UK (1996). Survival and the use of and costs of hospital services for London AIDS patients treated with AZT. *Int J STD AIDS* **7:** 507-512.

Beck, EJ, Mandalia S (2003). The cost of HIV treatment and care in England since HAART – part 1. *Br J Sex Med* **27:** 19-23.

Beck EJ, Mandalia S, Williams I, Pwer A, Newson R, Molesworth A, Barlow D, Easterbrook P, Fisher M, Innes J, Kinghorn G, Mandel B, Pozniak A, Tang A, Tomlinson D for the National Prospective Monitoring System Steering Group (1999). Decreased morbidity and use of hospital services in English HIV-infected individuals with increased uptake of anti-retroviral therapy 1996-1997. *AIDS* **13:** 2157-2164.

Becker NG, Watson LF, Carlin JB (1991). A method of non-parametric back-projection and its application to AIDS data. *Statistics in Medicine* **10:** 1527-1542.

Beral V, Babiker A, Carne C, Darbyshire JH, Evans BG, Gill ON, Gilson RJC, Goldberg D, Hawkins DA, Jeffries D, Johnson AM, Johnson MA, McMichael AJ, Mortimer PP, Phillips AN, Porter K, Pozniak A, Weber J, Wellsteed S (1998). The AIDS incubation period in the UK estimated from a national register of HIV serconverters. *AIDS* **12:** 659-667.

Berkelman RL, Stroup DF, Buehler JW (1997). Public health surveillance. In: Detels R, Holland WW, McEwan J, Omenn GS (eds). *Oxford Textbook of Public Health, 3rd edition, volume 2.* Oxford University Press, 1997, pp 735-50.

BHIVA (1999*). British HIV Association (BHIVA) guidelines for the treatment of HIV-related adults with antiretroviral therapy: Issued December 1999.*
URL: www.aidsmap.com/bhiva/bhivagd1299.htm (Last Accessed 22nd June 2005).

Bindels PJE, Mulder-Folkerts DKF, Schutte MF, Smit-van Wijk I, Boer K, Coutinho RA (1996). Resultaten van de screening op HIV-antistoffen bij zwangere vrouwen in de Amsterdamse peilstations 1998-1995. *Ned Tijdschr Geneeskd* **140:** 2296-8.

Blythe SP, Anderson RM (1989[a]). Distributed incubation and infectious periods in models of the transmission dynamics of the human immunodeficiency virus (HIV). *IMA Journal of Mathematics Applied in Medicine & Biology* **5:** 1-19.

Blythe SP, Anderson RM (1989[b]). Variable infectiousness in HIV transmission models. *IMA Journal of Mathematics Applied in Medicine & Biology* **5:** 181-200.

Boom FMLG Van Den, Jager JC, Reinking DP, Postma MJ, Albers CES (1992). AIDS up to the year 2000. *Epidemiologocal, sociocultural and economical scenario analysis for the Netherlands*. Scenario report commissioned by the Steering Committee on Future Health Scenarios. Kluwer Academic Publishers. London.

Brailsford S, Shahani A (1994). Operational Models for the Natural History of HIV and AIDS. In: Dangerfield B, Roberts C (eds). *OR Work in HIV/AIDS – Second Edition.* ORS Publication Unit, UK, pp15-22.

Brookmeyer R (ed) (1989). Special issue on statistical and mathematical modelling of the AIDS epidemic. *Statistics in Medicine* **8**(1): 1-139.

Brookmeyer R (1991). Reconstruction and future trends of the AIDS epidemic in the United States. *Science* **253:** 37-42.

Brookmeyer R, Damiano A (1989). Statistical methods for short-term projections of AIDS incidence. *Stat. Med.* **8:** 23-34.

Brookmeyer R, Gail MH (1988). A method for obtaining short-term projections and lower bounds on the size of the AIDS epidemic. *J. Am. Statist. Assoc.* **83:** 301-8.

Brookmeyer R, Gail MH (1994). *AIDS epidemiology: A Quantitative Approach.* Oxford University Press Inc., New York.

Brookmeyer R, Liao J (1990[a]). The analysis of delays in disease reporting: methods and results for the Acquires Immune Deficiency Syndrome. *American Journal of Epidemiology* **132:** 355-365.

Brookmeyer R, Liao J (1990[b]). Statistical modelling of the AIDS epidemic for forecasting Health Care Needs. *Biometrics* **46:** 1151-1163.

Cane PA, Aitkin C, Ward K, Clarke J, Parmar S, Zuckerman M, Smith M, Tilston P, O'Shea S, Pillay D (2004). Pilot scheme for performance assessment of HIV-1 genotypic resistance testing in the UK. *Communicable Disease and Public Health* **Vol. 7: No. 1**, March.

Cantoni M, Cozzi Lepri A, Grossi P, Pezzotti P, Rezza G, Verdecchia A (1995). Use of AIDS surveillance data to describe subepidemic dynamics. *Int J Epidemiology* **24:** 804-12.

Carter M (2003). *HIV Prevalence increases by 20% in UK in one year.* Aidsmap, NEWS; 24 November.

CASCADE Collaboration (2003). Determinants of survival following HIV-1 seroconversion after the introduction of HAART. *Lancet* **362:** 1267-74, October 18.

Castillo-Chavez C. (Ed) (1989). *Mathematical and Statistical Approaches to AIDS Epidemiology.* Berlin, Springer-Verlag.

CD and PH (2002). Sexual Health and HIV positive individuals: emerging lessons from the recent outbreaks of infectious syphilis in England. Editorials. *Communicable Disease and Public Health* **Vol 5: No. 1**, March.

CDC (1981[a]). Pneumocystis Pneumonia – Los Angeles. *Morbidity and Mortality Weekly Report* **30**: 250-252, 5th June.

CDC (1981[b]). Kaposi's Sarcoma and Pneumocystis Pneumonia among homosexual men – New York City and California. *Morbidity and Mortality Weekly Report* **30:** 305-308, 4th July.

CDC (1987). Revision of the CDC Surveillance Case Definition of the Acquired Immunodeficiency Syndrome. *MMWR* **36:** Suppl. 1S; pp 1S-15S.

CDC (1992[a]). 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescent and adults. *Morbidity and Mortality Weekly Report* **41:** 1-18, (RR-17, 18 December).

CDC (1992[b]). AIDS case projection and estimates of HIV-infected immunosuppressed persons in the United States, 1992-1994. *MMWR* **No. RR-18:** 1-27.

CDC (1994). AIDS cases ever classified as risk not reported of identified. *HIV/AIDS Surveillance Report* **6** (1): 20.

CDC (1995). Update: HIV-2 infection among blood and plasma donors – United States, June 1992-June 1995. *MMWR* **44**(32): 603-6, Aug 18.

CDC (1997[a]). Report of the NIH panel to define principles of therapy of HIV infection and guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents.

CDC (1997[b]). Update: trends in AIDS incidence, deaths and prevalence – United States, 1996. *MMWR* **46:** 165-73.

CDC (1997[c]). 1997 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons with human immunodeficiency virus. *Morbidity and Mortality Weekly Report* **46:** (RR-12; 27 June).

CDC (1998). Public health service task force recommendations for the use of antiretroviral drugs in pregnant women infected with HIV-1 for maternal health and for reducing parinatal HIV-1 transmission in the United States. *Morbidity and Mortality Weekly Report* **47:** (RR-2, 30 January).

CDC (1999[a]). 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons with human immunodeficiency virus. *Morbidity and Mortality Weekly Report* **48:** (RR-10; 20 August).

CDC (1999[b]). HIV/AIDS Prevention Research Synthesis Project. Compendium of HIV Prevention Interventions with Evidence of Effectiveness. Atlanta, GA: *Centers for Disease Control and Prevention* 1-64.

CDC (2000). Adoption of protective behaviours among persons with recent HIV infection and diagnosis – Alabama, New Jersey, and Tennessee, 1997-1998. *Morbidity and Mortality Weekly Report* **49:** 512-515. MEDLINE.

CDC (2001). CDC-funded study to examine critical questions in HIV vaccine research. *CDC Update*, April 2001.

CDC (2002). *HIV/AIDS Surveillance Report.* Cases of HIV infection and AIDS in the United States, 2002. **Vol. 14.**

CDR (1990). Interim Proposed World Health Organisation Clinical Staging System for HIV infection and Disease. PHLS; *CDR* **90/36:** p4.

CDR (1993). Case definitions for AIDS – Europe and the United States part company. PHLS; *CDR* **3 No. 4:** p13.

CDR (1995). Sexually transmitted diseases quarterly report: sexually transmitted diseases in England and Wales acquired through sexual intercourse between men. *Communicable Disease Report* **5** (52, 29 December): 300-301.

CDR (1998). Sexually transmitted diseases quarterly report: sexually transmitted diseases in England and Wales acquired through sexual intercourse between men. *Communicable Disease Report* **8** (5, 30 January): 42-43.

CDR (1999[a]). AIDS and HIV infection in the United Kingdom: monthly report. *Communicable Disease Report* **9** (5, 19 Jan): 45-48.

CDR (1999[b]). AIDS and HIV infection in the United Kingdom: monthly report. *Communicable Disease Report* **9** (18, 30 April): 163-165.

CDSC (2000). *HIV and AIDS in the UK.* An epidemiological review: 2000.

CDSC (2002). *HIV and AIDS in the UK in 2001.* An update: November 2002.

Celentano DD, Nelson KE, Lyles CM, Beyrer C, Elumtrakul S, Go VFL, Kuntalbutra S, Khamboonruang C (1998). Decreasing incidence of HIV and sexually transmitted diseases in young Thai men: evidence for success of the HIV/AIDS control and prevention programme. *AIDS* **12:** F29-F36.

Chang-Heok Soh, James M Oleske, Michael T Brady, Stephen A Spector, William Borkowsky, Sandra K Burchett, Marc D Foca, Edward Handelsman, Eleanor Jiménez, Wayne M Dankner, Michael D Hughes, for the Pediatric AIDS Clinical Trials Group (2003). Long-term effects of protease-inhibitor-based combination therapy on CD4 T-cell recovery in HIV-1-infected children and adolescents. *Lancet* **362:** 2045-51, 20th/27th December.

Chin J (1991). Global estimates of HIV infections and AIDS cases: 1991. *AIDS* **5** (Suppl. 2): S57-S61.

Cleveland WS (1979). Robust locally weighted regression and smoothing scatterplots. *J. Am. Stat. Assoc.* **74:** 829-836.

Clewly JP (2004). Phylodynamics: a conjunction of epidemiology and evolution? *Communicable Disease and Public Health* **Vol. 7: No. 1**, March.

Cox DR, Medley GF (1989). A Process of events with notification delay and the forecasting of AIDS. *Phil Trans. R. Soc. London* **325:** 135-145.

Dabis F (2003). Children and HIV in Africa: what is next? *Lancet* **362:** 1597-8, 15 November.

Dangerfield BC (1999): System dynamics applications to European health care issues. *Journal of the Operational Research Society* **50:** 345-353.

Dangerfield BC, Roberts CA (1989). A Role for System Dynamics in Modelling the Spread of AIDS. *Trans. Inst. Msmt. And Crtl.* **11:** 187-195.

Dangerfield B and Roberts C (1994). Fitting a model of the spread of AIDS to data from five European countries. In: Dangerfield B and Roberts C (eds). *OR Work in HIV/AIDS – Second Edition.* ORS Publication Unit, UK, pp 7-14

Dangerfield B and Roberts C (1996). Relating a Transmission Model of AIDS Spread to Data: Some International Comparisons. In: Isham V and Medley G (eds). *Models for Infectious Human Diseases: Their Structure and Relation to Data.* Publications of the Newton Institute, pp 473-476.

Dangerfield BC, Fang Y, Roberts CA (2001). Model-based scenarios for the epidemiology of HIV/AIDS: the consequences of highly active antiretroviral therapy. *Syst. Dyn. Rev* **17**(2): 119-150.

Davidovich V, de Wit JBF, Stroebe W (2000). Assessing sexual risk behaviour of young gay men in primary relationships: the incorporation of negotiated safety and negotiated safety compliance. *AIDS* **14:** 701-706.

Day Report (1993). The incidence and prevalence of AIDS and other severe HIV disease in England and Wales for 1992-1997: Projections using data to the end of June 1992. *Communicable Disease Report* **3** (Supplement 1), June 1993.

Day Report (1996). The incidence and prevalence of AIDS and prevalence of other severe HIV disease in England and Wales for 1995 to 1999: Projections using data to the end of 1994. Report of a Working Group. *Communicable Disease Report* **6** (Review Number 1, 5 January).

De Angelis D, Day NE, Gore SM, Gilks WR, McGee MA (1993). AIDS: the statistical basis for public health. *Stat. Meth. Med. Res.* **2:** 75-91.

De Angelis D, Gilks WR, Day NE (1998). Bayesian Projection of the acquired immune deficiency syndrome epidemic. *Applied Statistics* **47:** 1-33.

Deeks SG (2003). Treatment of antiretroviral-drug-resistant HIV-1 infection. *Lancet* **362:** 2002-11, 13 December.

Delta Co-ordinating Committee (1996). Delta: a randomised double-blind trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals. *Lancet* **348:** 283-291.

DH (1996). *Unlinked anonymous HIV prevalence monitoring programme England and Wales.* London: DoH, 1996.

DH (2000). *Prevalence of HIV and hepatitis infections in the United Kingdom 2000.* Annual report of the Unlinked Anonymous Prevalence Monitoring Programme. Department of Health; December 2001.

DH (2001[a]). *Prevalence of HIV and hepatitis infections in the United Kingdom 2001.*

DH (2001[b]). *The National Strategy for Sexual Health and HIV.* Department of Health, 2001, p. 11.

DH (2002). *Prevalence of HIV and hepatitis infections in the United Kingdom 2001.* Annual report of the Unlinked Anonymous Prevalence Monitoring Programme. Department of Health; December.2002.

DH1 (2002). Population Table 1 Estimated resident population as at 30 June 2002: sex and single years of age; and Age, sex and marital status Table 6 Deaths and death rates per 1,000 population: age-group and sex, 2002. Mortality Statistics general. Review of the Registrar General on deaths in England and Wales, 2002. *Series DH1* **no. 35.**

Dietz K (1991). The Dietz approach: Modelling the demographic impact of the AIDS epidemic. In: *Proceedings of the United Nations/ World Health Organisation workshop on modelling the demographic impact of the AIDS epidemic in pattern II countries: Progress to date and policies for the future, New York 13-15 December 1989: The AIDS epidemic and its demographic consequences.* New York, United Nations/Geneva, World Health Organisation, pp105-108.

Donovan B, Ross MW (2000). Preventing HIV: determinants of sexual behaviour. *Lancet* **355:** 1897-1901.

Dougan S, Brown AE, Logan LE, Patel B, Munro HL, Evans BG, Gill ON (2004). Epidemiology of HIV in young people in England, Wales and Northern Ireland. *Communicable Disease and Public Health* **Vol. 7: No. 1,** March.

Downs AM, Ancelle RA, Jager JC, Heisterkamp SH et al. (1988). The statistical estimation, from routine surveillance data, of past present and future trends in AIDS incidence in Europe. In: Jager JC, Ruitenberg EJ (eds). *Statistical Analysis and Mathematical Modelling of AIDS.* Oxford: Oxford University Press; pp 1-16.

Downs A, Houweling H (1997). *Proceedings from a joint meeting of the Working Group Modelling Support and Working Group Epidemiological Impact.* EC Concerted Action Multinational Scenario Analysis Concerning Epidemiological, Social and Economic Impacts of HIV/AIDS on Society Held at the National Institute of Public Health and the Environment (RIVM), Bilthoven, The Netherlands (3-4 July).

Druten JAM Van, Reintjes AGM, Jager JC, Heisterkamp SH, Poos MJ, Coutinho RA, Dijkgraaf MG, Ruitenberg EJ, Department of Medicial Statistics (MSA), University of Nijmegen, The Netherlands (1990). HIV infection Dynamics and intervention experiments in linked risk groups. Statistics in Medicine 9: 721-736.

Dukers NHTM, Goudsmit J, de Wit JBF, Prins M, Weverling G, Coutinho RA (2001). Sexual risk behaviour relates to the virological and immunological improvements during highly active antiretroviral therapy in HIV-1 infection. *AIDS* **15:** 369-378.

Dunn DT, Newell ML, Ades AE, Peckham CS (1992). Risk of human immunodeficiency virus type 1 transmission through breast feeding. *Lancet* **340:** 585-588.

EDITORIAL (2004). HIV/AIDS: not one epidemic but many. *Lancet* **364:** 1-2, 3 July.

Elford J, Bolding G, Maguire M, Sherr L (1999). Sexual risk behaviour among gay men in a relationship. *AIDS* **13:** 1407-1411.

Elford J, Bolding G, Sherr L (2001). Seeking sex on the internet and sexual risk behaviour among gay men using London Gyms. *AIDS* **15:** 1409-1415.

Elford J, Bolding G, Sherr L (2002). High-risk sexual behaviour increases among London Gay men between 1998 and 2001: what is the role of HIV optimism? *AIDS* **16:** 1537-1544.

England TJ (1997). *Approximate Analytic Solutions to AIDS Equations*. PhD Dissertation, University of Wales, Cardiff.

Erens B, McManus S, Prescott A, Field J with Johnson A, Wellings K, Fenton K, Mercer C, MacDowell W, Copas A and Nanchahal K (2003). National Survey of Sexual Attitudes and Lifestyles II: Reference Tables and Summary Report. *National Centre for Social Research* 1904599028.

EuroHIV (2003). *HIV/AIDS Surveillance in Europe*. End-year Report 2003 **No. 70.** European Centre for the Epidemiological Monitoring of AIDS. WHO and UNAIDS Collaborating Centre on AIDS.

European Collaborative Study (1991). Children born to women with HIV-1 infection: natural history and risk of transmission. *Lancet* **337:** 253-260.

European Study Group (1992). Comparison of female to male and male to female transmission of HIV in 563 stable couples. *British Medical Journal* **304:** 809-813.

Evans BG, Catchpole MA, Heptonstall J, Mortimer JY, McGarrigle CA, Nicholl AG, Waight P, Gill ON, Swan AV (1993). Sexually transmitted diseases and HIV-1 infection among homosexual men in England and Wales. *BMJ* **306:** 426-8.

Evans BG, McCormick A (1994). Completeness of reporting cases of acquired immune deficiency syndrome by clinicians. *Journal of the Royal Statistical Society Series A-Statistics in Society* **157:** 105-114.

Fennema JSA, van Ameijden EJC, Henquet CJM, van Doornum GJJ, Coutinho RA, van den Hoek JAR (1995). HIV-surveillance op een polikliniek voor seksueel overdraagbare aandoeningen in Amsterdam, 1991-1994: lage en stabiele prevalentie onder heteroseksuele bezoekers. *Ned Tijdschr Geneeskd* **139:** 1595-8.

Fischl MA, Richmann DD, Grieco MH, Gottlieb MS, Volberding PA, Laskin OL, Leedom JM, Groopman JE, Mildvan D, Schooley RT, Jackson GG, Durack DT, King D (1987). The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS nad AIDS-related complex – a double-blind, placebo controlled trial. *New England Journal of Medicine* **317:** 185-191.

Friedland G (1989). Parenteral drug users. In: Kaslow RA, Francis DP (eds). *The Epidemiology of AIDS.* Oxford University Press, New York; pp 153-178.

Freidrich TC, Dodds EJ, Yant LJ, Vojnov L, Rudersdorf R, Cullen C, Evans DT, Desrosiers RC, Mothe BR, Sidney J, Sette A, Kunstman K, Wolinsky S, Piatak M, Lifson J, Hughes AL, Wilson N, O'Connor DH, Watkins DI (2004). Reversion of CTL escape-variant immunodeficiency viruses in vivo. *Nat Med* **10:** 275-81.

Fusaro RE, Jewell NP, Hauck WW, Heilbron C, Kalbfleisch JD, Neuhaus JM, Ashby MA (1989). An annotated bibliography of quantitative methodology relating to the AIDS epidemic. *Statistical Science* **4:** 264-281.

Gail MH, Brookmeyer R (1988). Methods for projecting course of Acquired immunodeficiency syndrome epidemic. *Journal of the National Cancer Institute* **80:** 900-911.

Gail MH, Rosenberg PS, Goerdert JJ (1990). Therapy may explain recent deficits in AIDS incidence. *Journal of Acquired Immune Deficiency Syndrome* **3:** 296-306.

Gail MH, Rosenberg PS (1992). Perspectives on using back-calculation to estimate HIV prevalence and project AIDS incidence. In: Jewell NP, Dietz K, Farewell VT (eds). *AIDS Epidemiology: Methodological Issues.* Birkhauser, Boston.

Gallo RC, Montagnier L (1988). AIDS in 1988. *Scientific American* **259** (4, October): 25-32.

Garfield S (1994). *The End of Innocence.* Faber and Faber Ltd., London.

Garnett GP (2002). An introduction to mathematical models in sexually transmitted disease epidemiology. *Sex Transm Inf* **78:** 7-12.

Garnett GP, Anderson RM (1996). Antiretroviral therapy and the transmission dynamics of HIV-1. *Journal of Antimicrobial Chemotherapy* **37** (Suppl. B): 135-150.

Gayle H, Lange JMA (2004). Seizing the opportunity to capitalize on the growing access to HIV treatment to expand HIV prevention. HIV, TB & Reproductive Health, Bill & Melinda Gates Foundation; Centre for Poverty-related Communicable Diseases and International Antiretroviral Therapy Evaluation Centre, University of Amsterdam. *Lancet* **364:** 6-8, 3 July.

Gazzard B, Johnson M (2003). Can we reduce the cost of treating HIV/AIDS in the UK? *Clinical Issues in HIV/AIDS* **12:** 3-6.

Glass TR, Young J, Vernazza PL, Rickenbach M, Weber R, Cavassini M, Hirschel B, Battegay M, Bucher HC, and Swiss HIV Cohort Study (2004). Is unsafe sexual behaviour increasing among HIV-infected individuals? *AIDS* **18**(12): 1707-1714, August 20th 2004.

Goedert JJ (1990). Prognostic markers for AIDS. *Annals of Epidemiology* **1:** 129-139.

Goldberg D (2002). Estimated HIV prevalence: vindication of the Department of Health's decision to make HIV an infectious disease priority. *Communicable Disease and Public Health* **5**(2): 90-1.

Goldberg DJ, Emslie JA, Smyth W, Reid D (1992). A system for surveillance of voluntary HIV testing: results of the first 2 years, 1989-1990. *AIDS* **6:** 495-500.

Grenfall BT, Pybus OG, Gog JR, Wood JLN, Daly JM, Mumford JA, Holmes EC (2004). Unifying the epidemiological and evolutionary dynamics of pathogens. *Science* **303:** 327-32.

Griffiths JD, Williams JE and Wheeler K (1990). Modelling the course of the AIDS epidemic. In: Dangerfield B and Roberts C (eds). *OR Work in HIV/AIDS - first edition.* ORS Publication Unit, UK.

Griffiths J and Williams J (1994). Charting the AIDS Epidemic in the UK. In: Dangerfield B and Roberts C (eds). *OR Work in HIV/AIDS – Second Edition.* ORS Publication Unit, UK, pp 3-6.

Griffiths JD, Williams JE (1995). *Contribution to meeting of Modelling Working Group.* EC Concerted Action Multinational Scenario Analysis, Paris (8^{th}-9^{th} June).

Griffiths J, Lowrie D, Williams J (2000). An age-structured model for the AIDS epidemic. *European Journal of Operational Research* **124:** 1-14.

Grmek MD (1990). *History of AIDS: emergence and origins of a modern pandemic.* Princeton University, Princeton, New Jersey, 1990.

Gulick RM, Mellors JW, Havlir D, Eron JJ, Gonzalez C, McMahon D, Richman DD, Valentine FT, Jonas L, Meibohm A, Emini EA, Chodakewitz JA (1997). Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. *N Engl J Med* **337:** 734-739.

Gupta R, Irwin A, Raviglione MC, Yong Kim J (2004). Scaling-up treatment for HIV/AIDS: lessons learned from the multidrug-resistant tuberculosis. *Lancet* **363:** 320-24, 24 January.

Gutierrez JP, Johns B, Adam T, Bertozzi SM, Tan-Torres Edejer T, Greener R, Hankins C, Evans DB (2004). Achieving the WHO/UNAIDS antiretroviral treatment 3 by 5 goal: what will it cost? *Lancet* **364:** 63-64, 3 July.

Halperin D T, Epstein H (2004). Concurrent sexual partnerships help to explain Africa's high HIV prevalence: implications for prevention. Office of HIV-AIDS, US Agency for International Development and Center for Health and Wellbeing. *Lancet* **364:** 4-5, 3 July.

Hamers FF, Downs AM (2004). The changing face of the HIV epidemic in Western Europe: what are the implications for public health policies? *Lancet* **364:** 83-94, 3 July.

Hammer SM, Squires KE, Hughes MD, Grimes JM, Demeter LM, Currier JS, Eron JJ Jr, Feinberg JE, Balfour HH Jr, Deyton LR, Chodakewitz JA, Fischl MA (1997). A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. *N Engl J Med* **337:** 725-733.

Harris JE (1987). Delay in Reporting Acquired Immune Deficiency Syndrome (AIDS). Working Paper **no. 2279**, *National Bureau of Economic research*, Cambridge, Mass.

Haverkos H, Battjes R (1992). Female-to-male transmission of HIV. *Journal of American Medical Association* **268:** 1885.

Heisterkamp SH, Haan BJ de, Jager JC, Druten JAM Van, Hendriks JCM (1992). Short and medium term projections of the AIDS/HIV epidemic by a dynamic model with an application to the risk-group of homo/bisexual men in Amsterdam. *Statistics in Medicine* **Vol. 11:** 1425-1441.

Heisterkamp SH, Jager JC, Downs AM, Ruitenberg EJ, Van Druten JAM (1989). Correcting reported AIDS incidence: a statistical approach. *Statistics in Medicine* **8:** 963-976.

Hendriks J (1999). *The Incubation Period of AIDS: Staged Disease Progression and Prevalent Cohort Studies.* Ponsen & Looijen, Wageningen.

Hendriks JCM, Medley GF, Van Griensven GJP, Coutinho RA, Heisterkamp SH, Van Druten HAM (1993). The treatment-free incubation period of AIDS in a cohort of homosexual men. *AIDS* **7:** 231-239.

Hendriks JCM, Satten GA, Lomgini IM, Van Druten HAM, Schellekens PTA, Coutinho RA, Van Griensven GJP (1996). Use of immunological markers and continuous-time markov models to estimate progression of HIV infection in homosexual men. *AIDS* **10**: 1-8.

Hethcote HW, Van Ark JW (1980). *Modelling HIV Transmission and AIDS in the United States.* Lecture Notes in Biomathematics, Springer-Verlag, Berlin, Heidelberg.

Hethcote HW, Ark JW Van, Karon JM (1991). A simulation model of AIDS in San Francisco: I Model formulation and parameter estimation. II Simulations, therapy and sensitivity analysis. *Mathematical Biosciences* **106:** 203-247.

Hillman RJ, Beck EJ, Mandalia S, Satterthwaite H, Rogers PA, Forster BE, Goh BT (1997). Survival and treatment of AIDS patients 1984-1993: experience of a smaller East London HIV centre. *Genitourinary Medicine* **73:** 44-48.

HIV Paediatric Prognostic Markers Collaborative Study Group (2003). Short-term risk of disease progression in HIV-1 infected children receiving no antiretroviral therapy or zidovudine monotherapy: a meta-analysis. *Lancet* **362:** 1605-11, 15 November.

Hooke R, Jeeves TA (1961). '"Direct Search" Solution of Numerical and Statistical Problems', *Journal of the Association for Computing Machinery*, April 1961.

House of Commons (2003). *Sexual Health: Third Report of Session 2002-03.* Treatment and Service Provision. The Stationery Office. The United Kingdom Parliament, House of Commons Health Committee, Sexual Health.

Houweling H (1997). *Public Health Surveillance of AIDS and HIV infection in the Netherlands and Europe.*

Houweling H, Coutinho RA (1997). Epidemiological and public health aspects of AIDS and HIV infection. *Oxford Textbook of Public Health, 3rd edition.* Oxford: Oxford University Press, 1997: 1261-1289 under the title 'Acquired immunodeficiency syndrome'.

HPA (2003). *Renewing the Focus. HIV and other Sexually Transmitted Infections in the United Kingdom in 2002.* An Update: November 2003.

HPA (2004). *HIV and other Sexually Transmitted Infections in the United Kingdom in 2003.* Annual Report, November 2004.

HPA (2005). *AIDS/HIV Quarterly Surveillance Tables.* Cumulative UK Data to End June 2005. **No. 67**: 05/2. July 2005.

Isham V (1988). Mathematical modelling of the transmission dynamics of HIV infection and AIDS: a review. *J. Roy. Statist. Soc. A* **151:** 5-30.

Isham V (1989). Estimation of the incidence of HIV infection. *Phil. Trans. Roy. Soc. Lond. B* **325:** 113-121.

Isham V, Medley G (eds.) (1996). *Models for Infectious Human Diseases: Their structure and Relation to Data.* Publications of the Newton Institute.

Jacquez JA, Simon CP, Koopman JS (1988). Modelling and analysing HIV transmission: The effect of contact patterns. *Math. Biosci.* **92:** 119-199.

Jacquez JA, Koopman JS, Simon CP, Longini IM (1994). Role of the primary infection in epidemics of HIV infection in gay cohorts. *Journal of Acquired Immune Deficiency Syndrome* **7:** 1169-1184.

Jager JC, Heisterkamp SH, Brookmeyer R (1993). AIDS surveillance and prediction of HIV and AIDS epidemic: methodological developments. *AIDS* **7** (Supplement 1): S67-S71.

Jager JC, Ruitenberg EJ (eds) (1992). *AIDS impact assessment: modelling and scenario analysis.* Amsterdam: Elsevier.

Janssen RS, Satten GA, Stramer SL, Rawal BD, O'Brien TR, Weiblen BJ, Hecht FM, Jack N, Cleghorn FR, Kahn JO, Chesney MA, Busch MP (1998). New testing strategy to detect early HIV-1 infection for use in incidence estimates and for clinical and prevention purposes. *JAMA* **280:** 42-48.

Johnson AM, Gill ON (1989). Evidence for recent changes in sexual behaviour in homosexual men in England and Wales. *Philosophical Transactions of the Royal Society of London Series B – Biological Sciences* **325:** 151-161.

Johnson M, Wadsworth J, Wellings K, Bradshaw S, Field J (1992). Sexual lifestyles and HIV risk. *Nature* **360:** 410-412.

Keet IPM, Veugelers PJ, Koot M, de Weerd MH, Roos MTL, Miedema F, de Wolf F, Goudsmit J, Coutinho RA (1996). Temporal trends of the natural history of HIV-1 infection following seroconversion between 1984 and 1993. *AIDS* **10:** 1601-1602.

Kegeles SM, Hays RB, Pollack LM, Coates TJ (1999). Mobilizing young gay and bisexual men for HIV prevention: a two-community study. *AIDS* **13:** 1753-1762.

Kelly JA, Hoffmann RG, Rompa D, Gray M (1998). Protease inhibitor combination therapies and perceptions of gay men regarding AIDS severity and the need to maintain safer sex. *AIDS* **12:** F91-F95.

Kendall MG, Stuart A (1973). *The Advanced Theory of Statistics. Third Edition, Vol. 2.* (Inference and Relationship). Griffin, London.

Kippax S, Crawford J, Davis M, Rodden P, Dowsett G (1993). Sustaining safe sex: a longitudinal study of a sample of homosexual men. *AIDS* **7:** 257-263.

Kippax S, Noble J, Prestage G, Crawford JM, Campbell D, Baxter D, Cooper D (1997). Sexual negotiation in the AIDS era: negotiated safety revisited. *AIDS* **11:** 191-197.

Kirschner D (1996). Using mathematics to understand HIV immune dynamics. *Notices of the AMS* **43:** 191-202.

Klaucke DN, Buehler JW, Thacker SB, Parrish RG, Trowbridge FL, Berkelman RL (1988). Guidelines for evaluating surveillance systems. *MMWR* **37** (Suppl S-5): 1-18.

Kleeberger C A, Buechner J, Palalla F, Detels R, Riddler S, Godfrey R and Jacobson L P (2004). Changes in adherence to highly active antiretroviral therapy medications in the Multicenter AIDS Cohort Study. *AIDS* **18:** 683-688.

Koopman JS, Longini IM, Jacquez J, Simon CP, Martin W, Woodcock D (1991). Assessing risk factors for HIV transmission. *Am. J. Epidemiol.* **133:** 1199-1209.

Krivine A, Firton G, Cao L, Francoual C, Henrion R, Lebon P (1992). HIV replicationduring the first weeks of life. *Lancet* **339:** 1187-1189.

Kumarasamy N (2004). Generic Antiretroviral drugs – will they be the answer to HIV in the developing world? YRG Centre for AIDS Research and Education, VHS. *Lancet* **364:** 3-4, 3 July.

Laga M, Diallo MO, Buvé A (1994). Inter-relationship of sexually transmitted diseases and HIV: where are we now? *AIDS* **8** (Suppl 1): S119.

Lalezari JP, Henry K, O'Hearn M, Montaner JSG, Piliero PJ, Trottier B, Walmsley S, Cohen C, Kuritzkes DR, Eron JJ, Chung J, DeMasi R, Donatacci L, Drobnes C, Delehanty J, Salgo M, for the TORO 1 Study Group (2003). Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. *N Engl J Med* **348:** 2175-85.

Langmuir AD (1963). The surveillance of communicable diseases of national importance. *N Engl J Med* **268:** 182-92.

Last JM (1983). *A Dictionary of Epidemiology.* New York/Oxford/Toronto: Oxford University Press, 1983.

Lazzerin A, Clotet B, Cooper D, Reynes J, Arasteh K, Nelson M, Katlama C, Stellbrink HJ, Delfraissy JF, Lange J, Huson L, DeMasi R, Wat C, Delehanty J, Drobnes C, Salgo M, for the TORO 2 Study Group (2003). Efficacy of Enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. *N Engl J Med* **348:** 2186-95.

Leaity S, Sherr L, Wells H, Evans A, Miller R, Johnson M, Elford J (2000). Repeat HIV testing: high-risk behaviour or risk reduction strategy? *AIDS* **14:** 547-552.

Lehner T, Biberfeld P, Boucher C, Darbyshire J, Fenyö EM, Heeney JL, Jager JC, Lundgren JD, Newell ML, Rösch P, Rossi P, Virelizier JL (1997). European contribution to the science, prevention and management of HIV infection. *Vaccine* **15:** 465-8.

Leslie AJ, Pfafferott KJ, Chetty P, Draenert R, Addo MM, Feeney M, Tang Y, Holmes EC, Allen T, Prado JG, Altfeld M, Brander C, Dixon C, Ramduth D, Jeena P, Thomas SA, John AS, Roach TA, Kupfer B, Luzzi G, Edwards A, Taylor G, Lyall H, Tudor-Williams G, Novelli V, Martinez-Picado J, Kiepiela P, Walker BD, Goulder PJ (2004). HIV evolution : CTL escape mutation and reversion after transmission. *Nat Med* **10:** 282-89.

Lewin SR, Crowe SM (1994). Aids pathogenesis. *AIDS* **8** (Suppl 2): S3.

Longini IM, Clark WS, Byers RH, Lemp GF, Ward JW, Darrow WW, Hethcote HW (1989[a]). Statistical analysis of the stages of HIV infection using a Markov model. *Stat. Med.* **8:** 831-843.

Longini IM, Clark WS, Haber M, Horsburgh R (1989[b]). The stages of HIV infection: Waitng times and infection transmission probabilities. In: *Mathematical and Statistical Approaches to AIDS Epidemiology.* Lecture Notes in Biomathematics, 83 C. Castillo-Chavez (ed.), Springer-Verlag, New York; 112-137.

Longini IM (1990). Modelling the decline of CD4+T-lymphocyte counts in HIV-infected individuals. *JAIDS* **9:** 930-931.

Longini IM, Clark WS, Gardner LI, Brundage JF (1991). The dynamics of CD4+ T-lymphocyte decline in HIV-infected individuals: A Markov modelling approach. *JAIDS* **4:** 1141-1147.

Longini IM, Byers RH, Hessol NA, Tan WY (1992). Estimating the stage-specific numbers of HIV infection using a Markov model and back-calculation. *Stat. Med.* **11:** 831-843.

Longini IM, Clark WS, Karon J (1993). The effect of routine use of therapy on the clinical course of HIV infection in a population-based cohort. *Am. J. Epidemiol.* **137:** 1229-1240.

Longini IM Jr, Clark WS, Satten GA, Byers RH and Karon JM (1996). Staged Markov Models Based on CD4+ T-Lymphocytes for the Natural History of HIV infection. In: Isham V and Medley G (eds). *Models for Infectious Human Diseases: Their Structure and Relation to Data.* Publications of the Newton Institute, pp 439-459.

Low-Beer D (2004). The alphabet of AIDS prevention. Book: Edward C Green (2003): Rethinking AIDS prevention: Learning from the Successes in Developing Countries. *Lancet* **364:** 19-20, 3 July.

Lowrie DL (2000). *An age dependant model for the AIDS epidemic.* PhD Thesis, Cardiff University.

McAnulty JM, Rubin GL, Rushworth RL, Kaldor J (1992). Under-reporting of AIDS in New South Wales. *Medical Journal of Australia* **156:** 452-455,

McCarthy M (2003). HIV prevention efforts reach fewer than one in five at risk. *Lancet* **361:** 1711.

McDonald AM, Gertig DM, Crofts N, Kaldor JM (1994). A national surveillance system of newly acquired HIV infection in Australia. *Am J Public Health* **84:** 1923-8

McGarrigle CA, Mercer CH, Fenton KA, Copas AJ, Wellings K, Erens B, Johnson AM (2005). Investigating the relationship between HIV testing and risk behaviour in Britain: National Survey of Sexual Attitudes and Lifestyles 2000. *AIDS* **19**(1): 77-84, Jan 3rd 2005.

McHenry A, Evans BG, Sinka K, Shaheem Z, Macdonald N, De Angelis D (2002). Numbers of adults with diagnosed HIV infection 1996-2005 – adjusted totals and extrapolations for England, Wales and Northern Ireland. *Communicable Disease and Public Health* **5**(2): 97-100.

McKie R (1986). *PANIC: The Story of AIDS.* Thorsons, New York.

Meda N, Ndoye I, M'Boup S, Wade A, Ndiaye S, Niang C, Sarr F, Diop I, Caraël M (1999). Low and stable HIV infection rates in Senegal: natural course of the epidemic or evidence for success of prevention? *AIDS* **13**: 1397-1405.

Microsoft Excel User's Guide (1993-1994). Version 5.0. Microsoft Corporation.

Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, d'Arminio Monforte A, Knysz B, Dietrich M, Phillips A N, Lundgren J D, for the EuroSIDA study group (2003). Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet* **362:** 22-29, 5 July.

Mofenson LM, Harris DR, Moye J, Bethel J, Korelitz J, Read JS, Nugent R, Meyer W for the NICHD IVIG Clinical Trial Study Group (2003). Alternatives to HIV-1 RNA concentration and CD4 count to predict mortality in HIV-1-infected children in resource-poor settings. *Lancet* **362:** 1625-27, 15 November.

Morris M, Kretzschmar M (1997). Concurrent Partnerships and the spread of HIV. *AIDS* **11:** 681-83.

Moyle G, Boffito M (2004). Unexpected drug interactions and adverse events with antiretroviral drugs. Chelsea and Westminster Hospital. *Lancet* **364:** 8-10, 3 July.

Mukherjee J (2004). Basing treatment on rights rather than ability to pay: 3 by 5. Partners in Health. *Lancet* **363:** 1071-72, 27 March.

Murphy G, Charlett A, Brown AE, Gill ON, Parry JV (2004). Is HIV incidence increasing in homo/bisexual men attending GUM clinics in England, Wales and Northern Ireland? *Communicable Disease and Public Health* **Vol. 7; No 1,** March.

Nelson K (2003). GSK and Boehringer agree to generic AIDS drugs deal. Medicine and Health Policy. *Lancet* **362:** 2074, 20th/27th December.

NIAID (2004). *Clinical Research on HIV Vaccines.* US Department of Health and Human Services. National Institutes of Health. National Inststutes of Allergy and Infectious Diseases. November 2004.

NIAID (2005[a]). *HIV Vaccine Research.* US Department of Health and Human Services. National Institutes of Health. National Inststutes of Allergy and Infectious Diseases. Division of AIDS. January 2005.

NIAID (2005[b]). *Challenges in Designing HIV Vaccines.* Research opportunities. US Department of Health and Human Services. National Institutes of Health. National Inststutes of Allergy and Infectious Diseases. March 2005.

NIH (2002). *Treatment of HIV Infection.* Office of Communications and Public Liaison, National Institute of Allergy and Infectious Diseases, National Institutes of Health; Fact Sheet; January.

Padian NS, Shiboski SC, Jewell NP, (1991). Female-to-male transmission of human immunodeficiency virus. *Journal of the American Medical Association* **266:** 1664-1667.

Palacio H, Li X, Wilson TE, Sacks H, Cohen MH, Richardson J, Young M, Muñoz A for the Women's Interagency HIV Study (WIHS) (2004). Healthcare use by varied highly active antiretroviral therapy (HAART) strata: HAART use, discontinuation, and naivety. *AIDS* **18:** 621-630.

Panos Institute (1992). *The hidden cost of AIDS. The challenge of HIV to Development.* Panos Publications Ltd., London.

Pasqualucci C, Rava L, Rossi C, Schinaia G (1998). Estimating the size of the HIV/AIDS epidemic: complementary use of the empirical bayesian back-calculation and the mover-stayer model for gathering the largest amount of information. *Simulation* **71:** 213-227.

Peters B, Whittal T, Babaahmady K, Gray K, Vayghan R, Lehner T (2004). Effect of heterosexual intercourse on mucosal alloimmunisation and resistance to HIV-1 infection. *Lancet* **363:** 518-24, 14 February.

PHLS (2002[a]). Press Release; 2 July. 33 500 people are living with HIV in the UK, and unsafe sex is increasing UNAIDS report published in advance of International AIDS Conference. Protecting the population from infection. Public Health Laboratory Service.

PHLS (2002[b]). *Sexual Health in Britain: Recent changes in high-risk sexual behaviours and the epidemiology of sexually transmitted infections including HIV.* HIV/STI Division. PHLS Communicable Disease Surveillance Centre. July 2002.

Porter K, Johnson AM, Phillips AN, Darbyshire JH (1999). The practical importance of potential biases in estimates of the AIDS incubation period distribution in the UK register of seroconverters. *AIDS* **13:** 1943-1951.

Power L (2004). HIV and sexual health in the UK: politics and public health. *Lancet* **364:** 108-109, 3 July.

Pugh RN, Laverty S, Simms I, Morrall IA, Chandramani S, Joseph AT, Elsmore M, Morris C (2004). Syphilis clusters in Walsall: case profiles and public health implications. *Communicable Disease and Public Health* **Vol. 7; No 1,** March.

Rauner MS, Brandeau ML (2000). AIDS Policy Modeling for the 21st Century: An Overview of Key Issues. *Health Care Management Science* **4:** 165-180.

Redfield RR, Wright D, Tramont E (1986). The Walter Reed staging system classification for HTLV-III/LAV infection. *New Eng. J, Med.* **314:** 131-132.

Report of a Working Group (Chairman, Sir David Cox) (1988). *Short-term Prediction of HIV Infection and AIDS in England and Wales.* HMSO, UK.

Rietmeijer CA (2003). The max for the minimum: brief behavioural interventions can have important HIV prevention benefits. *AIDS* **Vol. 17; No. 10:** 1561-1562.

Riley VC (1991). Resurgent gonorrhoea in homosexual men. *Lancet* **337:** 183.

Roberts CA and Dangerfield BC (1990[a]). Modelling the Epidemiological consequences of HIV infection and AIDS: a contribution from operational research. *J. Opl. Res. Soc.* **41:** 273-289.

Roberts C and Dangerfield B (1990[b]). A system dynamics modelling framework for understanding the epidemiology of HIV/AIDS. In: Dangerfield B and Roberts C (eds). *OR Work in HIV/AIDS - first edition.* ORS Publication Unit, UK.

Rogers PA, Whitmore-Overton SE, Evans BG, Allardice GM, Noone A (1997). Survival of adults with AIDS in the United Kingdom. *Communicable Disease Report* **7** (Review No. 7, 27 June): R93-100.

Rosenberg PS (1990). A simple correction of AIDS surveillance data for reporting delays. *J Acq Immune Defic Synd* **3:** 49-54.

Rosenberg PS, Levy ME, Brundage JF, Petersen LR, Karon JM, Fears TR, Gardner LI, Gail MH, Goerdert JJ, Blattner WA, Ryan CC, Vermund SH, Biggar RJ (1992). Population-based monitoring of an urban HIV/AIDS epidemic: magnitude and trends in the district of Columbia. *JAMA* **268:** 495-503.

Rossi C, Schinaia G (1998). The mover-stayer model for the HIV/AIDS epidemic in action. *Interfaces* **28:** 127-143.

Sabin CA (2002). The changing clinical epidemiology of AIDS in the highly active antiretroviral era. *AIDS* **16** (Suppl. 4): S61-S68.

Sabin CA, Lee CA, Phillips AN (1994). The use of back-calculation to estimate the prevalence of severe immunodeficiency induced by the human immunodeficiency virus in England and Wales. *Journal of the Royal Statistical Society Series A – Statistics in Society* **157:** 41-56.

Satten GA, Longini IM (1994). Estimation of incidence of HIV infection using cross-sectional marker surveys. *Biometrics* **50:** 675-688.

Satten GA, Longini IM (1996). Markov chains with measurement error: estimating the 'true'course of a marker of the progression of human immunodeficiency disease. *Applied Statistics* **45:** 275-309.

Schmid GP, Buvé A, Mugyenyi P, Garnett GP, Hayes RJ, Williams BG, Calleja JG, De Cock KM, Whitworth JA, Kapiga SH, Ghys PD, Hankins C, Zaba B, Heimer R, Boerma JT (2004). Transmission of HIV-1 infection in sub-Saharan Africa and effect of elimination of unsafe injections. *Lancet* **363:** 482-88, 7 February.

Schwarcz S, Kellogg T, McFarland W, Louie B, Kohn R, Busch M, Katz M, Bolan G, Klausner J, Weinstock H (2001). Differences in the temporal trends of HIV seroincidence and seroprevalence among sexually transmitted disease clinic patients, 1989-1998: application of the serological testing algorithm for recent HIV seroconversion. *Am J Epidemiol* **153**(10): 925-34, 15 May.

Smith D E, Walker B D, Cooper D A, Rosenburg E S and Kaldor J M (2004). Is antiretroviral treatment of primary HIV infection clinically justified on the basis of current evidence? *AIDS* **18:** 709-718.

Smith E, Rix BA, Melbye M (1994). Mandatory anonymous HIV surveillance in Denmark: the results of a new system. *Am J Public Health* **84:** 1929-32.

Snary EL (2000). *Modelling Treatment Effects in the HIV/AIDS Epidemic.* PhD Thesis, University of Wales, Cardiff.

Solomon PJ (1996). AIDS: Modelling and Predicting. In: Isham V, Medley G (eds). *Models for Infectious Human Diseases: Their structure and Relation to Data.* Publications of the Newton Institute, pp 407-438.

Solomon PJ, Wilson SR (1990). Accommodating change due to treatment in the method of back projection for estimating HIV infection incidence. *Biometrics* **46:** 1165-1170.

Solomon PJ, Wilson SR, Swanson CE, Cooper DA (1990). Predicting the course of AIDS in Australia. *Med. J. Austral.* **153:** 386-394.

Solomon PJ, Wilson SR (1993). Prediction of new cases of disease or infection for small subgroups. *Biometr. J* **35:** 333-341.

Spielberg F, Levine RO, Weaver M (2004). Self-testing for HIV: a new option for HIV prevention? *The Lancet Infectious Diseases* **4:** 640-646.

Stolte IG, de Wit JBF, van Eeden A, Coutinho RA, Dukers NHTM (2004). Perceived viral load, but not actual HIV-1-RNA load, is associated with sexual risk behaviour among HIV-infected homosexual men. *AIDS* **18**(14): 1943-1949, Sept 24 2004.

Tavanyar J (1992). *The Terrence Higgins Trust HIV/AIDS book.* Thorsons, London.

Taylor JMG (1989). Models for the HIV infection and AIDS epidemic in the United States. *Stat. Med.* **8:** 45-58.

Thacker SB, Berkelman RL (1988). Public health surveillance in the US. *Epidemiological Reviews* **10:** 164-90.

The Antiretroviral Therapy (ART) Cohort Collaboration (2003). Prognostic importance of initial response in HIV-1 infected patients starting potent antiretroviral therapy: analysis of prospective studies. *Lancet* **362:** 679-86, 30 August.

The EXPORE Study Team (2004). Effects of a behavioural intervention to reduce acquisition of HIV infection among men who have sex with men: the EXPLORE randomized controlled study. *Lancet* **364:** 41-50, 3 July.

The PLATO Collaboration (2004). Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral drug classes. *Lancet* **364:** 51-62, 3 July.

Tindall B, Barker S, Donovan B, Barnes T, Roberts J, Kronenberg C, Gold J, Penny R, Cooper D (1988). Characterization of the acute clinical illness associated with human immunodeficiency virus infection. *Archives of Internal Medicine* **148:** 945-49.

UNAIDS (2002). *The Barcelona Report: Report on the Global HIV/AIDS Epidemic.*

UNAIDS and WHO (2002). *AIDS epidemic update. December 2001.*

Van de Ven P, Kippax S, Knox S, Prestage G, Crawford J (1999). HIV treatments optimism and sexual behaviour among gay men in Sydney and Melbourne. *AIDS* **13:** 2289-2294.

Van Duynhoven YTPH, Houweling H, Wiessing LG, Esveld MI, Nieste HLJ, Katchaki JN (1996). Laboratory based HIV surveillance with information on exposure: importance of discriminating person-based from test-based results. *Int J STD AIDS* **7:** 117-22.

Van Sighem AI, Van de Wiel MA, Ghani AC, Jambroes M, Reiss P, Gyssens IC, Brinkman K, Lange JMA and de Wolf F, on behalf of the ATHENA cohort study group (2003). Mortality and Progression to AIDS after starting highly active antiretroviral therapy. *AIDS* **17:** 2227-2236.

Verdecchia A, Mariotto A, Capocaccia R, Mariotti S (1992). *Age, period and cohort model to estimate prevalence and incidence of HIV infection.* VIII International Conference on AIDS/ III STD World Congress, Amsterdam [WeC 1091].

Waight PA, Rush AM, Miller E (1992). Surveillance of HIV infection by voluntary testing in England. *CDR Review* **2:** R85-R90.

Waldo CR, Stall RD, Coates TJ (2000). Is offering post-exposure prevention for sexual exposures to HIV related to sexual risk behaviour in gay men? *AIDS* **14:** 1035-1039.

Wasserheit JN (1992). The inter-relationship between STD and HIV. *Sexually Transmitted Diseases* **19:** 61.

Waugh MA (1991). Resurgent gonorrhoea in homosexual men. *Lancet* **337:** 375.

Weinhardt LS, Carey MP, Johnson BT, Bickham NL (1999). Effects of HIV counseling and testing on sexual risk behaviour: a meta-analytic review of published research, 1985-1997. *Am J Public Health* **89:** 1397-1405. MEDLINE.

Wellings K, Field J, Johnson AM, Wadsworth J (1994). *National Survey of Sexual Attitudes and Lifestyles I.* Penguin, 1994, 0140158146.

Wheeler K (1990). *Modelling the Spread of the AIDS Epidemic.* PhD Thesis, University of Wales, College of Cardiff (UWCC).

Whithers CS (1989). *Aids: References on modelling – with comments. Update.* Wellington: Applied Mathematics Division; September 22.

Wiessing LG, Houweling H, Spruit IP, Korf DJ, van Duynhoven YTHP, Fennema JSA, Borgdorff M (1996). HIV among drug users in regional towns near the initial focus of the Dutch epidemic. *AIDS* **10:** 1448-9.

Williams JR, Anderson RM (1994). Mathematical models of the transmission dynamics of human immunodeficiency virus in England and Wales: mixing between different risk groups. *Journal of the Royal Statistical Society Series A – Statistics in Society* **157:** 69-87.

Winklestein W, Wiley J, Padian N, et al (1988). The San Francisco men's health study: continued decline in HIV seroconversion rates among homosexual/bisexual men. *American Journal of Public Health* **78:** 1472-1474.

Youle M (2001). Salvage treatment in HIV disease. *Int J STD AIDS* **12:** 286-293.

Zeger SL, See L-C, Diggle PJ (1989). Statistical methods for monitoring the AIDS epidemic. *Stat. Med.* **8:** 3-21.