Title The Mathematical Modelling of the Transmission Dynamics of HIV/AIDS and the Impact of Antiviral the Therapies

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The Mathematical Modelling of the Transmission Dynamics of HIV/AIDS and the Impact of the Antiviral Therapies

by

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To: My parents

Author's Declaration

I declare that this thesis is my own unaided work. It is being submitted for the degree of Doctor of Philosophy at the University of Luton. It has not been submitted before for any degree or examination at any other University.

Signature

Date

Abstract

This thesis is concerned with the structure, analysis and numerical solution of the mathematical models used to estimate the transmission dynamics of the Human Immunodeficiency Virus (HIV), the causative agent of Acquired Immune Deficiency Syndrome (AIDS).

Investigations show that the devised deterministic mathematical models in term of system of first-order non-linear ordinary differential equations (ODEs) follow the stochastic nature of the problem at any time. In this thesis a generic form of the deterministic mathematical models is introduced which mirrors the transmission dynamics of HIV/AIDS in populations with different states of affairs, which leads to the division of large-scale and complex mathematical models.

When analysing and/or solving a large-scale system of ODEs numerically, the key element in speeding up the process is selecting the maximum possible time step. This work introduces some new techniques used to estimate the maximum possible time step, avoiding the appearance of chaos and divergence in the solution when they are not features of the system.

The solution to these mathematical models are presented graphically and numerically, aiming to identify the effect of the anti-HIV therapies and sex education in controlling the disease. The numerical results presented in this thesis indicate that lowering the average number of sexual partners per year is more effective in controlling the disease than the current anti-HIV treatments.

For the purpose of this study the mathematical software *'Mathematica 3.0'* was used to solve the system of differential equations, modelling HIV/AIDS propagation. This package also provided the graphical detail incorporated in the thesis.

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Acquired Immune Deficiency Syndrome (AIDS) caused by *Human Immunodeficiency Virus* (HIV) emerged in the early 1980's in several widely separated locations, from the United States of America to Zaire, and Zambia. The first medical reports, relating to a cluster among homosexual men in the United States, appeared in 1981. Since then a world-wide attempt has been made to tackle this life-threatening virus.

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ematics and on the mathematician's part, the lack of knowledge of the underlying medical problem. It can take years to come to terms with all the medical jargon, especially in a continually evolving area. This can be overcome through serious cross-training of interdisciplinary scientists whose goal will be doing good science, which in turn would advance knowledge in both disciplines.

The next section is concerned with the immunology of the human body.

1.1 The human immune system

When a foreign substance (antigen) is introduced into the body, the body elicits an immune response in an attempt to clear the object from the body as quickly as possible. This response is characterised in two ways: a *cellular immune response* and a *humoral immune response*. The antigen is first encountered by the *macrophages*, cells that scavenge, engulf, and examine foreign particles, then presenting their findings to the CD4 positive T lymphocytes ($CD4^+$ T cells). The 'CD4' denotes a protein marker in the surface of T cells and the T refers to *thymus*, the organ responsible for maturing these cells after they migrate the bone marrow (where they are manufactured). These cells, more commonly referred to as *helper T cells* (which normally average 1000 per cubic mm of blood), serve as the command centre for the immune system. If they deem an immune response is necessary, a *primary immune response* is issued. First, the helper T cells reproduce to build up command forces, which can then elicit both cellular and humoral response. In addition to this build up, the cellular immune response also activates a second type of T cell, the CD8 positive T lymphocytes ($CD8^+$ T cells). Referred to as the *killer T cell*, once given a target, they seek out and destroy

cells infected with those pathogens.

In the humoral immune response (more commonly known as the antibody response) the helper T cell signal a third set of cells which produce the chemical weapons called *antibodies*. Antibodies are specifically engineered to destroy the pathogen at hand and therefore act as direct antigen killing devices. Figure 1.1.1 shows a schematic diagram of the entire immune response process.

Once the immune response is successful, certain cells of each type retain knowledge of the attack. These cells are referred to as memory cells. If the same pathogen (or a close cousin) is introduced into the body again, a much quicker and more aggressive campaign can be launched. and antigen is eradicated more accurately at a much faster rate. This is the idea behind vaccines. A small, weaker version of the pathogen is introduced, eliciting a primary immune response; then, if the individual become infected with the more aggressive relative, the response is immediate and powerful, and the pathogen does not take hold. (See [83] and [100] for full discussion of immunology).

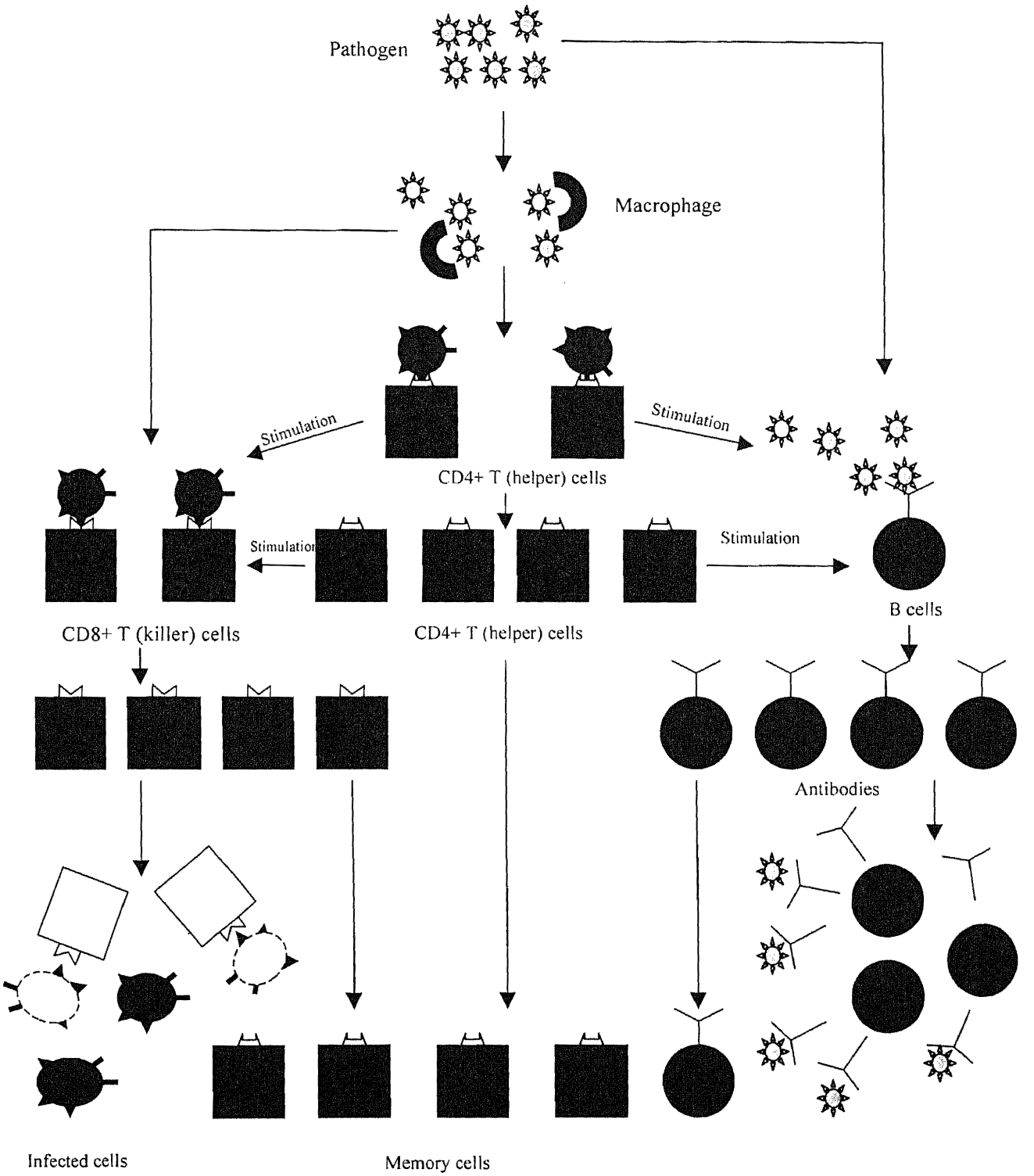

Figure 1.1.1: *Schematic diagram of the working human immune system. Pathogen stimulated immune activation by increasing the numbers of CD4 and CD8 T-cells and B cells that leads to pathogen clearance.*

1.1.1 HIV infection

Like most viruses, HIV is a very simple creature. Viruses do not have the ability to reproduce independently. Therefore, they most rely on a host to aid reproduction. Most viruses carry copies of their DNA (the blueprint of itself) and insert this into the host cell's DNA. Then, when the host cell is stimulated to reproduce (often through the presence of the same pathogen), it produces copies of the virus.

When HIV infects the body, its target is $CD4^+$ T cells. Since $CD4^+$ T cells play the key role in the immune response, this is the cause for alarm and a key reason for HIV's devastating impact. A protein (GP120) on the surface of the virus has a high affinity for the CD4 protein on the surface of the T cell. Binding takes place, and the content of HIV is injected into the host T cell. HIV differs from most viruses in that it is a retrovirus.: it carries a copy of its RNA (a precursor to the blueprint DNA) which must first be transcribed into DNA (using an enzyme it also carries called reverse transcripts). One of the mysteries to the medical community is why this class of virus has evolved to include this extra step.

After the DNA of the virus has been duplicated by the host cell, it is reassembled and new virus particles bud from the surface of the host cell. This budding can take place slowly, sparing the host cell; or rapidly, bursting and killing the host cell.

The course of the infection with HIV is not clear-cut. Clinicians are still arguing about what causes the eventual collapse of the immune system, resulting in death. What is widely agreed upon, however, is that there are four main stages of disease progression. First is the initial innoculum, when the virus is introduced into the body. Second is the initial transient, a relatively

short period of time when both the T cell population and virus population are in great flux. This is followed by the third stage, clinical latency, a period of time when there are extremely large numbers of virus and T cells undergoing incredible dynamics, the overall result of which is an appearance of latency (disease steady state). Finally, there is AIDS this is characterised by the T cell dropping to very low numbers (or even zero)and the virus growing without bound, resulting in death. The transitions between these four stages are not well understood, and presently there is controversy concerning whether the virus directly kills all of the T cells in this final stage or if there is some other mechanism(s) at work (see [74] and [67] for complete overview of HIV infection).

1.1.2 Treatment of HIV infection

Clearly, there is a necessity for treatment of HIV infection. To this end, there are several drugs now used: AZT (Zidovudine) was approved for treatment of HIV infection in 1987, three other drugs, DDC, DDI, and D4T have since been approved. Also different combinations of theses drugs have been administered. These drugs all work as inhibitors transcriptase. The role of these transcriptase inhibitors is to interfere with the transcription of the RNA to DNA, thus halting cellular infection and hence viral spread. Unfortunately, these drugs are not cures for the infection, but serve only as a maintenance program to temporarily prevent further progress of the virus. Despite this drawback, there is much clinical evidence to support the use of these chemotherapies in HIV infected individuals. Aside from the possibility of prolonging the life in an HIV positive individual, it may make them less infectious to their sexual partners as well as reduce rates of mother-to-foetus transmission, (see [4]). Controversy exists among clinicians, however, as to

who should be treated, when they should be treated and what treatment scheme should be used.

There is much more data available on AZT treatment (see [78]). In addition many laboratories and clinics keep close accounts of patient treatment courses. These provide conflicting evidence as to which is better: early treatment (defined as $CD4^+$ T cell counts between 200-500mm^{-3}) Other questions regarding chemotherapy are whether the dosage should be small or large, what should be the duration of treatment, and what periodicity of dose should be used i.e. should the drug be administered every 4 hours, 8 hours, etc.. All these questions could be addressed through the use of mathematical models.

1.2 The Origin of the AIDS virus

The AIDS virus has relatives in man as well as other primates. Studies of related viruses (C. A. Struthers *et al.*, [103]) indicate that some have evolved disease-free in coexistence with their animal hosts.

The sudden appearance and rapid spread of a previously unknown infectious disease such as AIDS raises a series of compelling questions.

i) What is the causative agent?

ii) What is its structure and how does it function?

iii) How and from where did it start?

vi) What is the future of the disease?

My work has addressed the fourth problem, that of the mathematical modelling of the transmission dynamics of HIV/AIDS. Understanding the

spread of the virus may reveal ways to control the AIDS virus and its disease. For the modelling purpose knowledge of the AIDS virus is also important. The aim of this section is to learn more about HIV and viruses related to it, and also understand how HIV has evolved the unique and deadly properties that lead to AIDS.

One way to begin searching out the origin of HIV is to look for similar viruses in non human primates. Monkeys and apes are often the only animal species other than the human that are infected with important human viruses such as *Yellow fever* and *Marburgh.*

In certain cases it is even thought that wild monkeys harbour the pathogens and can be the source of human infections. In February 2000, a sum of 225 Macaques monkeys were killed in Woburn Safari park in Bedfordshire, England, in fear of carrying the virus causing AIDS. The search for primate viruses related to HIV had a precedent in the discovery of a primate counterpart of another human retrovirus.

The first retroviruses to infect human were discovered in 1980 by Robert C. Gallo [49] of the National Cancer Institute. They were two Human T-Lymphographic Viruses: HTLV-1 (the cause of a rare form of T-cell Leukaemia in people) and a very closely related HTLV-II.

Two years later Isao Miyoshi [82], of Kochi University described a related virus in a monkey, the Macaque. The virus was remarkably similar to HTLV's and was designated the Simian T-Lymphographic Virus, STLV. In 1988 M. Essex and P. J. Kanki [45], in the New England Regional primate Research Centre showed that monkeys with malignant lymphoma (a cancer of lymphoid cells) had much higher rates of STLV infection than healthy Macaque. It appeared that STLV was capable of inducing a lymphoid cancer in monkeys

similar to how HTLV induced lymphoid cancer in people.

The biological and biophysical properties of the SIV proteins are very similar to those of the HIV proteins (see M. Essex, P. J. Kanki [45]). Like human infected with HIV, Asian Macaques with SIV suffered a decrease in T-4lymphocytes with ensuring immunosuppression; the animal died of opportunistic infections very similar to those seen in human AIDS.

The monkey virus could have been transmitted to the Macaques from another monkey species housed in the same facility or even by experimental manipulation. However, seroepidemiological studies of wild captive Asian monkeys including Macaques failed to find evidence of SIV or HIV like agent (see M. Essex, P. J. Kanki [45]). Studies by many investigators confirmed that SIV infection in the Asian Macaques was limited to small number of monkeys in captivity, where it was highly associated with SAIDS. The data suggested that SIV did not naturally infect Asian monkeys in the wild. It seemed quite possible that the primate-centre Macaques had been exposed to SIV in captivity. If the Asian Macaque monkey was not the natural host for SIV, then, what was? And how (if at all) were the primate viruses related to the observed emergence of HIV in people?

In 1985, the highest rates of HIV were reported in the US and Europe, but disturbing reports from central Africa indicated the highest rates of HIV infection and AIDS prevailed there, at least in some urban centres. The reported rates of infection were so high that many workers thought the AIDS epidemic in central Africa might have predated the emergence of the disease elsewhere in the world.

On the assumption that the distribution of HIV in human population might be correlated with the distribution of the related viruses in monkeys,

it seems to be important to determine whether HIV related viruses were present in primate species in Africa.

In 1998, M. Essex and P. J. Kanki [45], obtained blood samples from representative African primates, including wild-caught chimpanżees, African green monkeys, baboons and monkeys. They found no evidence of SIV infection in chimpanzees, baboons and monkeys but more than 50 percent of the wild African green monkeys did show evidence of an SIV infection.

From 30 to 70 percent of African green monkeys caught in various regions of sub-Sahara Africa and from many other in house research facilities throughout the world found to be SIV infected. Yet they show no sign of immunosuppression or of SAIDS.

Moreover, in spite of their having the highest rates of SIV infection, the various green monkeys subspecies are among the most ecologically successful African primates, suggesting that the high infection rate in these monkeys has not been exerting long-term adverse selection pressure on the species.

Why SIV is endemic in these wild African monkeys but seems to do no harm, but also found in captive Asian Macaques where it causes disease, was and still is an enigma. It seems quite possible that captive Asian monkeys might have been infected when they where accidentally exposed to African monkeys in holding facilities.

1.3 WHO's report on AIDS in the 21^{st} century

As the 20^{th} century drew to a close, some 33.6 million men, women and children face a future dominated by a fatal disease unknown just a few decades ago. The Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organisation (WHO), reported 32.4 million adults and 1.2 million children living with HIV at the end of 1999.

Over the course of 1999, some 5.6 million people became infected with the human immunodeficiency virus (HIV), which causes AIDS.

1999 also saw 2.6 million deaths from HIV/AIDS (a higher global total than in any year since the beginning of the epidemic), despite antiretroviral therapy which staved off AIDS and AIDS deaths in the richer countries. Deaths among those already infected will continue mounting for some years even if prevention programmes managed to cut the number of new infections to zero. However, with the HIV-positive population still expanding (there were 5.6 million new infections in the year 1999 alone) the annual number of AIDS deaths can be expected to increase for many years before peaking.

Around half of all people who acquire HIV become infected before they turn 25 and typically die of the life-threatening AIDS related illnesses before their 35^{th} birthday. This age factor makes AIDS uniquely threatening to children. By the end of 1999, the epidemic had left behind a cumulative total of 11.2 million AIDS orphans, defined as those having lost their mother before reaching the age of 15. Many of these maternal orphans have also lost their father.

The overwhelming majority of people with HIV (some 95% of the global

total) live in the developing world. That proportion is set to grow even further as infection rates continue to rise in countries where poverty, poor health systems and limited resources for prevention and care fuel the spread of the virus.

HIV is still a challenge in industrialised countries. There is evidence that safe sexual behaviour is being eroded among gay men in some Western countries, perhaps because of complacency now that life-prolonging therapy is available. If this is the case, the complacency is misplaced. The disease remains fatal, and information from North America and Europe suggests that the decline in number of deaths due to antiretroviral therapy is tapering off.

HIV infections in the former Soviet Union have doubled in just two years. Injecting drugs use gave the Eastern European and Central Asian region the world's steepest HIV curve in 1999. Drug-injecting is also a major concern in the industrialised countries, as it is in the Middle East, where total AIDS cases are still relatively low but drug-injecting accounted for two-thirds of cases in Bahrain, half in the Islamic Republic of Iran and over a third in Tunisia.

Some Latin American countries are managing to expand efforts to provide treatment to those infected. However, there is evidence that infections are on the rise in Central America and in the Caribbean basin, which has some of the worst HIV epidemics outside Africa.

Strong prevention programmes seem to have reduced HIV risk and lowered or stabilised HIV rates in some countries of Asia, such as Thailand and the Philippines. Other Asian countries have raised warning flags after collecting new information showing that injecting drug use is spreading and that condom use is uncommon, including among clients of prostitutes and men who

have sex with men. In many places prevention efforts are hampered by the shame and stigma attached to AIDS.

Sub-Sahara Africa continues to bear the brunt of HIV and AIDS, with close to 70% of the global total of HIV-positive people. Most will die in the next 10 years, joining the 13.7 million Africans already claimed by the epidemic and leaving behind shattered families and crippled prospects for development.

Because of AIDS, companies doing business in Africa are hurting and are bracing themselves for far worse as their workers sicken and die. According to a survey of commercial farms in Kenya, illness and death have already replaced old-age retirement as the leading reason why employees leave service. Retirement accounted for just 2% of employee drop-out by 1997.

Life expectancy at birth in southern Africa, which rose from 44 years in the early 1950s to 59 in the early 1990s, is set to drop to just 45 between 2005 and 2010 because of AIDS. In contrast, South Asians, who could barely reach their 40th birthday in 1950, can expect by 2005 to be living 22 years longer than their counterparts in AIDS-ravaged southern Africa.

New information suggests that between 12 and 13 African women are currently infected for every 10 African men. There are a number of reasons why female prevalence is higher than male in this region, including the greater efficiency of male-to-female HIV transmission through sex and the younger age at initial infection for women.

In 1999, an estimated 570,000 children aged 14 or younger became infected with HIV. Over 90% were babies born to HIV-positive women, who acquired the virus at birth or through their mother's breast milk. Of these, almost nine-tenths were in sub-Sahara Africa. Africa's lead in mother-to-

child transmission of HIV was firmer than ever despite new evidence that HIV ultimately impairs women's fertility: once infected, a woman can be expected to bear 20% fewer children than she otherwise would.

In short, the huge gap in HIV infection rates and AIDS deaths between rich and poor countries, and more particularly between Africa and the rest of the world, is likely to grow even larger in the next century. Likely, but not certain. Massive national and international efforts may yet help to end the stifling silence that continues to surround HIV in many countries, to explode myths and misconceptions that translate into dangerous sexual practices, to expand prevention initiatives such as condom promotion that can reduce sexual transmission, to create conditions in which young children have the knowledge and the emotional and financial support to grow up free of HIV and to devote real money to providing care for those infected with HIV and support to their families. A trail of successful responses has already been blazed by a small number of dedicated communities and governments. The challenge for the leaders of Africa and their partners in development is to adapt and massively expand successful approaches that make it harder for the virus to spread, and that make it easier for those affected to live full and rewarding lives.

Contrary to expectations when AIDS was first identified, the epidemic has taken different forms in different parts of the world. In some areas HIV rapidly became common among men and women throughout the population. In others it became entrenched in certain sub-populations whose sexual or drug-injecting behaviour carries an especially high risk of contracting or passing on the virus, particularly sex workers and their customers, men who have sex with men, and drug injectors.

The extent to which HIV spreads between groups with high-risk beha-

viour and any larger population depends on whether members of those groups have sex with people who do not share their high-risk behaviour, and whether condoms are used in those sexual encounters. For an HIV epidemic to take off in a country's general population, there also has to be a substantial amount of sexual mixing among adults. To sustain a heterosexual epidemic, on average each person must have unprotected sex with a minimum of two partners, becoming infected by one and passing on the infection to at least one other. Indeed, since not every encounter between an HIV-positive and an HIV-negative partner will result in a new infection, a sustained heterosexual epidemic suggests that a substantial proportion of the population, both male and female, have a number of sex partners over their lifetimes. Tables 1.1 and 1.2 represent the global and regional statistics of the HIV/AIDS epidemic (WHO's report 1999).

Table 1.1: *Global statistics of the HIV/AIDS epidemic 1999.*

Number of people contracted HIV in 1999	Total	5.6 million
	Women	2.3 million
	Men	2.6 million
	Children < 15	570,000
Number of people living with HIV/AIDS	Total	33.6 million
	Women	14.8 million
	Men	17.6 million
	Children < 15	1.2 million
AIDS death in 1999	Total	2.6 million
	Women	1.1 million
	Men	1 million
	Children < 15	547,000
Total number of AIDS death since	Total	16.3 million
the beginning of the epidemic	Women	12.7 million
	Men	6.2 million
	Children < 15	3.6 million

Table 1.2: *Regional HIV/AIDS statistics 1999.*

Region	Epidemic started	Adults and children living with HIV/AIDS	Adults and children newly infected with HIV	Adult prevalence rate	Percent of HIV-positive adults who are women	Main mode(s) of transmission for adults
Sub-Sahara Africa	late '70s-early '80s	23.3 million	3.8 million	8.0%	55%	Hetero
North Africa & Middle East	late '80s	220,000	19,000	0.13%	20%	IDU, Hetero
South & Southeast Asia	late '80s	6 million	1.3 million	0.69%	30%	Hetero
East Asia & Pacific	late '80s	530,000	120,000	0.068%	15%	IDU, Hetero, Homo
Latin America	late '70s-early '80s	1.3 million	150,000	0.57%	20%	Homo, IDU, Hetero
Caribbean	late '70s - early '80s	360,000	57,000	1.96%	35%	Hetero, Homo
Eastern Europe & Central Asia	early '90s	360,000	95,000	0.14%	20%	IDU, Homo
Western Europe	late '70s - early '80s	520,000	30,000	0.25%	20%	Homo, IDU
North America	late '70s - early '80s	920,000	44,000	0.56%	20%	Homo, IDU, Hetero
Australia & New Zealand	late '70s - early '80s	12,000	500	0.1%	10%	Homo, IDU
TOTAL		**33.6 million**	**5.8 million**	**1.1%**	**46%**	

1.4 AIDS epidemic and mathematical sciences

The AIDS epidemic, which reached the public awareness in the early 1980's, has generated a vast literature of mathematical modelling and statistical analysis. The reasons for this are threefold. Firstly, AIDS itself has a very high public profile, for a variety of sociological, political and economical reasons. Government money has been made available for research, and undoubtedly the desire for academic kudos and publicity has played a part: the story of the discovery of the causative virus HIV and the litigation involved is testimony to this! (see Connor and Kingman, [32]). Secondly, the statistical and mathematical problems peculiar to HIV infection and AIDS have stimulated

the development of new techniques to overcome these difficulties. Some of these difficulties are described in Section 1.4.2.

However it can be argued that the main justification for this tremendous world-wide modelling effort is the outcome of the epidemic in terms of human lives and suffering. This is especially the case in the developing countries, where the economic implications are disastrous. Although in the West the disease is still mainly confined to certain subpopulations, the developing countries are currently seeing an explosion in the numbers of cases among young heterosexuals, and at the 15th International Conference on AIDS held in Florence in June 1999, the World Health Organisation predicted that by the end of the century 40 million people world-wide would be carrying the virus. Despite a comparable effort in the fields of medical, microbiological and pharmacological research, there is still no cure for AIDS or even an effective treatment.

1.4.1 Terminology

This section is not intended to provide a detailed description of the development of the AIDS epidemic or the natural history of the disease itself. (Strictly speaking, AIDS is not a disease but a syndrome, a set of diseases). For further information about the clinical and historical aspects of the epidemic, see Adler [1] and Connor and Kingman [32].

In the terminology of disease modelling, a susceptible (healthy) person acquires HIV (the causative agent of AIDS) from an infected individual through the transfer of body fluids: that is, mainly via sexual intercourse, sharing drug-injecting equipment, via blood or blood product transfusion or from mother to child. Many models have been developed to study the transmis-

sion dynamics of HIV, the way the virus spreads in a community (see 2). The transmission dynamics of HIV are rather more complex than those of airborne infections like measles or solely sexually transmitted diseases like gonorrhoea.

After a latent period of 4-6 weeks antibodies to HIV begin to be produced (a process known as *seroconversion*) and can be detected in the blood. However, physical symptoms may not appear for many years. The time between infection with HIV and diagnosis with AIDS is known as the *incubation period.* Estimation of this period is the object of much modelling work (see 1.5.1).

Although diagnosis with AIDS is officially the end-point of the incubation period, many people have a variety of illnesses before then. These include *generalised Lymphadenopathy* (swollen lymph glands, a sign that the body is fighting an infection), diarrhoea, severe weight loss, oral thrush and other infections, and night sweats. Thus, the use of the term incubation period may be misleading, suggesting as it does an asymptomatic period like that associated with measles, for example. Another area of modelling work has been the study of the natural history of HIV infection in more detail, and the progression of the disease through various states (see 1.5.2).

It is currently thought that a person's ability to transmit the virus may fluctuate through time (Anderson and May, [11]: Blythe and Anderson, [17]). The commonly accepted view is that there are two peaks of infectivity, the first during seroconversion and the second on the appearance of clinical symptoms. It is obviously important from a health education and disease prevention standpoint to know when a person is most likely to transmit the infection, and this has been the subject of much modelling effort (see 1.5.3). Clearly the nature of infectivity will also affect the spread of the epidemic,

since a person who is equally infectious throughout the long incubation period is likely to cause more new infections than someone whose infectivity drops after seroconversion.

A major area of research, especially research commissioned by or on behalf of health care planners and Government departments, has been the prediction of the size of the epidemic. Making provision for caring for future AIDS cases requires some estimate of the likely numbers of patients. The drugs and resources required by AIDS sufferers are expensive and the epidemic will make heavy demands on national resources. In the developing countries, these demands may be crippling to the national economy. Section 1.4.4 describes some such modelling work.

Since the development in 1985 of an accurate blood test for antibodies to HIV, the issue of screening for AIDS has been contentious. While there is no cure or arguably no effective treatment, the benefit to an individual of a screening test is dubious. Indeed many AIDS charities (notably the Terence Higgins Trust) strongly advocate against screening. However without adequate information about the prevalence of HIV, many researchers feel their work is severely hampered.

Associated with the problems of estimating the future size of the epidemic are the problems of estimating the costs of caring for these AIDS patients. In both the developed and the developing countries the sums of money involved are considerable and represent a significant proportion of the national health budget. Not the least of these problems is the fact that new drugs and treatments are continually being developed, and planning care for the future is extremely difficult.

A number of large-scale studies have been dedicated to the collection of

data on HIV and AIDS, and many of the models mentioned in this thesis use data from these. Fusaro *et al.* list six of the most well-known studies:

- The San Francisco City Clinic Cohort or Hepatitis B Cohort: A sample of homosexual men recruited from patients at the City Clinic to participate in Hepatitis B vaccine trials, some subsets of which have been followed over time. See Jaffe *et al.* [66].

- The San Francisco General Hospital Cohort: A mixture of samples of homosexual men, some from sexually transmitted disease clinics, some randomly selected, and some partners of AIDS cases, all followed over time. See Moss, Osmond, Bacchetti, Cherman, Barre-Sinoussi and Carlson [89].

- The Multicenter AIDS Cohort Studies (MACS): A set of volunteer samples of homosexual men from selected urban areas throughout the United States, followed over time. See Chniiel *et al.* [31].

- The San Francisco Men's Health Study: A probability sample of homosexual men from San Francisco, followed over time. See Winkelstein *et al.* [115].

- CDC Transfusion-Associated AIDS Cases: A retrospective follow-up of AIDS cases associated with blood transfusions. See Lui *et al.* [77] and Medley, Anderson, Cox and Billard [81].

- The National Cancer Institute Multicenter Haemophiliac Cohort: A follow-up study of haemophiliacs from several haemophilia treatment centres in the United States. See Brookmeyer and Goedert [25].

Several academic journals have devoted special issues to AIDS. Many of the papers referred to below are to be found in such special issues. For

example, the Journal of the Royal Statistical Society, Series A, 341 (1997), the Philosophical Transactions of the Royal Society of London (Biology), 325 (1989), Statistics in Medicine, 8, No. 1 (1995), Simulation, 56, No. 1 (1996), and Interfaces, 21, No. 3 (1996). Another excellent collection of papers is Mathematical and Statistical Approaches to AIDS Epidemiology, edited by C. Castillo-Chavez, Lecture Notes in Biomathematics, 83, Springer-Verlag (1994).

A glossary of medical and epidemiological terms can be found in Section 1.6.

1.4.2 Difficulties encountered in modelling

Some of the problems in modelling are not specific to AIDS: there are general criticisms that have been levelled at the mathematical modelling of any disease. For example, it has been argued that the simplifying assumptions necessary to make models tractable to solution render them useless in practice, as the real-life processes they are trying to model are so complex. In the case of HIV and AIDS this criticism may be even more justified: not only is the underlying disease process extremely complicated, but our knowledge of this process is incomplete. There are also problems with data, the raw material for all models. Lack of data and poor quality data are hazards encountered in all modelling work, but these hazards are magnified in the case of AIDS by an exceptionally high degree of uncertainty and the long time periods involved.

A partial reply to the first criticism might be that although real-life phenomena may appear complex, they may be governed by a simple process, and that it is important to try the simple approach first, if only to eliminate

it (Anderson [7]). Moreover, the process of modelling requires these assumptions to be made explicit and this can lead to improved understanding. This is particularly relevant to AIDS, where our knowledge of the underlying process, although currently inadequate, is increasing rapidly. It can be argued that in an area where everything is new and unknown, even a simple model can be helpful. Decisions still have to be taken which will not wait for the "perfect" model or the "exact" data, and even a rough guide is useful.

The problems with data are considerable. To begin with there are problems of censoring. Much life data is incomplete, since failure times or origin times are unknown. AIDS data is particularly badly affected because of the very long time periods involved. There are a number of different types of censoring. In the terminology of life data analysis, right-censored units are those who have not yet failed by the present time. Left-censored units are those whose failure times are only known to have been before a certain specified time. Singly-censored data occur if all the units are started on test together and the data are analysed before all units fail. Multiply-censored data arise when the units all have different running times, i.e. started on test at different times. Interval censoring occurs when the units are inspected more than once, and the only information we have is that a unit failed within a certain interval. AIDS data is subject to all these forms of censoring.

For example, suppose we are studying a set of people known to be infected with HIV. To begin with, there is uncertainty about the time of infection. Apart from exceptional circumstances, as for example people infected by blood transfusions, the date of infection is unknown. Even in the case of transfusion-associated AIDS, many patients die from the cause for which they were transfused before they would have had time to seroconvert. Moreover, because of the long time periods involved, data is missing because a per-

son has been lost to follow-up before they have developed symptoms. These problems give rise to biased data: the data is biased in favour of individuals with short incubation periods, since those who would have had longer incubation times have not been included in the data set.

Secondly, there are problems with the notification of cases of AIDS. The Centers for Disease Control (CDC) in Atlanta, Georgia is the body responsible for collecting AIDS data in the USA and they have laid down strict case definitions for clinical AIDS [1996, 1997], which are used all over the world. However these surveillance definitions have changed several times since records began, reflecting increasing medical knowledge. Therefore some AIDS deaths were not notified as such, because they did not meet the official case definitions at the time. In addition, some AIDS deaths may not have been identified because the doctor wished to spare the feelings of relatives, so the death certificate gave a non-AIDS-specific cause of death, such as "heart failure". The same problem occurred in the UK and elsewhere. Furthermore, there is often a time-lag between someone dying of AIDS and that death being reported to the data collecting agency.

Problems specific to detailed progression models include a paucity of data on the pre-AIDS clinical states. As we have seen, even data on the basic incubation period is problematic. Cost and resource data is a little less difficult, since such information is often now available to health planners, but many AIDS treatments are still at an experimental stage and it is almost impossible to estimate the future costs of new drugs.

Finally, another problem common to all modelling work is that of communication: between mathematician and clinician, statistician and epidemiologist. It is not surprising that mathematical models are regarded with suspicion, and thus not accepted, if they cannot be understood. Even if the

internal mathematics is extremely complex, it is important that the modeller should be able to interpret and explain the results given by the model in meaningful terms.

1.4.3 Transmission dynamics models

Most of the models for the transmission dynamics of AIDS have been deterministic, and have tended to concentrate on the epidemic in male homosexual communities. An excellent review of modelling work in this area is to be found in the paper by Isham [63]. Isham is one of the first researchers who has cited several basic deterministic models. However, she argues that although deterministic models only give an approximate solution, and that problems are likely to arise at the early stages of the epidemic when numbers are small, stochastic models are so difficult to solve that the current emphasis on deterministic models is justified. However she does draw attention to areas where the use of deterministic models could give rise to misleading answers. One way in which many deterministic models incorporate variability is by grouping individuals into classes with different behaviour.

The models developed by Anderson, Medley, May and Johnson [13] typify this approach. They discuss previous models of sexually transmitted diseases and review the epidemiological parameters necessary for such models: for example the duration of the incubation period and the infectious period, and the proportion of HIV-positives who will develop AIDS. They formulate a series of models of increasing complexity, and consider what processes affect the course of the epidemic. They show that highly heterogeneous levels of sexual behaviour diminish the size of the epidemic: in other words, the very active individuals die before they have time to spread the disease.

Anderson [6] develops these ideas in a model with variable incubation times and infectivity, as well as heterogeneous sexual behaviour. He shows that knowledge of these parameters is essential in order to use the model to predict future trends. Bailey [15] introduces a simple compartmental model for the incubation period, which assumes that all scroconverters will go on to develop AIDS. The model parameters are estimated using data from the San Francisco City Clinic cohort. Blythe and Anderson [16] consider a compartmental model with variable incubation and infectious periods but with homogeneous mixing. They model the incubation and infectious periods with exponential, Weibull, Gamma and rectangular distributions. In another paper [17] they consider two other methods for modelling variable infectivity: in the first method infected people pass through a series of subclasses with different constant levels of infectivity, where the lengths of stay are exponentially distributed with different constant means. The second approach uses a description of the relationship between the infectious and incubation periods based on changes in viraemia (levels of virus in the blood). They compare these models with those in which infectivity is taken to be constant, and in particular they study models with two peaks in infectivity. They found that the initial peak in infectivity determines the early doubling time of the epidemic (the time taken for the number of cases to double), although both phases affect the size of the epidemic and the endemic equilibrium state.

In a third paper [18] they study the effects of heterogeneous sexual activity by using a compartmental model with proportionate mixing: that is, where the proportion of sexual contacts between people in class i made with people in class j is proportional to the total number of contacts made by the population due to people in class j. Initially they treat sexual activity as a continuous variable: this model is a set of integro-partial-differential

equations, but they approximate this discretely to obtain a set of ordinary differential equations.

The work of Anderson has undoubtedly been fundamental in developing the theory of transmission models. His name appears on papers too numerous to list in full. His work with May and McLean [12] has concentrated on modelling the demographic consequences of AIDS, with special reference to the developing countries: these models are for heterosexual communities.

Dietz and Hadeler [41] develop a transmission model which accounts for pair formation and separation. They introduce non-linear pair formation and separation rates, assume a constant rate of sexual contact and an exponentially distributed infectious period, with constant infectivity throughout. They conclude that endemic equilibrium is attained only if the separation rate is sufficiently large to ensure enough new partners. Dietz [40] extends this to a heterosexual transmission model, which accounts for partnership duration and the number of contacts per partnership: most models assume that partner contacts all occur instantaneously. He outlines model refinements such as heterogeneous contact rates, and concludes that the heterosexual epidemic will spread more slowly than the homosexual epidemic, under the same assumptions about the incubation period, infectivity and contact rates.

Another type of mixing is preferential mixing, where each group reserves a fraction of its sexual contacts for members of that group, and otherwise uses proportional mixing. A model which uses preferential mixing is that of Jacquez, Simon, Koopman, Sattenspiel and Perry [65], which considers a male homosexual community characterised by rate of sexual contact. They model the incubation period as a series of stages, each with exponential dwelling times, which gives a Gamma distribution for the overall incubation period. They find that a small increase in the contact rate between high and

low activity classes causes a large increase in the size of the epidemic in the low-activity groups.

A model developed specifically for IV drug users is that of Kaplan [68]. He modeled the sharing of injecting equipment in "shooting galleries", which are places where drug users go to inject themselves, often using communal equipment. A user selects a gallery according to a Poisson process at a constant rate. Equipment becomes infected when used by an infective person, but is cleansed (with constant probability) when it is used by a susceptible. Using infected equipment transmits HIV with constant probability. The model assumed that the size of the addict population remained stable and that individual infectivity is constant. The model is formulated as a set of differential equations. It is then extended to incorporate heterogeneous equipment sharing rates: the conclusions are the same as May, Anderson and Johnson's [80] for heterogeneous sexual behaviour, i.e. increased heterogeneity ultimately diminishes the size of the epidemic since the smaller high-activity group becomes saturated earlier.

Kaplan [69] also considered the homosexual epidemic in a model where men are classified according to the rate of risky sexual practice (i.e. unprotected anal intercourse). This model assumes random partner selection and constant infectivity, and an exponential incubation period (although the author claims the model is fairly robust to the choice of distribution). The model used data from the San Francisco Men's Health Study (Winkeistein *et al.* [115]) and the author concludes that the gay population may have modified their behaviour to reduce risky practices. Kaplan and Abramson [70] used a similar model to study the effects of an education program which temporarily reduces high-risk behaviour, and concluded that even a temporary reduction can significantly retard HIV transmission.

These deterministic models generally consist of sets of differential or integro-differential equations. Other techniques have been applied to modelling the transmission dynamics of AIDS, notably simulation. The systems dynamics approach is used by Ahlgren and Stein [2], who developed a series of deterministic models using STELLA, a systems dynamics language for the Apple Macintosh. Their basic model simulates HIV transmission within a single risk group. They extended this template model to models for heterosexual transmission and needle-sharing. They introduced a program which uses the template model to optimise key epidemiological parameters such as infectivity in the early stages of the epidemic, using data from San Francisco. They showed that infectivity in the very early stages of infection (before seroconversion) may be significantly higher than later on in the antibody-positive stage, and therefore screening for viral antigens in the very high risk-groups would be justified by the subsequent reduction in transmission.

Another systems dynamics model is that of Roberts and Dangerfield [99], [98]. The program was written using DYSMAP2 and runs on a PC. It simulates a male homosexual community and can incorporate heterogeneous sexual activity, variable infectivity and changes in sexual behaviour over time. The model can also be used to evaluate the effects of prolonging the symptom-free period by the use of drugs such as AZT. This model also uses parameter optimisation techniques, implemented using the program DYSMOD, based on data on UK male homosexuals.

A model using simulation is that of Kiessling, Stannat, Schedel and Deicher [72]. This simulates the morbidity and mortality rates of AIDS in the Federal Republic of Germany, where the population is divided into six compartments according to sexual behaviour.

Simulation has also been used by Gonzalez, Koch *et al.* [53], in a model

which classed individuals according to age and sexual preference, with variable incubation period. They developed a program called ASSP (AIDS-Spread Simulations and Projections) which is an extension of an earlier program by Dorner [39]. In the ASSP model the population is divided up into many (up to 100 or more) compartments which differ according to sexual behaviour. Infection-transmitting contacts between people in different compartments, and flows of individuals from one compartment to another are considered. The underlying model is a large system of difference equations with a constant time interval (one month). Although probability distributions are used for the incubation period and the duration of illness, the model itself is not stochastic because random sampling is not done.

Another simulation study is that of Stigum *et al.* [102]. This modeled the heterosexual population of Norway, grouped according to age, sex and whether paired or single. The model parameters were estimated using data from a population-based survey. The model is sensitive to changes in sexual behaviour and to the shape of the transmission probability distribution, although not to the initial conditions. The simulation results indicated that without inflow from other risk groups, the Norwegian heterosexual epidemic is unlikely to sustain itself unless the average transmission probability per intercourse is greater than 1%: current estimates of this probability are in the region of 0.1%.

Leslie and Brunham [73] describe a discrete-event simulation model developed using SIMSCRIPT 11.5. Individuals (known as Victims in the terminology of the program!) may be either active, immunised or susceptible. Active Victims pass through a series of disease stages which are controlled stochastically by a matrix of transition probabilities. Susceptible victims acquire the virus by means of contact events, which depend on the type of

activity in which a Victim participates. The underlying assumption is that the model satisfies the conditions for a Markov chain. The model is used to verify the May-Anderson prediction relating contact rate heterogeneity to the rate of HIV spread, and can be used to study a wide range of risk-group dynamics.

A similar approach was employed by Bongaarts [20], using a compartmental model simulated as a Markov chain. The program allows the epidemiological and behavioural parameters to vary with the age of an individual, and the incubation process is modelled as a series of infection stages with exponentially distributed waiting times, giving rise to a Gamma distribution for the overall incubation period. The infection stages are Uninfected (Immune or Susceptible), Infectious (AIDS risk or No AIDS risk), AIDS and Death. The model is primarily aimed at estimating the demographic consequences of the epidemic, and is implemented as sets of linear differential equations. The simulated population is stratified according to age, gender, sexual behaviour, marital status and infection/disease status. Simulation results are reported for a run of 25 years in an African-pattern heterosexual population with no gay or IV drug-using transmission.

The wider use of transmission dynamics models as predictive tools has been hampered by their dependence on key parameters and processes which are, as yet, little understood. However they certainly help to focus attention on the areas where further information is required, and have been used to interpret observed trends: for example, changes in sexual behaviour as reflected in lower levels of other sexually transmitted diseases. Moreover much recent work has been in the area of stochastic modelling, and this may turn out to have more practical relevance.

An early stochastic model is that of Mode, Goliwitzer and Herrmann [85].

This model is extended by Mode, Gollwitzer, Salsburg and Sleeman [86] to a non-linear stochastic model with recruitment of infectives. The model is formulated by probability generating functions for the monthly probability that a susceptible individual becomes infected with HIV, assuming that the probability of transmission varies with the duration of infection. The model can incorporate condom use. The stochastic process is a series of iterations of non-linear difference equations, starting with an initial conditional expectation. The model is tested by Monte Carlo experimentation.

1.4.4 Short term predictions

Much of the work in this area has concentrated on the need to provide reasonable estimates of the numbers of AIDS cases over one to five years. Such estimates are required for resource planning and allocation, and this research has often been at the behest of Government departments. Indeed one of the best-known collaborative efforts was the Working Party set up in 1988 by the Department of Health, under the chairmanship of Sir David Cox. Cox Report [36] contained the results of this collaboration and has been the basis for providing predictions for many other models. The Working Party recommended that in view of the rapidly changing nature of the epidemic, and the paucity of knowledge about the factors determining its spread, the Report should be updated at least annually. The result of this was the Day Report [37], which contained a reduction in some of the forecasts.

The methods commonly employed are empirical curve-fitting techniques, extrapolating future incidence from past data, based on the choice of a suitable distribution function. Parameter estimates for a given function are obtained using maximum likelihood methods or weighted least-squares meth-

ods. Some of the problems encountered with the data (for example, reporting delays and censored data) can be dealt with, and new techniques have been developed directly as a result of the specific difficulties of the AIDS data (for example, the method of back calculation).

The choice of a suitable distribution function is a difficult one, since more than one function may be consistent with historical data. This is where the simple mathematical models described in Section 2 can help, by providing an insight into the rationale for choosing one function in preference to another. The mathematical models suggest that an exponential rate of growth in the very early stages of the epidemic will be superseded by a slower rate, for instance logistic or log-linear.

Apart from the data problems already mentioned, difficulties arise as a result of different patterns of growth in different risk groups. Anderson [7] argues that the reliability of short-term predictions for the developed countries will decrease as the epidemic slows in particular risk groups. Effectively, we are seeing the net results of several separately identifiable but interlinked epidemics within the different risk-groups, and this makes general trends difficult to discern and interpret. Model-based estimates will probably be more reliable for the developed countries. Purely statistical short-term predictions are now likely to be most useful in the developing countries, where the pattern of infection is more homogeneous.

The method of back calculation was introduced by Brookmeyer and Gail [24], [22] and developed by Bacchetti and Moss [14]. This method forecasts future numbers of AIDS cases from estimates of those already infected with HIV. It calculates the number of infections from the (known) number of AIDS cases diagnosed up to a certain point in time, using a parametric model for the (unknown) infection times.

Brookmeyer and Gail [23] used a Weibull distribution for incubation period distribution and assumed that all transmission ceased at the end of 1985 in order to obtain a minimum estimate for the size of the epidemic in the USA. They used data for the numbers of AIDS cases reported to the CDC, and estimated $A(t)$ from cases of transfusion-associated AIDS. The Cox Report [36] also used a Weibull distribution, with a mean of 7.4 years. As time goes by and information on the incubation period distribution improves, these back calculation methods will provide more accurate forecasts. The incubation distribution is not stationary, due to the rapid mutation of HIV, and neither is HIV incidence, because of changes in sexual behaviour.

Downs, Ancelle, Jager and Brunet [42] analyse European AIDS data reported to the WHO, and fit simple exponential models by regression for the period of the epidemic and for successive overlapping 3-year time windows. They estimate doubling times for ten individual countries and the whole European Community. They predict and construct confidence intervals for one-and-a-half year periods by extrapolating from the curves for the most recent time windows.

Gonzalez and Koch [53] study the effects of "transients" on short-term forecasts. They argue that these biasing transitional effects can be very misleading, and suggest that the apparent initial decline in the growth rate of AIDS cases may be spurious, and, in fact, due to a positive onset transient. They assume that the initial stages of the epidemic are approximated by exponential growth. They study the effects of the onset transient on the incubation distribution.

Harris [59] provides maximum likelihood estimates, using an EM algorithm, of the empirical distribution of the delay in reporting AIDS cases. He projects cumulative US AIDS incidence until 1999 by extrapolating CDC

data adjusted for reporting delays.

Healy and Tillett [60] fit a variety of curves to UK cases until 1995, adjusted for reporting delays. These include an unweighted linear model using a log scale and a log-linear model with Poisson errors, which give similar results. They also fit a quadratic term in the above models, which fits the data quite well but yields different results.

Morgan and Curran [87] fit a quadratic polynomial to adjusted CDC data and project the results to 2001, assuming the trends remain unchanged over time. Rees [96] fits a normal distribution to the incubation period of US transfusion-associated AIDS cases, and predicts the number of HIV infections in the UK and US over the next 30 years that will arise as a result of current HIV infections. A long series of comments and rejoinders, mainly criticising Rees' choice of the normal distribution.

Taylor [105] uses a variant of the back-calculation technique. He models the numbers of cases of AIDS developing in different time periods by multinomial random variables whose cell probabilities are the convolution of the incidence distribution and the incubation period distribution. He uses 5 different models for the incidence distribution: double exponential, root exponential, logistic, logistic prevalence and quadratic. Taylor considers 21 non-parametric distributions for the incubation period. He fits these 105 models, using maximum likelihood methods, to adjusted CDC data from 1982 to 1993. The double exponential incidence distribution generally seems to provide the best fit, but no obvious pattern is observed for the incubation period distributions.

Tennison and Hagard [106] predict short-term UK AIDS incidence through trend extrapolation. They use Box-Cox analysis to determine the appropriate

power transformations for weighted logarithmic linear and quadratic regression models. They give emphasis to recent data by using a series of weights which decrease exponentially into the past, with a common ratio.

1.5 Natural history models

The majority of research studying the actual disease process have concentrated on the incubation period, that is the time between infection with HIV and the official diagnosis of AIDS. Knowledge about the incubation period distribution is necessary for many of the transmission and prediction models described above. One of the difficulties with modelling AIDS is the bewildering variety of conditions which all come under the umbrella of "HIV infection". This has led to changes over time in the official surveillance definitions of AIDS, and also gives rise to ambiguities when modelling the natural history in detail.

In view of the long incubation period of the disease, research has also concentrated on identifying which clinical, immunological and virological parameters best predict the rate of progression of disease in individual patients. Four such markers have been identified: a decline in CD4 lymphocyte counts over time, presence of the p24 antigen to HIV, high levels of serum β-microglobulin, and high levels of serum neopterin (Moss [88]). However, there is a high degree of variability between patients and so models which attempt to predict the rate of progression of disease from these parameters should be stochastic in nature. Bacchetti and Moss [14] give an excellent review of the statistical modelling of disease progression.

Another reason for modelling the disease process in detail is to study the effects of treatments. The drugs given for AIDS are powerful (and expens-

ive) and often have unpleasant side-effects. There are ethical and practical difficulties in designing clinical trials for new drugs. These detailed models can also investigate resource use.

A third area of modelling work has been research into infectivity. Knowledge about how infectivity varies over the different stages of disease is required for some of the transmission models above. Moreover, if we know when a person is particularly infectious we can decide whether or not to screen certain sections of the population, or how to target education campaigns.

1.5.1 Modelling the incubation period

One approach to modelling the incubation period is to divide it up into a series of stages. It is then possible to regard these stages as a Markov process and to estimate the dwelling times in each stage from data. The incubation period is then the aggregate of all the individual dwelling times. An example of this approach is that of Longini *et al.* [75], who fit a five-stage time-homogeneous Markov model by numerical maximum likelihood techniques to right-, left- and interval-censored data from the San Francisco Hepatitis B cohort, haemophiliacs and transfusion-associated AIDS data. An advantage of dividing up the incubation period into a series of sub-intervals is that less information is lost from heavily censored data like this because of the shorter time periods in each stage. The stages they select are the following:

i) Antigen-positive but antibody-negative.

ii) Seropositive, asymptomatic.

iii) Clinical signs and symptoms, pre-AIDS.

iv) Clinical AIDS.

v) Death due to AIDS.

Based on this model, they estimate the incubation period distribution and the survival times from each stage of infection. The estimated mean incubation time is 9.8 years. They also discuss some of the problems of censored and biased data..

They use the same technique with a different staging classification, based on CD4 lymphocyte counts. Since an individual's CD4 cell count may fluctuate considerably for a number of physiological reasons, a persistence criterion was used to ensure that a genuine decline had occurred. This model has 8 stages, based on CD4 counts: stage 7 is clinical AIDS, stage 8 is Death from AIDS, and the other six states are:

i) > 899

ii) 700- 899

iii) 500- 699

iv) 350- 499

v) 200- 349

vi) 0- 199

This model uses data from the US Army. The Army uses the Walter Reed staging system (Redfield, Wright and Tramont, [95]) to categorise the progression of disease: this system is partially based on CD4 counts. Age is found to be an important cofactor: the overall mean incubation period is

found to be 9.6 years, but for the youngest age group (under 25) it is 11.1 years whereas for the over-30 age group it is 8.9 years. Ale estimated rate of CD4-cell decline was higher for people with initially high CD4 counts, but once the cell count dropped below 500 the rate of decline remained relatively constant. Bongaarts [20] models the incubation period as a Markov chain and points out that exponential waiting times for each stage result in a Gamma distribution for the incubation period.

Another approach to modelling the incubation period is to assume an underlying parametric distribution and to attempt to estimate the parameters from data. A strong candidate for this distribution is the Weibull, which has frequently been used for survival analysis because of its statistical properties: for example, its wide variety of functional forms and its increasing hazard function. Lui *et al.* [77] fit a Weibull distribution to data from cases of transfusion-associated AIDS and obtain maximum-likelihood estimates of its parameters. The Weibull distribution is favoured by the Cox Report [36] and its successor the Day Report [37]: the mean incubation period is taken to be 10 years.

1.5.2 Detailed progression models

The number of clinically detailed models is comparatively small. Some models have already been mentioned in previous sections. Although these models were only developed in order to estimate the incubation period, they can also be used to estimate the survival times from each stage of infection. These models have the advantage of being able to make efficient use of heavily censored data and a variety of sources.

Another previously-mentioned model is the simulation of Leslie and Brun-

ham [73], where the disease states are represented by a Markov process with dwelling times sampled from Gamma distributions (although for most transitions the shape parameter is set to unity, giving exponential dwelling times). A number of possible state descriptions are allowed: the simplest is

$$Infected \rightarrow Dead,$$

the next is

$$Asymptomatic \rightarrow ARC \rightarrow AIDS \rightarrow Dead,$$

and the third is

$$Asymptomatic \rightarrow CNS \quad infection \rightarrow ARC \rightarrow AIDS \rightarrow Dead,$$

where CNS stands for Central Nervous System and ARC is AIDS Related Complex. The main purpose of this model is to study the transmission dynamics of HIV, but the model allows the probability of transmission to vary according to the state of health of the individual.

The model of Mode, Fife and Troy [84] is based on Longini's model but makes several modifications, in order to incorporate the effects of treatments on the dwelling times in each state. Longini's model was time-homogeneous, but in order to allow for changes over time in the probabilities that a person passes from one state to the next, due to the availability of new treatments, Mode, Fife and Troy's model is time-inhomogeneous. Moreover, the probabilities of the various types of primary disease (the disease at diagnosis of AIDS, for example Kaposi's sarcoma or pneumocystis carinii pneumonia)

may change over time. They also modify Longini's model so that the risk of death following a diagnosis of AIDS depends on the type of primary disease. Unlike Longini's continuous time model, this one is formulated in discrete time units of one month. Instead of looking at the sojourn time distributions, they consider the risk or hazard functions.

An advantage of using stochastic methodology is that Monte Carlo simulation can be used to calculate confidence bounds for the projections. The model is tested using data from the City of Philadelphia, for two types of data input: time series estimates for the numbers of HIV-infected people, and reported time-series of AIDS cases adjusted for reporting delays.

Another Markov model for the transition dynamics of HIV infection is that of Nagelkerke *et al.* [91]. Their model is similar to that of Longini *et al.*, only it allows transitions between stages to be reversible. They use a four-stage model:

i) Asymptomatic Seropositive

ii) PGL

iii) AIDS

iv) Death

Their data is obtained from a study of Nairobi prostitutes. The natural history of HIV infection in Africa differs from that in the West, in that the incubation period is generally shorter, and the spectrum of diseases seen is different. The women were staged "blindly" at each visit and it was clear from the data that reversions to previous stages do occur, with symptoms disappearing and reappearing.

Brailsford and Shahani [21] use discrete-event simulation to model the natural history of HIV infection. They use three different models of increasing levels of complexity, starting with a simple three-state model (HIV-positive, AIDS and Death). The intermediate model has seven states and is based on a classification system proposed by the World Health Organisation. The most complex model has 13 states and uses the internationally-accepted CDC staging system [48].

These models simulate the life-histories of a set of HIV-positive patients. As the patients progress through the various stages of disease, data is collected about the resources they use in each state and the costs incurred in providing this resource. The models are intended for two user-groups: clinical users interested in the numbers of patients in each state and the time people remain in each state, and health planners who are interested in resource allocation and costs. Their data is at present based on collaboration with clinical consultants at the Royal Victoria Hospital, Bournemouth. Work on data from other UK centres and from the San Francisco Men's Health Study is currently in hand.

An area where detailed progression models are also useful is in actuarial forecasting. Wilkie [114] describes a Markov stochastic process model where transition intensities may vary by age, calendar year and duration in the previous state. Living individuals are in one of four states: Clear, At Risk, HIV-Positive, and Sick with AIDS. From each state, it is possible to move to a corresponding Dead state (Dead from Clear, Dead from At Risk, and so on): however there are two possible transitions from Sick with AIDS, Dead from Sick and Dead from AIDS. The incubation intensity is modelled by a Gompertz formula and the model itself is a set of differential equations, which Wilkie proposes to solve numerically.

Another example of the actuarial approach is that of Panjer [92]. This model describes the progression of HIV-positive individuals through the Walter Reed stages (Redfield, Wright and Tramont, [95]) as a continuous time Markov chain. These stages are:

i) (At-risk) Healthy person at risk for HIV but testing negative.

ii) (HIV+) Asymptomatic persons testing positive.

iii) (LAS) Persons with HIV infection and Lymphadenopathy syndrome (LAS), plus moderate cellular immune deficiency.

iv) (ARC) Patients with HIV infection and LAS, plus severe cellular immune deficiency (AIDS-Related Complex).

v) (AIDS) Patients with AIDS.

It assumes constant hazard functions for passing from one stage to the next. The survival analysis produces numerical maximum likelihood estimates for the overall hazard function (for time to death) and expected time to the next stage. The model uses German data from a longitudinal study (Cowell and Hoskins [35]).

In a subsequent work [92] Panjer develops a Poisson process model for estimating the number of AIDS cases that have not yet emerged as deaths or health benefit claims, enabling actuaries to adjust insurance company reserves. This model uses an exponential Poisson rate function to model new infectives in the population and a Gamma or Erlang model, based on the previous [57] one, for the incubation period distribution. The Erlang model is the sum of three exponential variables representing the transitions

- from seropositivity to Lymphadenopathy syndrome (LAS);

- from LAS to AIDS-Related Complex (ARC);
- from ARC to AIDS.

The concept of modelling has also been applied at a microbiological level, to understand cell processes like viral replication and immune response. An example of this type of model is that of Allen [3], who models the pathophysiological effects of AIDS in terms of changing T4:T8 ratios. Munoz, Carey *et al.* [90] use an autoregressive model relating CD4 cell counts to fixed and time-dependent predictor variables, while adjusting for previous CD4 counts, in order to identify predictors of CD4 cell decline. They use longitudinal data from a cohort of homosexual seroconverters in the Multicenter AIDS Cohort Studies (Chmiel *et al.* [31]).

A simulation model to describe the natural history of CD4 cells in HIV-positive individuals is described by Taylor, Tan, Detels and Giorgi [104]. The model uses data from the Multicenter AIDS Cohort Study (Chmiel *et al.*, [31]) and incorporates the following features:

- variability in within-person and between-person CD4 cell counts;
- variation in the rates of decline of CD4 cell counts;
- variation in the level of CD4 at which clinical AIDS is diagnosed;
- greater absolute variation in CD4 values in men with high CD4 levels, compared with men with low CD4 levels.

Applications of the model to the design and interpretation of clinical trials are discussed, as well as other clinical aspects of the CD4 cell count.

Another aspect of HIV infection which has received attention has been the existence of cofactors which facilitate the spread of HIV. There is growing

medical evidence that the presence of other sexually transmitted diseases (STDs) such as genital ulceration and chancroid, which cause skin lesions and mcrease the risk of viral transmission (Piot and Laga, [93] Quinn, Glasser, Cannon *et al.* [94]). Anderson [7] formulates a simple deterministic model to describe the interaction between an endemic STD and HIV. He argues that in practice, such models are of limited use because of the fact that people with high rates of partner change are more likely to acquire both HIV and the other STD, regardless of the role of the latter in promoting transmission of the former. Anderson believes that stochastic models are far more appropriate for modelling the relative risks involved.

1.5.3 Infectivity

Several of the models previously mentioned have incorporated the concept of variable infectivity over the different stages of disease. For the purposes of studying the transmission dynamics of HIV infection, and for predicting the future numbers of AIDS cases, it is important to understand the nature of infectivity. Current medical thinking is that there are two peaks in infectivity, one around the time of seroconversion and the other at the time when symptoms begin to emerge. The first peak is obviously very important since at this stage an infectious person has no idea that they are carrying the virus, and consequently will not modify their behaviour to reduce the chance of infecting someone else. For this reason screening high-risk groups has been proposed. Before seroconversion levels of virus in the blood may be high, but after antibody production has started blood virus levels fall again. (Anderson and May, [11]).

An example of this sort of model is that of Blythe and Anderson [18],

which was described in section 2. Byers *et al.* [27] estimates the HIV infection rate in the San Francisco City Clinic Hepatitis B cohort by fitting survival curves to the interval censored serological data by maximum likelihood techniques. They find that log-logistic model fits the data better than the Gompertz, Weibull or logistic models. For comparison they also produce a life-table simulated survival curve, inputing the censored seroconversion times by first assuming the infection distribution to be uniform interval, choosing the best-fitting survival curve by life-table methods, and then imputing the infection time under the best survival distribution.

DeGruttola, Seage, Mayer and Horsburgh [38] estimate the risk of HIV transmission by receptive anal intercourse from a study of gay and bisexual men. They assume a constant risk for each exposure and fit a binomial model by maximum likelihood estimation. The (unknown) number of contacts since the (unknown) time of infection was estimated by performing several analyses truncating the total exposures at various levels, but this model tended to underestimate the number of men with few contacts and to overestimate the number with many contacts. This suggests that there is considerable individual variation in infectivity. They then fit a model assuming that the risk per exposure is constant within each partnership, but that these risks are sampled from a beta distribution. Estimation of the parameters of this distribution requires longitudinal data.

Eisenberg [43] proposes a simple model which relates the probability of acquiring HIV infection to the number of partners and the type of sexual contact. In a later paper [44] he extends this model to incorporate variable infectivity, in terms of the number of sexual contacts and the duration of infection in an individual. He concludes that the effects of variability lead to a greater risk from multiple partners than previously thought. This is

similar to the model of Grant, Wiley and Winkelstein [54] which estimates the infectivity of HIV resulting from unprotected receptive anal intercourse, i.e. the per partner probability that such contacts with an infected partner will result in transmission of the virus. Wiley, Herschkom and Padian [113] consider heterogeneous infectivity in male-to-female transmission, and conclude that the number of different partnerships, rather than the frequency of contacts within a partnership, may have the greatest effect on the risk of transmission.

1.6 Glossary

AIDS: Acquired Immune Deficiency Syndrome.

Antibody: A defensive chemical produced by the body in response to the action of a foreign substance, like a toxin or virus.

Antibody-positive: In HIV infection, an individual who has been found to have antibody to HIV in their blood.

Antigen: A substance which stimulates the production of an antibody.

Antigen-positive: In HIV infection, a person who has been found to have the virus HIV in their blood.

ARC: AIDS-Related Complex, a variety of symptoms including sudden unintentional weight loss, severe diarrhoea, night sweats, fever, oral thrush.

Assortative sexual activity group (like with like): individuals from assortative sexual activity choose sexual partners only from their own group.

Asymptomatic: Having no signs or symptoms of disease: apparently healthy.

AZT: Aziothiaprine (also known as Retrovir or Zidovudine): a drug used

in the treatment of HIV infection, thought to inhibit viral replication, and delay the onset of serious symptoms.

CD4 cells: Cells in the blood which help fight infection, and are particularly affected by HIV.

CDC: Centers for Disease Control: the organisation in the USA responsible for collecting epidemiological data.

CDSC: Communicable Disease Surveillance Centre: the equivalent body to the CDC in the UK.

Dis-assortative sexual activity group (like with unlike): individuals from the dis-assortative sexual activity group only choose sexual partners from other groups.

Endemic: Describing a disease which is always present in a community.

Epidemiology: The study of disease in the community.

Epidemic: Describing a disease which breaks out at a particular time in a community.

HIV: Human Immunodeficiency Virus, the causative agent of AIDS.

HIV-negative: Having no detectable antibody to HIV in the blood.

HIV-positive: Having antibody to HIV in the blood: having a positive result to an HIV-test.

Immune: In epidemiological terms, an individual who is not capable of being infected.

Immune system: A complex system of the body responsible for defence against infections, foreign substances and cancers: formed jointly by white blood cells, lymph glands and chemicals produced within the body.

Incidence: The rate at which new cases of a disease appear.

Incubation period: The time between an individual acquiring the causative agent of a disease, and being clinically diagnosed with that disease.

Infection: A disease which is passed from one individual to another.

IV: Intravenous: as in IV drug user, someone who injects drugs.

Kaposils sarcoma: A form of skin cancer commonly associated with AIDS: formerly rare.

LAS: Lymphadenopathy Syndrome (the same as PGL).

Latent period: The time between an individual acquiring the causative agent of a disease, and developing signs of illness.

Lymph glands: Glands in the body which help fight infection by producing white blood cells.

Lymphadenopathy: Abnormally swollen lymph glands: a sign that the body is responding to an infection.

Lymphoeytes: White blood cells: part of the body's defence system.

Lymphoma: Cancer of the lymph glands: associated with AIDS.

Pathogenic: Causing disease.

Partially assortative sexual activity group (random mixing): individuals from a randomly mixed sexual activity group choose sexual partners from other sexual activity groups.

PCP: Pneumoeystic Carinii Pneumonia, a formerly rare type of pneumonia now characteristic of AIDS.

PGL: Persistent Generalised Lymphadenopathy: swollen lymph glands throughout the body which persist more than 4 weeks.

Prevalence: The number of cases of a disease at any one time in a community.

Seroprevalence: The number of HIV-positive individuals in a community.

Sensitivity: The true positive rate of a screening test.

Speciricity: The true negative rate of a screening test.

Seroconversion: The initial production of detectable antibody to HIV: the time at which antibody becomes detectable in the blood.

Seronegative: The same as HIV-negative.

Seropositive: The same as HIV-positive.

STD: Sexually transmitted disease.

Susceptible: In epidemiological terms, an individual who is capable of being infected.

Syndrome: A collection of symptoms or illnesses.

T-helper cells: White blood cells which help fight infection.

T-4 cells: The same as CD4 cells: a subclass of T-helper cells.

Viraemia: The presence of detectable virus in the blood.

Virus: An organism capable of replication, which cannot multiply outside a living host.

WHO: World Health Organisation.

Chapter 2

The mathematics of the transmission dynamics of HIV/AIDS

This chapter discusses a mathematical approach to the modelling of the transmission dynamics of HIV/AIDS epidemic.

Section 2.2 is concerned with the mathematical modelling structure of the transmission dynamics of HIV/AIDS. This includes a deterministic approximation in the form of ordinary differential equations (*ODEs*) used to approximate the transmission dynamics of HIV/AIDS. Section 2.2.1 discusses the stability analysis of the system of ordinary differential equations.

Section 2.3 introduces some novel algorithms used in the analysis of the transmission dynamic models. These include the computational methods and algorithms to reduce the size of the problem and bypass some standard algorithms involved in model analysis. Finally Section 2.4 concludes this chapter.

2.1 Introduction

Mathematical modelling of the epidemics dates back to 1920 (Kermack and McKendrick [71]). Most of the studies in this field are concerned with infectious diseases. Infectious diseases pass from one person to another by physical contact or even through the air.

Since 1980, special attention has been paid to the mathematical modelling and statistical analysis of the AIDS epidemic. Some of the reasons are;

1. AIDS is as yet a fatal disease endangering the future of the human race.

2. Existence of AIDS effects all the sociological, political and economical profiles of the populations.

3. Government money has been made available for research.

4. The complicated nature of the spread of the disease has created a challenge for mathematical modellers and statistical analysts. These have stimulated the development of new techniques to deal with and overcome the complexity of the problem.

However, it can be argued that the main justification for this significant world-wide modelling effort is the outcome of the epidemic in terms of human lives and suffering.

Developing countries are currently seeing an explosion in the numbers of cases among young heterosexuals. World Health Organisation (WHO) estimates that currently 50 million people world-wide are carrying the virus. Despite the efforts in the fields of medical, microbiological and pharmacological research, there is still no cure for AIDS or even an effective treatment.

In the terminology of disease modelling, a susceptible (healthy) person acquires HIV (Human Immunodeficiency Virus), the causative agent of AIDS from an infected individual through the transfer of body fluids. This is mainly via sexual intercourse, sharing drug- injecting equipment, blood or blood product transfusion, consuming infected flesh from some kind of monkey or from mother to child.

In general, mathematical models of biomedical systems are described in terms of stochastic behaviour. Therefore, equations considered would usually be those of a deterministic approximation using systems of ordinary and partial differential equations. This is the standard approach to the mathematical modelling of the transmission dynamics of HIV/AIDS (see Anderson *et al.* [5] and [8]).

Some advantages of using deterministic approximation instead of stochastic model include,

1. whenever a specified stochastic model is approximated by a deterministic process then the interpretation of the latter is fairly clear,

2. a particular deterministic process may reasonably approximate a variety of stochastic models,

3. a unique set of stochastic assumptions cannot be deduced from a set of deterministic equations.

It is known that the growth of HIV/AIDS in homosexual populations is higher than heterosexual populations. Therefore, most of the models describing the transmission dynamics of AIDS have tended to concentrate on the epidemic in male homosexual communities. However, recent data show a bigger rise in heterosexual population.

An excellent review of the history of AIDS modelling is to be found in the paper by Isham [63]. She argues that although deterministic models only give an approximate solution, and that problems are likely to arise at the early stages of the epidemic when numbers are small, stochastic models are so difficult to solve that the current emphasis on deterministic models is justified. However, she does draw attention to areas where the use of deterministic models could give rise to misleading answers. One way in which many deterministic models incorporate variability is by grouping individuals into sub-populations according to their HIV status or sexual behaviour.

Deterministic approximations are usually presented by system of ordinary differential equations (ODEs).

2.2 Using system of ODEs to model the transmission dynamics

Suppose a population of size N is stratified into m groups of individuals according to their sex, age and HIV status and modelled by a non-linear system of ordinary differential equations of the form of

$$\begin{cases} \frac{dx_1(t)}{dt} \equiv f_1(t; x_1, x_2, \cdots, x_m), & x_1(t_0) = x_1^0, \\ \frac{dx_2(t)}{dt} \equiv f_2(t; x_1, x_2, \cdots, x_m), & x_2(t_0) = x_2^0, \\ \qquad\qquad \vdots & \\ \frac{dx_m(t)}{dt} \equiv f_m(t; x_1, x_2, \cdots x_m), & x_m(t_0) = x_m^0, \\ \qquad t > 0 & \end{cases} \tag{2.2.1}$$

in which

$x_j = x_j(t)$: represents the number of individuals in group j at time t, for $j = \{1, 2, \cdots, m\}$.

$\frac{dx_j(t)}{dt} = f_j(t; x_1, x_2, \cdots x_m)$: is the rate of change of the number of individuals in group j at time t, for $j = \{1, 2, \cdots, m\}$.

$x_j(t_0) = x_j^0$: is the number of the individual in group j at time t_0, for $j = \{1, 2, \cdots, m\}$.

A system is *autonomous*, whenever $f_1, f_2, \cdots, f_m$ depend explicitly on the independent variable t, otherwise the system is *non-autonomous*. Therefore, the system of ordinary differential equations presented by (2.2.1), non-autonomous.

The system (2.2.1) reaches to a *steady state* whenever all the derivatives vanish, that is whenever,

$$\frac{dx_1(t)}{dt} = \frac{dx_2(t)}{dt} = \cdots = \frac{dx_m(t)}{dt} = 0$$

Suppose the steady state happens at time t^* and let, $x_j(t^*) = x_j^*$ for $j = \{1, 2, \cdots, m\}$. The steady state $X^* = [x_1^*, x_2^*, \cdots, x_m^*]^T$ is obtained by solving the non-linear algebraic system, using *Newton-Raphson method* (see [112])

$$F(X) = 0, \tag{2.2.2}$$

where, $F = [f_1, f_2, \cdots, f_m]^T$ and $0 = [0, 0, \cdots, 0]^T$ is the zero vector of order m. $X^* = [x_1^*, x_2^*, \cdots, x_m^*]^T$ is called *equilibrium point* of the system of ordinary differential equations (2.2.1). It is important to note that the equilibrium point X^*, which is sometimes called *critical point*, is not necessarily unique.

Generally, in an infected population the epidemic is either developing or disappearing. Of course, the epidemic may happen to be in static state, which is the border between disappearing and developing states. Therefore, there are always two critical points (X_1^*, X_2^*) representing the epidemic in

the disappearing and developing states respectively.

Condition

$$x_j^* \geq 0, \ \ \forall j \in \{1, 2, \cdots, m\}$$

is imposed on the elements of the critical points. This follows the nature of the problem. In other words, x_j^*'s representing the number of individuals in group j at steady state may not take any negative value.

The critical point representing the epidemic in disappearing stage is called *trivial* critical point denoted by X_1^*. At the trivial critical point there are no sign of infected individuals. At the developing stage the critical point is called *non-trivial* critical point denoted by X_2^*.

2.2.1 Stability analysis of the critical points

Stability analysis plays an important role in understanding and solving the system of ordinary differential equations. The mathematical model (2.2.1), describing the transmission dynamics of HIV/AIDS in a population, will be analysed. This is to ensure that it does not predict chaos or divergence in the biomedical system under investigation, when chaos and divergence are not features of such system. This eliminates the observance of the diverted or chaotic behaviour in the solution.

To examine the stability of such a system at a particular critical point, the *Jacobian* is generated

$$J \equiv \frac{\partial F}{\partial X} = \begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \cdots & \frac{\partial f_1}{\partial x_m} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \cdots & \frac{\partial f_2}{\partial x_m} \\ \vdots & \vdots & & \vdots \\ \frac{\partial f_m}{\partial x_1} & \frac{\partial f_m}{\partial x_2} & \cdots & \frac{\partial f_m}{\partial x_m} \end{bmatrix}, \tag{2.2.3}$$

followed by an evaluation of the Jacobian at that particular critical point X^*, therefore

$$J^* = \frac{\partial F}{\partial X}|_{X=X^*} \tag{2.2.4}$$

The stability of the system (2.2.1) at a critical point depends on the eigenvalues of the Jacobian of the form (2.2.4) represented by

$$\lambda = [\lambda_1, \lambda_2, \cdots, \lambda_m]^T. \tag{2.2.5}$$

These are the roots of the equation

$$Det(J^* - \lambda I) = 0 \tag{2.2.6}$$

where I is the $m \times m$ identity matrix.

The system of ordinary differential equations is stable if all the eigenvalues are real and negative or complex with a negative real part. It is neutrally stable if at least one of the eigenvalues is equal to zero, otherwise the system is unstable.

2.3 Novel computational algorithms for analysing large-scale transmission dynamics models

When dealing with large-scale problems, simplifications and reducing the size of the problem are significant. In this section, I have presented some novel computational techniques which play important rules in handling large-scale mathematical models of transmission dynamics of HIV/AIDS. These methods bypass some extra calculations involved in model analysis and speed up the algorithms, hence it is more economical.

2.3.1 Computing critical points

To proceed with the analysis of the transmission dynamic models, only the trivial critical point (X_1^*) is required. The logical justification for this is that the system of ODEs representing the transmission dynamic models only have up to 2 valid critical points (see section 2.2). Therefore, when the trivial critical point is stable the non- trivial critical point is unstable and vice versa. Therefore, there is no need to examine the non-trivial critical point.

The definition of the trivial critical point (X_1^*), follows the fact that the elements representing the number of infectives at steady state are equal to zero, therefore

$$X_1^* = [x_1, \cdots, x_S, 0, \cdots, 0]^T \tag{2.3.7}$$

S represents the number of sexual activity groups. Therefore, the size of the non-linear algebraic system (2.2.2) is reduced from m to S. This is done by inserting zero instead of x_j's to represent infective groups, ($j \in \{S+1, \cdots, m\}$).

2.3.2 Computing reproductive rate

In the concept of the HIV/AIDS modelling, reproductive rate (R) is the number of secondary cases acquiring the virus from one primary infective case per unit of time. In general, properties of the reproductive rate include:

$R < 1$: the epidemic is disappearing,

$R = 1$: the epidemic remains static,

$R > 1$: the epidemic is developing.

To compute the reproductive rate (R), only the trivial critical point (X_1^*)

is required.

In the modelling of the transmission dynamics of HIV/AIDS, studying the effect of sexual behaviour changes in transmission success of the disease is of importance. Therefore, the parameter k representing the rate of the number of new sexual partners per unit of time is under investigation.

The determinant of the Jacobian (2.2.3) at the trivial critical point (X_1^*) denoted by $(|J_1^*|)$, vanishes for $k = k^*$. This unique, real value of k is regarded as bifurcation parameter. The properties of the bifurcation parameter include,

$k < k^*$: the trivial critical point is stable, which means that the epidemic is disappearing.

$k = k^*$: the trivial critical point coincides with non-trivial critical point which means that, the size of the epidemic is not changing.

$k > k^*$: the trivial critical point is unstable. In other words, the epidemic is in developing state.

Therefore, the algebraic relation between the reproductive rate (R), and the bifurcation parameter (k^*) is given by

$$R = \frac{k}{k^*} \tag{2.3.8}$$

This algorithm bypasses some of the complicated algebraic calculations in standard stability analysis and produces some easy to understand results.

2.4 Conclusion

This chapter has provided an outline of the methods and novel techniques used in the analysis of the system of ordinary differential equations devised

to model transmission dynamics of HIV/AIDS throughout this thesis.

These methods reduce the size of the problem when obtaining the critical points, hence it is more economical. In addition, they bypass some of the complicated algebraic calculations in standard stability analysis and produce some easy to understand results.

Chapter 3

Solution techniques of the transmission dynamic models

This chapter provides the algorithms and techniques used to solve the system of ordinary differential equations (2.2.1). Section 3.2 focuses on the principles of the numerical analysis, whilst section 3.2.3 presents a novel analytical algorithm to find optimum time step for convergence.

Section 3.3 discusses two numerical methods employed as the solver engines in the implementations. In Section 3.3.2, I have tried to generalise the alternative method (see E. H. Twizell *et al.* [107]) for the purpose of modelling the transmission dynamics of HIV/AIDS.

3.1 Introduction

The numerical methods used to solve a mathematical model should not predict chaos or divergence when chaos and divergence are not features of the system.

The efficiency of the numerical integration of the systems of non-linear differential equations over the largest possible time step, bearing in mind accuracy and stability, is of importance. The stability properties, which restrict the use of a large time step, are also investigated. This is to avoid the presence of chaos or divergence in the solution of the model equations.

3.2 Numerical analysis

In general, the time variable $t \geq 0$ will be discretized at the point $t_n = nh$, for $(n = 0, 1, 2, \cdots)$ where $h > 0$ is regarded as time step.

Suppose solution of the system of non-linear equations (2.2.1) at time t_n is $X(t_n) = [x_1(t_n),\ x_2(t_n),\ \cdots,\ x_m(t_n)]^T$, and this is denoted by $X^n = [x_1^n,\ x_2^n,\ \cdots,\ x_m^n]^T$. The development of the numerical methods will be based on the first-order approximations

$$\begin{cases} \frac{dx_1(t)}{dt} = \frac{x_1(t+h)-x_1(t)}{h} + O(h) & as \quad h \to 0, \\ \frac{dx_2(t)}{dt} = \frac{x_2(t+h)-x_2(t)}{h} + O(h) & as \quad h \to 0, \\ \qquad\qquad \vdots & \\ \frac{dx_m(t)}{dt} = \frac{x_m(t+h)-x_m(t)}{h} + O(h) & as \quad h \to 0, \end{cases} \tag{3.2.1}$$

in which $t = t_n = nh$, $n = 1, 2, \cdots$.

Approximating the derivatives in the system (2.2.1) by (3.2.1), and evaluating the variables on the right-hand side, after re-arranging gives

$$\begin{cases} x_1^{n+1} = g_1(x_1^n, x_2^n, \cdots, x_m^n), & n = 0, 1, 2, \cdots, \\ x_2^{n+1} = g_2(x_1^n, x_2^n, \cdots, x_m^n), & n = 0, 1, 2, \cdots, \\ \qquad\qquad \vdots & \\ x_m^{n+1} = g_m(x_1^n, x_2^n, \cdots, x_m^n), & n = 0, 1, 2, \cdots \end{cases} \tag{3.2.2}$$

The numerical solution is convergent after a certain number of iterations converge to one of its fixed points from any initial value, $X^0 = [x_1^0, x_2^0, \cdots, x_m^0]^T$. In other words, at steady state $x^n = x^{n+1} = x$. Therefore, substituting x^n and x^{n+1} with x in (3.2.2) gives

$$\begin{cases} x_1 - g_1(x_1, x_2, \cdots, x_m) = 0 \\ x_2 - g_2(x_1, x_2, \cdots, x_m) = 0 \\ \vdots \\ x_m - g_m(x_1, x_2, \cdots, x_m) = 0 \end{cases} \tag{3.2.3}$$

Solving the above system associated with (3.2.2) produces the numerical method's fixed point(s) denoted by $X^* = [x_1^*, x_2^*, \cdots, x_m^*]^T$. The fixed point(s) of the numerical method should be the same as the critical point(s) of the system (2.2.1).

It remains to establish the condition(s) under which the numerical solution will converge to one of the fixed/critical points from any initial values, $X^0 = [x_1^0, x_2^0, \cdots, x_m^0]$.

3.2.1 Theory of convergence of the numerical methods

Numerical method of the form (3.2.2) converges to a fixed point if, and only if, the spectral radius (ρ), of the Jacobian

$$J \equiv \frac{\partial G}{\partial X} = \begin{bmatrix} \frac{\partial g_1}{\partial x_1} & \frac{\partial g_1}{\partial x_2} & \cdots & \frac{\partial g_1}{\partial x_m} \\ \frac{\partial g_2}{\partial x_1} & \frac{\partial g_2}{\partial x_2} & \cdots & \frac{\partial g_2}{\partial x_m} \\ \vdots & \vdots & & \vdots \\ \frac{\partial g_m}{\partial x_1} & \frac{\partial g_m}{\partial x_2} & \cdots & \frac{\partial g_m}{\partial x_m} \end{bmatrix} \tag{3.2.4}$$

evaluated at the fixed point X^*, where ρ represents the multiplication of the eigenvalues (λ_j) and hence,

$$J^* = \frac{\partial G}{\partial X}|_{X=X^*}, \tag{3.2.5}$$

do not exceed unity. Which means

$$\rho(J^*) < 1. \tag{3.2.6}$$

where $G = [g_1, g_2, \cdots, g_m]^T$.

It then follows that; the numerical method is convergent if, and only if the condition

$$|\lambda_j| < 1, \quad \forall j \in \{1, 2, \cdots, m\} \tag{3.2.7}$$

is satisfied. Where $\lambda = [\lambda_1, \lambda_2, \cdots, \lambda_m]^T$ are the eigenvalues of the Jacobian at the critical point given by (3.2.5).

It can be concluded that, a fixed point is stable or attracting if, and only if, equation (3.2.6) is satisfied. In addition, it is unstable or repelling if, $\rho(J^*) > 1$ and is neutrally stable if, $\rho(J^*) = 1$.

3.2.2 An extension to the theory of convergence

In this part, I present a novel theory as an extension to the theory of convergence. The aim is to ensure that in the transient state the numerical solution will follow the stochastic nature of the problem and finally reach to a critical point at the steady state.

A numerical method is *monotonically convergent* whenever neither oscillation nor divergence exists in the transient part of the solution. A numerical method is *oscillatory convergent* whenever the transient part of the solution contain oscillations and, at a steady state, converges to a fixed point.

The conditions applied on the eigenvalues of the Jacobian at the trivial critical point include

$$\lambda_j \in \Re \quad and \quad 0 < \lambda_j < 1, \quad \forall j \in \{1, 2, \cdots, m\} \tag{3.2.8}$$

whenever the numerical method is monotonically convergent and

$$\lambda_j \in \Re \quad and \quad -1 < \lambda_j < 0 \quad \forall j \in \{1, 2, \cdots, m\} \tag{3.2.9}$$

whenever the numerical method is oscillatory convergent, otherwise divergent.

3.2.3 Time step estimations -a new technique

The aim is to estimate time step boundaries regarded as h-boundaries, with which the numerical solution converges monotonically, oscillatory or even diverges. This section introduces a novel approach to finding time step boundaries. This is to choose the largest possible time step in computational process.

So far, no attention has been paid to the estimation of time step (h). By default, it is usually taken as a small constant figure at around 0.01-0.2. Choosing small time steps will increase the number of iterations require to converge to the steady state. However, in some circumstances even 0.01 is not small enough and will cause chaos or divergence, which are not features of the system.

Eigenvalue (λ_j) is a function of time step (h) for $j = \{1, 2, \cdots, m\}$, therefore

$$\lambda_j = \psi_j(h) \tag{3.2.10}$$

gives

$$h = \psi_j^{-1}(\lambda_j) \tag{3.2.11}$$

where ψ_j^{-1} is a reverse function of ψ.

In the equation (3.2.8) substituting λ_j by its equivalent $\psi_j(h)$ gives

$$0 < \psi_j(h) < 1, \quad \forall j \in \{1, 2, \cdots, m\}, \tag{3.2.12}$$

therefore

$$0 < h < min\{\psi_j^{-1}(1)\}, \quad j = \{1, 2, \cdots, m\} \tag{3.2.13}$$

represents the h-boundary for monotonic convergence.

The same principle applies in computing h-boundary for oscillatory convergence. Therefore, in equation (3.2.9) substituting λ_j by its equivalent $\psi_j(h)$ gives

$$-1 < \psi_j(h) < 0, \quad \forall j \in \{1, 2, \cdots, m\} \tag{3.2.14}$$

adding (-1) to the above equation gives

$$\psi_j(h) \in \Re \quad and \quad 0 < \psi_j(h) + 1 < 1, \quad \forall j \in \{1, 2, \cdots, m\} \tag{3.2.15}$$

Let

$$\Omega_j(h) = \psi_j(h) - 1,$$

therefore

$$0 < \Omega_j(h) < 1, \quad \forall j \in \{1, 2, \cdots, m\},$$

therefore

$$0 < h < min\{\Omega_j^{-1}(1)\}, \quad j = \{1, 2, \cdots, m\} \tag{3.2.16}$$

represents h-boundaries for oscillatory convergent.

3.3 Numerical methods

In order to investigate the performance and accuracy of alternative method (see E. H. Twizell *et al.* [107] and F. Fakhr [46]) in solving system of first-

order non-linear ordinary differential equations (2.2.1), *Euler's* method is used as a base line.

3.3.1 Euler's method

The well known Euler's method for approximation of first-order ordinary differential equations may be extended to include system of first-order differential equations. Therefore, the initial-value problem

$$\begin{cases} \frac{dx_1(t)}{dt} \equiv f_1(t; x_1, x_2, \cdots x_m), & x_1(t_0) = x_1^0, \\ \frac{dx_2(t)}{dt} \equiv f_2(t; x_1, x_2, \cdots x_m), & x_2(t_0) = x_2^0, \\ \qquad\vdots & \qquad\vdots \\ \frac{dx_m(t)}{dt} \equiv f_m(t; x_1, x_2, \cdots x_m), & x_m(t_0) = x_m^0, \\ \qquad t > t_0 \end{cases}$$

is approximated at each step by recursive relationship based on Taylor's expansion of $X = [x_1, x_2, \cdots, x_m]^T$:

$$\begin{cases} x_1^{n+1} = x_1^n + hf_1(x_1^n, x_2^n, \cdots, x_m^n) \\ x_2^{n+1} = x_2^n + hf_2(x_1^n, x_2^n, \cdots, x_m^n) \\ \qquad\vdots \\ x_m^{n+1} = x_m^n + hf_m(x_1^n, x_2^n, \cdots, x_m^n) \\ \qquad n = 0, 1, 2, \cdots \end{cases}$$

where $x^n = x(t_n)$ and $t_n = t_0 + nh$.

The numerical solution goes from a transient to steady state whenever $x_j^n = x_j^{n+1} = x_j$ for all $j \in \{1, 2, \cdots, m\}$.

Therefore, at the steady state,

$$\begin{cases} x_1 = x_1 + hf_1(x_1, x_2, \cdots, x_m) \\ x_2 = x_2 + hf_2(x_1, x_2, \cdots, x_m) \\ \vdots \\ x_m = x_m + hf_m(x_1, x_2, \cdots, x_m) \end{cases}$$

after simplifications

$$\begin{cases} f_1(x_1, x_2, \cdots, x_m) = 0 \\ f_2(x_1, x_2, \cdots, x_m) = 0 \\ \vdots \\ f_m(x_1, x_2, \cdots, x_m) = 0 \end{cases}$$

proves that the fixed points of Euler's method are the same as the critical points of the system of ODE's (2.2.1) given by (2.2.2).

3.3.2 Alternative method

This section introduces *a general* form of the alternative numerical method (see E. H. Twizell *et al.* [107]), used by F. Fakhr [46] to solve systems of ordinary non-linear differential equations devised for the purpose of population modelling of the transmission dynamics of HIV/AIDS .

The derivatives at the left-hand side of the system (2.2.1) are approximated by equation (3.2.1).

Whenever f_j, $j \in \{1, 2, \cdots, m\}$ is a first order polynomial function of $x_1, x_2, \cdots, x_m$ the right-hand side of f_j is evaluated as follow

$$\frac{x_j^{n+1} - x_j^n}{h} = f_j(x_1^{n+1}, \cdots, x_j^{n+1}, x_{j+1}^n, \cdots, x_m^n), \quad n = 0, 1, 2, \cdots, \qquad (3.3.17)$$

Whenever f_j, $j \in \{1, 2, \cdots, m\}$ is a quotient of first order polynomials of

the form

$$f_j(x_1, x_2, \cdots, x_m) = \frac{\zeta_j(x_1, x_2, \cdots, x_m)}{\eta_j(x_1, x_2, \cdots, x_m)} \tag{3.3.18}$$

the right-hand side of f_j is evaluated as follow

$$\frac{x_j^{n+1} - x_j^n}{h} = \frac{\zeta_j(x_1^{n+1}, \cdots, x_j^{n+1}, x_{j+1}^n, \cdots, x_m^n)}{\eta_j(x_1^{n+1}, \cdots, x_{j-1}^{n+1}, x_j^n, \cdots, x_m^n)}, \quad n = 0, 1, 2, \cdots. \tag{3.3.19}$$

Using equations (3.3.17) and (3.3.19) in setting up the numerical method to solve the system of non-linear ordinary differential equations (2.2.1) gives

$$\begin{cases} \frac{x_1^{n+1} - x_1^n}{h} = f_1(x_1^{n+1}, x_2^n, x_3^n, \cdots, x_m^n), & n = 0, 1, 2, \cdots, \\ \frac{x_2^{n+1} - x_2^n}{h} = f_2(x_1^{n+1}, x_2^{n+1}, x_3^n, \cdots, x_m^n), & n = 0, 1, 2, \cdots, \\ \frac{x_3^{n+1} - x_3^n}{h} = f_3(x_1^{n+1}, x_2^{n+1}, x_3^{n+1}, \cdots, x_m^n), & n = 0, 1, 2, \cdots, \\ \vdots & \vdots \\ \frac{x_m^{n+1} - x_m^n}{h} = f_m(x_1^{n+1}, x_2^{n+1}, x_3^{n+1}, \cdots, x_m^{n+1}), & n = 0, 1, 2, \cdots \end{cases} \tag{3.3.20}$$

Which, after re-arranging gives

$$\begin{cases} x_1^{n+1} = g_1(x_1^n, x_2^n, x_3^n, \cdots, x_m^n), & n = 0, 1, 2, \cdots, \\ x_2^{n+1} = g_2(x_1^{n+1}, x_2^n, x_3^n, \cdots, x_m^n), & n = 0, 1, 2, \cdots, \\ x_3^{n+1} = g_3(x_1^{n+1}, x_2^{n+1}, x_3^n, \cdots, x_m^n), & n = 0, 1, 2, \cdots, \\ \vdots & \vdots \\ x_m^{n+1} = g_m(x_1^{n+1}, x_2^{n+1}, x_3^{n+1}, \cdots, x_{m-1}^{n+1} x_m^n), & n = 0, 1, 2, \cdots, \end{cases} \tag{3.3.21}$$

Substituting for $x_1^{n+1}, x_2^{n+1}, \cdots, x_m^{n+1}$ from (3.3.21) into the right-hand side of $g_2, g_3, \cdots, g_m$ gives

$$\begin{cases} x_1^{n+1} = g_1(x_1^n, x_2^n, x_3^n, \cdots, x_{m-1}^n, x_m^n), & n = 0, 1, 2, \cdots, \\ x_2^{n+1} = g_2(g_1, x_2^n, x_3^n, \cdots, x_{m-1}^n, x_m^n), & n = 0, 1, 2, \cdots, \\ x_3^{n+1} = g_3(g_1, g_2, x_3^n, \cdots, x_{m-1}^n, x_m^n), & n = 0, 1, 2, \cdots, \\ \vdots & \vdots \\ x_m^{n+1} = g_m(g_1, g_2, g_3, \cdots, g_{m-1}, x_m^n), & n = 0, 1, 2, \cdots, \end{cases} \tag{3.3.22}$$

giving

$$\begin{cases} x_1^{n+1} = g'_1(x_1^n, x_2^n, x_3^n, \cdots, x_m^n), & n = 0, 1, 2, \cdots, \\ x_2^{n+1} = g'_2(x_1^n, x_2^n, x_3^n, \cdots, x_m^n), & n = 0, 1, 2, \cdots, \\ x_3^{n+1} = g'_3(x_1^n, x_2^n, x_3^n, \cdots, x_m^n), & n = 0, 1, 2, \cdots, \\ \qquad\qquad \vdots & \qquad\qquad \vdots \\ x_m^{n+1} = g'_m(x_1^n, x_2^n, x_3^n, \cdots, x_m^n), & n = 0, 1, 2, \cdots. \end{cases} \tag{3.3.23}$$

Equations (3.3.21) are used for the implementation of the method while (3.3.23) are used for the analysis.

Therefore, the system of equations

$$\begin{cases} x_1 = g'_1(x_1, x_2, x_3, \cdots, x_m), \\ x_2 = g'_2(x_1, x_2, x_3, \cdots, x_m), \\ x_3 = g'_3(x_1, x_2, x_3, \cdots, x_m), \\ \vdots \\ x_m = g'_m(x_1, x_2, x_3, \cdots, x_m) \end{cases} \tag{3.3.24}$$

associated with (3.3.23) give the numerical method's fixed points. It is necessary to show that the numerical method fixed points are the same as critical point of the system of ODE's (2.2.1).

3.4 Conclusion

In this chapter an attempt has been made to provide an outline of the methods and computational techniques used for the solution of the system of first order non-linear ordinary differential equations devised to model transmission dynamics of HIV/AIDS throughout this thesis.

The speed and performance of the computational tools were significantly increased by choosing the suitable numerical method using the maximum

possible time step (h), bearing in mind the accuracy and stability. In addition, it eliminates the occurrence of the solution, which does not match the stochastic nature of the problem. This occurs whenever a large-scale model is to be analysed and solved.

Computational experience shows that solving large-scale problems is time consuming and expensive. Therefore, a maximum possible time step h is desired. Because as h increase, the number of iterations to converge to the steady state decreases. The theory of convergence and its novel extension are the keys to calculate the maximum time step h.

Chapter 4

Detailed analysis of some mathematical models of the transmission dynamics of HIV/AIDS

This chapter applies the algorithms and techniques described in Chapters 2 and 3 upon three existing models. In addition, both Euler's method and alternative method are used as solver engines in implementations. The accuracy and performance of the two numerical methods, over large time steps, are compared.

Section 4.2 describes a basic model stratifying the population into two groups of susceptibles and infectives. Section 4.3 describes the mathematical models predicting the transmission dynamics for longer periods of time. This model stratifies the population into three groups of susceptible, infective and full-blown AIDS patients. Section 4.4 stratifies the population into

five groups of susceptible, infectives who ultimately develop AIDS, infectives who do not develop AIDS, full-blown AIDS patients and non-infectious seropositives.

4.1 Introduction

Understanding the concept of the mathematical models used to estimate the transmission dynamics of HIV/AIDS is of great importance as they help to investigate the effect of the parameters influencing the spread of the disease. Changes in the population's sexual behaviour influences the spread of the disease. Mathematical models are used to estimate the effect of such changes on the transmission dynamics of HIV/AIDS. The transmission dynamics of HIV/AIDS is a stochastic problem, usually approximated deterministically (May and Anderson [79], Anderson *et al.* [5] and [8]).

The numerical methods proposed in this thesis will be solved using the Fourth Generation Programming Language (*Mathematica* Version 3.0).

4.2 A basic mathematical model

To avoid algebraic complications, a simple mathematical model is considered, which pay attention to the detailed analysis of the mathematical models and numerical methods (see Anderson *et al.* [5]).

Figure 4.2.1 is a flow diagram illustrating the flow of individuals entering and leaving different groups.

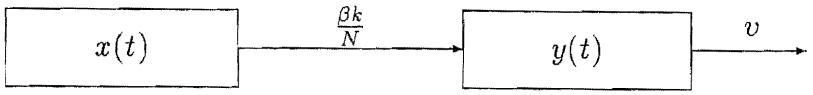

Figure 4.2.1: *A flow diagram illustrating the basic model.*

This model divides the total population $N(t)$, into two groups of susceptible and infected where,

$x(t)$: represents the number of susceptibles at time t,

$y(t)$: denotes the number of infected individuals at time t,

$N(t)$: represents the total population at time t,

$\frac{y(t)}{N(t)}$: is the probability of a randomly chosen sexual partner to be infected at time t,

$\frac{1}{v}$: denotes the mean incubation period, therefore

v : indicates the mean rate of withdrawal from the infected group per unit of time,

β : is the probability that a susceptible acquires the infection from a particular infected partner,

k : represents the average rate of new sexual partners acquired by an individual per unit of time.

Construction of the deterministic model is based on the system of ordinary differential equations

$$\begin{cases} \frac{dx(t)}{dt} = -\beta k x(t)\frac{y(t)}{N(t)}, & x(0) = x^0, \\ \frac{dy(t)}{dt} = \beta k x(t)\frac{y(t)}{N(t)} - vy(t), & y(0) = y^0, \\ \quad t > 0 \end{cases} \tag{4.2.1}$$

It is assumed that the incubation period of AIDS is the same as the HIV infectious period, and has the expectation of $\frac{1}{v}$. The appropriate form of $N(t)$ depends on the assumptions made about the pool of possible sexual partners. At one extreme this could be the whole population, so that $N(t) = N$, while if withdrawn individual cases play no further part in the spread of infection then $N(t) = x(t) + y(t)$.

4.2.1 Model analysis

The system of ordinary differential equations (4.2.1), will be analysed to ensure that it does not predict chaos or divergence when chaos or divergence are not features of the system. It has been assumed that $N(t) = x(t) + y(t)$, represents the total population as a dynamic variable. Substituting $N(t)$ by $x(t) + y(t)$ in equations (4.2.1) gives

$$\begin{cases} \frac{dx(t)}{dt} \equiv f_1(x,y) = -\beta k x(t)\frac{y(t)}{x(t)+y(t)}, & x(0) = x^0 \\ \frac{dy(t)}{dt} \equiv f_2(x,y) = \beta k x(t)\frac{y(t)}{x(t)+y(t)} - vy(t), & y(0) = y^0 \\ t > 0 \end{cases} \tag{4.2.2}$$

The steady state of (4.2.2) occurs whenever the time derivatives vanish as follows:

$$\begin{cases} \frac{dx}{dt} = 0 \\ \frac{dy}{dt} = 0 \end{cases}$$

The solution of the above non-linear algebraic equations gives the critical points

$$x^* \in \Re - \{0\}, \quad y^* = 0 \tag{4.2.3}$$

The number of susceptibles (x^*), is not fixed at any value, which means there are an infinite number of possible critical points. All the critical points

are trivial because at steady state ($t \to \infty$) there are no infected individual left in the population.

A critical point is stable if eigenvalues of the Jacobian (2.2.3), of the forms

$$J = \begin{bmatrix} \frac{\partial f_1}{\partial x} & \frac{\partial f_1}{\partial y} \\ \frac{\partial f_2}{\partial x} & \frac{\partial f_2}{\partial y} \end{bmatrix} \tag{4.2.4}$$

evaluated at the critical point (4.2.3) and are real and negative or complex with negative real part. The Jacobian associated with f_1, f_2 is the form of

$$J = \begin{bmatrix} -\frac{\beta k y^2}{(x+y)^2} & -\frac{\beta k x^2}{(x+y)^2} \\ \frac{\beta k y^2}{(x+y)^2} & \frac{\beta k x^2}{(x+y)^2} - v \end{bmatrix}.$$

The associated Jacobian at the trivial critical point, $x^* \neq 0, y^* = 0$ gives

$$J^* = \begin{bmatrix} 0 & -\beta k \\ 0 & \beta k - v \end{bmatrix},$$

the eigenvalues of which are the roots of the equation

$$Det(J^* - \lambda I) = \lambda[\lambda - (\beta k - v)] = 0,$$

where I is the 2×2 identity matrix. Therefore,

$$\lambda_1 = 0, \quad \lambda_2 = -\beta k + v.$$

λ_1 is fixed at zero. Therefore, the trivial critical point is neutrally stable whenever $\lambda_2 \leq 0$. Otherwise, the system is unstable. In other words the system is neutrally stable whenever $k \leq \frac{v}{\beta}$ and unstable for $k > \frac{v}{\beta}$. The unique value of

$$k^* = \frac{v}{\beta} \tag{4.2.5}$$

is regarded as the bifurcation parameter.

The bifurcation parameter is used to calculate the reproductive rate (2.3.8), of the form of

$$R = \frac{k}{k^*} = \frac{k\beta}{v}.$$

The reproductive rate (R) is the average number of secondary HIV cases made by one primary infected individual per unit of time.

Investigations show that whenever $R = 1$ the epidemic is in steady state and whenever $R < 1$ the epidemic is disappearing. The system above does not represent the population for $R > 1$ as there is no critical point present. This comes with the nature of the problem which does not allow immigration to the susceptible group. This causes susceptible population to shrink to zero as all individuals eventually acquire the virus and leave the susceptible group.

Stability properties of the model (4.2.1) is summarised in Table 4.1.

Table 4.1: *Stability properties of the trivial critical point*

Reproductive rate	Sexual partners	Trivial critical point
$R < 1$	$k < k^*$	stable
$R = 1$	$k = k^*$	neutrally stable
$R > 1$	$k > k^*$	non-existence

4.2.2 Numerical method *I*

Replacing the derivatives in (4.2.2) by their first-order, forward-difference approximations given by (3.2.1) and considering the right-hand side at the

base time level $t = t_n$ (Euler's method, see F. Fakhr [46]) gives

$$\begin{cases} \frac{x^{n+1}-x^n}{h} = -\beta k x^n \frac{y^n}{x^n+y^n}, \\ \frac{y^{n+1}-y^n}{h} = \beta k y^n \frac{x^n}{x^n+y^n} - v y^n, \end{cases} \tag{4.2.6}$$

with $n = 0, 1, 2, 3, \cdots$.

Rearranging the above equations to explicitly gives

$$\begin{cases} x^{n+1} \equiv g_1(x^n, y^n) = x^n + h[-\beta k x^n \frac{y^n}{x^n+y^n}], \\ y^{n+1} \equiv g_2(x^n, y^n) = y^n + h[\beta k y^n \frac{x^n}{x^n+y^n} - v y^n], \end{cases} \tag{4.2.7}$$

for $n = 0, 1, 2, \cdots$.

The numerical method is convergent if the solution finally] converges to a fixed point, which means at the steady state stage $x^n = x^{n+1} = x$ and $y^n = y^{n+1} = y$. Considering the associated equations

$$\begin{cases} x = g_1(x, y) = x + h[-\beta k x \frac{y}{x+y}] \\ y = g_2(x, y) = y + h[\beta k y \frac{x}{x+y} - v y], \end{cases} \tag{4.2.8}$$

gives fixed points

$$x^* \in \Re - \{0\}, \quad y^* = 0. \tag{4.2.9}$$

This shows that the fixed points are the same as the critical points (4.2.3). Therefore, the Jacobian of the form (3.2.4) evaluated at the trivial fixed point

$$J^* = J|_{[x^* \neq 0,\, y^* = 0]} = \begin{bmatrix} 1 & -hv\beta \\ 0 & 1 - h(v - k\beta) \end{bmatrix} \tag{4.2.10}$$

gives the eigenvalues

$$\lambda_1 = 1, \quad \lambda_2 = 1 - h(v - k\beta). \tag{4.2.11}$$

The first eigenvalue is equal to unity. Therefore, λ_2 is the only eigenvalue which rules the stability of the numerical method.

The numerical method will converge monotonically to the trivial fixed point if, and only if, equation (3.2.8) is satisfied, therefore

$$0 < \lambda_2 < 1$$

gives

$$0 < 1 - h(v - k\beta) < 1.$$

Therefore

$$0 < h < \frac{1}{v - k\beta}$$

is interpreted as the expected h-boundary for monotonic convergence.

The numerical method will oscillatory converge only if the equation (3.2.9) is satisfied. Therefore,

$$-1 < \lambda_2 < 0$$

gives

$$\frac{1}{v - k\beta} < h < \frac{2}{v - k\beta}$$

which is regarded as the h-boundary for oscillatory convergence.

For parameter values $\beta = 0.23$ and $v = \frac{1}{4.75}$ and various reproductive rates $0 < R \leq 1$, expected h-boundaries for monotonic convergence, oscillatory convergence and chaos or divergence are tabulated in Table 4.2.

For the initial values $x(0) = x^0 = 19900$ and $y(0) = y^0 = 100$ the steady state values of the numerical solution and real (observed) h-boundaries for monotonic convergence, oscillatory convergence and divergence are presented in Table 4.3.

For $R = 1$, after the time step of length $h = 0.2$ in the computation, the number of infected has shrunk to zero (to the nearest integer). The number of susceptibles (to the nearest integer 101), though further iterations show

Table 4.2: *Expected h-boundaries for numerical method I*

R	Monotonic convergence	Oscillatory convergence	chaos or Divergence
0.01	$0 < h \leq 4.8$	$4.8 < h \leq 9.6$	$h > 9.6$
0.10	$0 < h \leq 5.2$	$5.2 < h \leq 10.4$	$h > 10.4$
0.30	$0 < h \leq 6.7$	$6.7 < h \leq 13.5$	$h > 13.5$
0.50	$0 < h \leq 9.5$	$9.5 < h \leq 19.0$	$h > 19.0$
0.70	$0 < h \leq 15.8$	$15.8 < h \leq 31.6$	$h > 31.6$
0.90	$0 < h \leq 47.5$	$47.5 < h \leq 95.0$	$h > 95.0$
1.00	$0 < h < \infty$	——	——

that both infected y and susceptibles x continue to approach zero to the accuracy of the computer, with y approaching zero faster than x.

Statistical hypotheses show that there is no significant difference between columns of Table 4.2 and Table 4.3. In theory, when $R = 1$ the numerical method should converge to the fixed point regardless of the h value. However, in practice, the upper boundary for monotonic convergence is 950 years. However it may be considered as an infinity value for time step h because using very large time steps may not be required.

4.2.3 Numerical method *II*

The development of the numerical method *II* will be based on the alternative method, (see Section 3.3.2). Approximating the derivatives in (4.2.2) by

Table 4.3: *Fixed points and observed h-boundaries for numerical method I*

R	x	y	Monotonic convergence	Oscillatory convergence	chaos or Divergence
0.01	19899	0	$0 < h \leq 4.80$	$4.80 < h \leq 9.60$	$h > 9.60$
0.10	19889	0	$0 < h \leq 5.20$	$5.20 < h \leq 10.40$	$h > 10.40$
0.30	19857	0	$0 < h \leq 6.75$	$6.75 < h \leq 13.50$	$h > 13.50$
0.50	19801	0	$0 < h \leq 9.50$	$9.50 < h \leq 19.00$	$h > 19.00$
0.70	19670	0	$0 < h \leq 15.80$	$15.80 < h \leq 31.60$	$h > 31.60$
0.90	19027	0	$0 < h \leq 45.20$	$47.50 < h \leq 95.00$	$h > 95.00$
1.00	101	0	$0 < h \leq 950.00$	$950.00 < h \leq 1900.00$	$h > 1900.00$

(3.2.1) and evaluating the variables on the right hand side as follows

$$\begin{cases} \frac{x^{n+1}-x^n}{h} = -\beta k x^{n+1}\frac{y^n}{x^n+y^n}; & n = 0,1,2,\cdots, \\ \frac{y^{n+1}-y^n}{h} = \beta k y^{n+1}\frac{x^{n+1}}{x^{n+1}+y^n} - v y^{n+1}; & n = 0,1,2,\cdots, \end{cases} \tag{4.2.12}$$

gives, after re-arranging,

$$\begin{cases} x^{n+1} \equiv g_1(x^n, y^n) = \frac{x^n(x^n+y^n)}{x^n+(1+hk\beta)y^n}; & n = 0,1,2,\cdots, \\ y^{n+1} \equiv g_2(x^{n+1}, y^n) = \frac{y^n}{1+hv-\frac{hk\beta x^{n+1}}{x^{n+1}+y^n}}; & n = 0,1,2,\cdots. \end{cases} \tag{4.2.13}$$

After substituting x^{n+1}, for g_2 it gives the set of equations used in the analysis detailed below.

It is not difficult to show that the fixed point of the numerical method *II* is the same as the critical point (4.2.3) of the system of ODE's (4.2.12).

It is shown before that the trivial critical point is stable if, and only if, $k < k^*$. The eigenvalues of the Jacobian associated with the method at the

Table 4.4: *Fixed points and observed h-boundaries for numerical method II*

R	x^*_{max}	x^*_{min}	y^*	Monotonic convergence
0.01	19899	187	0	$0 < h < \infty$
0.1	19889	19	0	$0 < h < \infty$
0.3	19858	6	0	$0 < h < \infty$
0.5	19799	4	0	$0 < h < \infty$
0.7	19666	3	0	$0 < h < \infty$
0.9	19020	2	0	$0 < h < \infty$
1	100	2	0	$0 < h < \infty$

trivial fixed point (4.2.3) are

$$\lambda_1 = 1, \quad \lambda_2 = \frac{1}{1 + h(v - k\beta)}$$

It is clear that λ_2 is positive and less than unity regardless of h whenever $k < k^*$. Therefore, it is expected that numerical method *II* converge to the fixed point for any value of h. Using the same parameter values and initial conditions as the numerical method *I* in Section 4.2.2, fixed points and expected h-boundaries are presented in Table 4.4.

The numerical results represented in Table 4.4 show that the numerical method *II* is monotonically convergent for considerably large values of h. On the other hand, as h increases to much larger values, the accuracy of the numerical method is suspected.

Comparing Table 4.3 and 4.4 shows that the numerical method *II* converges much faster than the numerical method *I*.

4.3 Mathematical models used for longer periods of time

To devise mathematical models to predict the dynamics population for longer periods of time it is necessary to allow immigration to the group of susceptibles and death from all groups.

Figure 4.3.1 is a flow diagram illustrating the model describing the flows of the individuals to and from all groups.

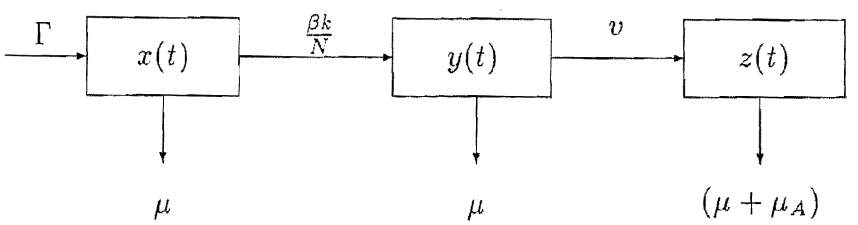

Figure 4.3.1: *A flow diagram illustrating the model for longer periods of time.*

In addition to the variables and parameters defined in Section 4.2, let

Γ: be the immigration rate to the susceptible group,

μ: present the natural mortality rate,

μ_A: be the additional mortality rate due to AIDS occurring within the AIDS patients group and

$z(t)$: represent the number of full blown AIDS patients at time t.

The system of ordinary differential equations simulating Figure 4.3.1 is

modified as follows

$$\begin{cases} \frac{dx(t)}{dt} \equiv f_1(x,y,z) = \Gamma - \beta k x(t)\frac{y(t)}{N(t)} - \mu x(t), & x(0) = x^0 \\ \frac{dy(t)}{dt} \equiv f_2(x,y,z) = \beta k x(t)\frac{y(t)}{N(t)} - (v+\mu)y(t), & y(0) = y^0 \\ \frac{dz(t)}{dt} \equiv f_3(x,y,z) = vy(t) - (\mu + \mu_A)z(t), & z(0) = z^0 \\ \qquad t > 0 \end{cases} \tag{4.3.14}$$

where

$$N(t) = x(t) + y(t) + z(t).$$

It is assumed that diagnosed AIDS patients are withdrawn from the population; as long as the number of AIDS cases ($z(t)$) is relatively small, their inclusion in $N(t)$ would have little effect.

It can also be assumed that the immigration of susceptibles occurs at a rate proportional to the total population $N(t)$. This means

$$\Gamma = \Gamma_0 N(t)$$

rather than being a constant. Neither modification will have much effect in the initial stage of the epidemic, and as the epidemic of AIDS gets underway it is quite plausible that changing behaviour could have the effect of reducing the rate of immigration into the homogeneously mixing male homosexual community being modelled.

The behaviour of this model is explored in the following section in addition to the investigation of the effects of the sexual behaviour changes on the transmission dynamics of the disease.

4.3.1 Model analysis

The system of equations under investigation given by (4.3.14) will be analysed to ensure that it does not predict chaos or divergence in the system, when

chaos or divergence is not a feature of the system.

The steady state of (4.3.14) occurs when the time derivatives vanish. Therefore, $\frac{dx}{dt} = \frac{dy}{dt} = \frac{dz}{dt} = 0$ gives the critical points

$$X_1{}^* = \left[\begin{array}{ccc} \frac{\Gamma}{\mu}, & 0, & 0 \end{array} \right]^T \tag{4.3.15}$$

and

$$X_2{}^* = \left[\begin{array}{ccc} \frac{\Gamma(v+\mu+\mu_A)}{k\beta\mu-\mu_A(v-k\beta)}, & \frac{\Gamma(v-k\beta+\mu)(\mu+\mu_A)}{(v+\mu)[\mu_A(v-k\beta)-k\beta\mu]}, & \frac{v\Gamma(v-k\beta+\mu)}{(v+\mu)[\mu_A(v-k\beta)-k\beta\mu]} \end{array} \right]^T. \tag{4.3.16}$$

The first equilibrium/critical point (4.3.15) is trivial because as $t \to \infty$ there will be no exposed or infectious individual left in the population.

The stability of the critical points $X_1{}^*$ and $X_2{}^*$ is examined by generating the Jacobian (J), of the form (2.2.3), at the trivial critical point $J_1^* = J|_{X=X_1{}^*}$. Therefore

$$J_1^* = \left[\begin{array}{ccc} -\mu & -k\beta & 0 \\ 0 & k\beta-\mu-v & 0 \\ 0 & v & -\mu-\mu_A \end{array} \right].$$

The determinant of the Jacobian, associated with (4.3.14) at the critical points (4.3.15) and (4.3.16) are given by

$$\begin{aligned} |J_1^*| &= -\mu(v-k\beta+\mu)(\mu+\mu_A), \\ |J_2^*| &= -\frac{(v+\mu)(\mu+\mu_A)(v-k\beta+\mu)[\mu_A(v-k\beta)-\mu k\beta]}{k\beta(v+\mu+\mu_A)} \end{aligned} \tag{4.3.17}$$

respectively.

The determinant of the Jacobian at a particular critical point is the product of its eigenvalues. Therefore, when the determinant is equal to zero,

at least one of the eigenvalues of the Jacobian is equal to zero. This means that the particular critical point is neutrally stable.

The determinant of J_1^*, represented by $|J_1^*|$, vanishes when $k = k_1^* = \frac{v+\mu}{\beta}$. Also, the determinant of J_2^* represented by $|J_2^*|$ vanishes whenever $k = k_1^* = \frac{v+\mu}{\beta}$ and $k = k_2^* = \frac{v\mu_A}{\beta(\mu+\mu_A)}$. The bifurcation parameter is unique, therefore to identify the bifurcation parameter of the system, the eigenvalues of J_1^* and J_2^* will be examined simultaneously.

At the trivial critical point (4.3.15) the eigenvalues of J_1^* are the roots of the equation

$$D(\lambda) = (\lambda + \mu)(\lambda - k\beta + \mu + v)(\lambda + \mu + \mu_A).$$

Therefore,

$$\lambda_1 = -\mu, \quad \lambda_2 = -\mu - v + k\beta, \quad \lambda_3 = -\mu - \mu_A$$

are the eigenvalues of the trivial critical point (4.3.15).

The eigenvalues of J_1^* are real and negative whenever $k < k_1^*$, which means that the trivial critical point $(X_1{}^*)$ is stable and whenever $k > k_1^*$ the trivial critical point is unstable. The stability properties of the model is summarised in Table 4.5.

Table 4.5 shows that there is only one unique value of k (in this case $k = k_1^*$). This will be regarded as the bifurcation parameter of the system of ordinary differential equations. Therefore, the reproductive rate

$$R = \frac{k}{k_1^*} = \frac{k\beta}{v + \mu}.$$

For $R < 1$ all the eigenvalues of the Jacobian at the trivial critical point are negative real numbers, meaning that the trivial critical point is stable and for $R > 1$ all the eigenvalues of the non-trivial critical point are negative

Table 4.5: *Stability analysis for the long-time period model*

	$k < k_2^*$	$k = k_2^*$	$k_2^* < k < k_1^*$	$k = k_1^*$	$k > k_1^*$
$\lvert J_1^* \rvert$	-	-	-	0	+
x_1^*	stable	stable	stable	neutrally stable	unstable
$\lvert J_2^* \rvert$	-	0	+	0	-
x_2^*	unstable	∞	unstable	neutrally stable	stable

Table 4.6: *Stability properties of the long-time period model*

		Trivial critical point	Non-trivial critical point
$R < 1$	$k < k_1^*$	stable	unstable
$R = 1$	$k = k_1^*$	neutrally stable	neutrally stable
$R > 1$	$k > k_1^*$	unstable	stable

real numbers or complex with negative real part, which means that the non-trivial critical point is stable. Finally, whenever $R = 1$ the non-trivial and trivial critical points coincides, which is neutrally stable.

Overall, both critical points of the system (4.3.14) exchange their stability properties as k passes through k_1^* or equally as R passes through unity. This is summarised in Table 4.6.

By using the parameter values $\beta = 0.23$, $\Gamma = \frac{4000}{3}$, $v = \frac{1}{4.75}$, $\mu = \frac{1}{32}$ and $\mu_A = 1$ the steady state solution for populations with different levels of the sexual activity (or reproductive rate) are summarised in Table 4.7.

Table 4.7 indicates the susceptibles (x^*), infected (y^*) and AIDS cases (z^*) change rapidly, whenever reproductive rate (R) increase from 1 to 2.

Table 4.7: *Steady state solution for the long-time period model*

R	k	x^*	y^*	z^*
50.0	52.60	135	5497	1122
20.0	21.00	347	5470	1117
10.0	10.50	725	5421	1107
5.0	5.30	1598	5308	1084
2.0	2.10	5746	4772	974
1.0	1.00	42667	0	0
0.9	0.95	42667	0	0

4.3.2 Numerical method *I*

Replacing the derivatives in (4.3.14) by their first-order, forward-difference approximations given by (3.2.1) and considering the right hand side at the base time level (Euler's method) gives,

$$\begin{cases} \frac{x^{n+1}-x^n}{h} = \Gamma - \beta k x^n \frac{y^n}{x^n+y^n+z^n} - \mu x^n, \\ \frac{y^{n+1}-y^n}{h} = \beta k y^n \frac{x^n}{x^n+y^n+z^n} - (v+\mu) y^n, \\ \frac{z^{n+1}-z^n}{h} = v y^n - (\mu+\mu_A) z^n, \end{cases} \tag{4.3.18}$$

for $n = 0, 1, 2, 3, \cdots$.

Rearranging the above equations to find, x^{n+1}, y^{n+1} and z^{n+1} explicitly gives,

$$\begin{cases} x^{n+1} \equiv g_1(x^n, y^n, z^n) = x^n + h[\Gamma - \beta k x^n \frac{y^n}{x^n+y^n+z^n} - \mu x^n], \\ y^{n+1} \equiv g_2(x^n, y^n, z^n) = y^n + h[\beta k y^n \frac{x^n}{x^n+y^n+z^n} - (v+\mu) y^n], \\ z^{n+1} \equiv g_3(x^n, y^n, z^n) = z^n + h[v y^n - (\mu+\mu_A) z^n], \end{cases} \tag{4.3.19}$$

for $n = 0, 1, 2, 3, \cdots$.

The numerical method is convergent if the numerical solution finally converge to a fixed point, which means at steady state $x^n = x^{n+1} = x$, $y^n = y^{n+1} = y$ and $z^n = z^{n+1} = z$. Therefore, equations

$$\begin{cases} x = g_1(x,y,z) = x + h[\Gamma - \beta k x \frac{y}{x+y+z} - \mu x], \\ y = g_2(x,y,z) = y + h[\beta k y \frac{x}{x+y+z} - (v+\mu)y], \\ z = g_3(x,y,z) = z + h[vy - (\mu+\mu_A)z], \end{cases} \tag{4.3.20}$$

give the numerical method fixed points. It is easy to show that the fixed points of the numerical method are the same as the critical points of the system (4.3.14).

The eigenvalues of the Jacobian of the form (3.2.4) evaluated at the trivial critical point

$$J^* = J|_{X=X_1^*} = \begin{bmatrix} 1-h\mu & -hk\beta & 0 \\ 0 & 1+h(k\beta - v - \mu) & 0 \\ 0 & hv & 1-h(\mu+\mu_A) \end{bmatrix},$$

are

$$\lambda_1 = 1 - h\mu, \;\; \lambda_2 = 1 - h(v + \mu - k\beta), \;\; \lambda_3 = 1 - h(\mu + \mu_A) \tag{4.3.21}$$

The numerical method will converge monotonically to the fixed point if, and only if, the equation (3.2.8) is satisfied. Therefore,

$$0 < \lambda_i < 1, \;\; \forall i \in \{1,2,3\}$$

gives

$$0 < 1 - hv < 1, \;\; 0 < 1 - h(v + \mu - k\beta) < 1, \;\; 0 < 1 - h(\mu + \mu_A) < 1,$$

and

$$0 < h < min(\frac{1}{v}, \frac{1}{v + \mu - k\beta}, \frac{1}{\mu + \mu_A})$$

is the expected h-boundary for monotonic convergence.

The numerical method is oscillatory convergent if, and only if, equation (3.2.9) is satisfied. Therefore,

$$-1 < \lambda_i < 0, \quad \forall i \in \{1, 2, 3\}$$

gives

$$-1 < 1 - hv < 0, \quad -1 < 1 - h(v + \mu - k\beta) < 0, \quad -1 < 1 - h(\mu + \mu_A) < 0$$

and

$$min(\frac{1}{v}, \frac{1}{v + \mu - k\beta}, \frac{1}{\mu + \mu_A}) < h < min(\frac{2}{v}, \frac{2}{v + \mu - k\beta}, \frac{2}{\mu + \mu_A})$$

is regarded as the expected h-boundary for oscillatory convergence.

These principles lead to the construction of Table 4.8. This table represents the expected h-boundaries for monotonic convergence , oscillatory convergence and chaos or divergence.

Table 4.8 shows that as R decreases, upper limit of h-boundaries increases, therefore bigger time steps may be chosen for populations with relatively smaller reproductive rate (R), which means less number of iterations to converge.

With the same parameter values as used in Section 4.3.1 and the initial values $x(0) = x^0 = 94300$, $y(0) = y^0 = 5000$ and $z(0) = z^0 = 200$, the real (observed) h-boundaries of the numerical method I for monotonic convergence, oscillatory convergence and divergence are presented in Table 4.9.

Statistical hypothesis shows that there is no significant difference between the columns of Table 4.8 and Table 4.9 representing expected and observed h-boundaries. Therefore, it can be concluded that the theory of convergence matches the computational results.

Table 4.8: *Expected h-boundaries for the numerical method I*

R	k	Monotonic convergence	Oscillatory convergence	Divergence
50.0	50.6	$0 < h \leq 0.104$	$0.104 < h \leq 0.208$	$h > 0.208$
20.0	20.0	$0 < h \leq 0.278$	$0.278 < h \leq 0.557$	$h > 0.557$
10.0	10.5	$0 < h \leq 0.671$	$0.67 < h \leq 1.340$	$h > 1.340$
5.0	5.3	$0 < h \leq 1.116$	$1.12 < h \leq 2.240$	$h > 2.240$
2.0	2.1	$0 < h \leq 0.994$	$0.994 < h \leq 1.988$	$h > 1.988$
1.0	1.0	$0 < h \leq 0.969$	$0.969 < h \leq 1.939$	$h > 1.939$
0.9	0.95	$0 < h \leq 0.969$	$0.969 < h \leq 1.939$	$h > 1.939$

Table 4.9: *Observed h-boundaries for the numerical method I*

R	k	Monotonic convergence	Oscillatory convergence	Divergence
50.0	50.6	$0 < h \leq 0.094$	$0.094 < h \leq 0.207$	$h > 0.207$
20.0	21.0	$0 < h \leq 0.275$	$0.275 < h \leq 0.557$	$h > 0.557$
10.0	10.5	$0 < h \leq 0.571$	$0.571 < h \leq 1.180$	$h > 1.180$
5.0	5.3	$0 < h \leq 1.105$	$1.105 < h \leq 1.991$	$h > 1.991$
2.0	2.1	$0 < h \leq 0.992$	$0.992 < h \leq 1.954$	$h > 1.954$
1.0	1.0	$0 < h \leq 0.954$	$0.954 < h \leq 1.921$	$h > 1.921$
0.9	0.95	$0 < h \leq 0.954$	$0.954 < h \leq 1.921$	$h > 1.921$

4.3.3 Numerical method *II*

The development of the numerical method *II* will be based on the alternative method, (see Section 3.3.2). Approximating the derivatives in (4.3.14) by (3.2.1), and evaluating the variables on the right hand side of (4.3.14) as follows

$$\begin{cases} \frac{x^{n+1}-x^n}{h} = \Gamma - \beta k x^{n+1}\frac{y^n}{x^n+y^n+z^n} - \mu x^{n+1}, \\ \frac{y^{n+1}-y^n}{h} = \beta k y^{n+1}\frac{x^{n+1}}{x^{n+1}+y^n+z^n} - (v+\mu)y^{n+1}, \\ \frac{z^{n+1}-z^n}{h} = v y^{n+1} - (\mu+\mu_A)z^{n+1}, \end{cases} \tag{4.3.22}$$

for $n = 0, 1, 2, \cdots$. After re-arranging, gives

$$\begin{cases} x^{n+1} \equiv g_1(x^n, y^n, z^n) = \frac{\Gamma h + x^n}{1+\mu h + \frac{hk\beta y^n}{x^n+y^n+z^n}}, \\ y^{n+1} \equiv g_2(x^{n+1}, y^n, z^n) = \frac{y^n}{1+h(\mu+v-\frac{k\beta x^{n+1}}{x^{n+1}+y^n+z^n})}, \\ z^{n+1} \equiv g_3(x^{n+1}, y^{n+1}, z^n) = \frac{z^n+hvy^{n+1}}{1+h(\mu+\mu_A)}, \end{cases} \tag{4.3.23}$$

for $n = 0, 1, 2, \cdots$.

After substituting for x^{n+1} and y^{n+1} gives a set of equations used in the analysis detailed below.

It is possible to show that the fixed points of the numerical method *II* are the same as critical points (4.3.15) and (4.3.16) of the system of ODEs (4.3.14).

The eigenvalues of the Jacobian associated with (4.3.23) at the trivial critical point (4.3.15) are

$$\lambda_1 = \frac{1}{1+h(v+\mu-k\beta)}, \quad \lambda_2 = \frac{1}{1+h\mu}, \quad \lambda_3 = \frac{1}{1+h(\mu+\mu_A)}$$

For $k < k_1^*$, eigenvalues $\lambda_{1,2,3}$ are positive and less than unity regardless of the h value. This means that the numerical method is expected to converge for very big values of h.

For $k = k_1^*$, $\lambda_1 = 1$, this means that the numerical solution is neutrally stable.

For the non-trivial fixed/critical point, it is not possible to present the analysis of the numerical method parametrically, as they are very large algebraic expressions. By using the same parameter values as used in Section 4.3.2, Table 4.10 is generated to indicate the expected h-boundaries for monotonic, oscillatory convergence and chaos or divergence.

It is expected that whenever $0 < \lambda_i < 1$, the numerical method converge monotonically and whenever $-1 < \lambda_i < 0$, the numerical solution exhibits oscillatory convergence, for $i = \{1, 2, 3\}$. (Note that all the h-boundary values are rounded down to make sure that the eigenvalues do not exceed unity.)

Table 4.11 represents the real (observed) h-boundaries for monotonic and oscillatory convergence and chaos and divergence. The initial values $x(0) = x^0 = 94300$, $y(0) = y^0 = 5000$ and $z(0) = z^0 = 200$ were used to generate computational results.

For $R > 1$, the statistical hypotheses show some minor differences between the columns of Tables 4.10 and 4.11.

It can be concluded that in some cases numerical results are inconsistent with the theoretical predictions.

Table 4.10: *Expected h-boundaries for the the numerical method II*

R	k	Monotonic convergence	Oscillatory convergence	Divergence
50.0	52.60	$0 < h \leq 4.23$	$4.23 < h \leq 8.30$	$h > 8.30$
20.0	21.00	$0 < h \leq 4.40$	$4.40 < h \leq 8.37$	$h > 8.37$
10.0	10.50	$0 < h \leq 4.72$	$4.72 < h \leq 8.57$	$h > 8.57$
5.0	5.30	$0 < h \leq 5.40$	$5.40 < h \leq 9.24$	$h > 9.24$
2.0	2.10	$0 < h \leq 8.66$	$8.66 < h \leq 13.85$	$h > 13.85$
1.0	1.00	$0 < h < \infty$	——	——
0.9	0.95	$0 < h < \infty$	——	——

Table 4.11: *Observed h-boundaries for the numerical method II*

R	k	Monotonic convergence	Oscillatory convergence	Divergence
50.0	50.6	$0 < h \leq 0.08$	$0.08 < h \leq 0.13$	$h > 0.13$
20.0	21.0	$0 < h \leq 0.22$	$0.22 < h \leq 0.37$	$h > 0.37$
10.0	10.5	$0 < h \leq 0.47$	$0.47 < h \leq 0.74$	$h > 0.74$
5.0	5.3	$0 < h \leq 1.10$	$1.10 < h \leq 1.70$	$h > 1.70$
2.0	2.1	$0 < h \leq 2.00$	$2.00 < h \leq 7.30$	$h > 7.30$
1.0	1.0	$0 < h < \infty$	——	——
0.9	0.95	$0 < h < \infty$	——	——

4.4 Mathematical models of two infected groups

This model separates the infected population into two groups, according to whether or not they ultimately develop AIDS (Anderson *et al.* [8] and Van *et al.* [109]). This admits the possibility of allowing the mean incubation period for AIDS to be different from the mean infectious period among those seropositives who do not develop AIDS.

Figure 4.4.1 is a flow diagram illustrating the model.

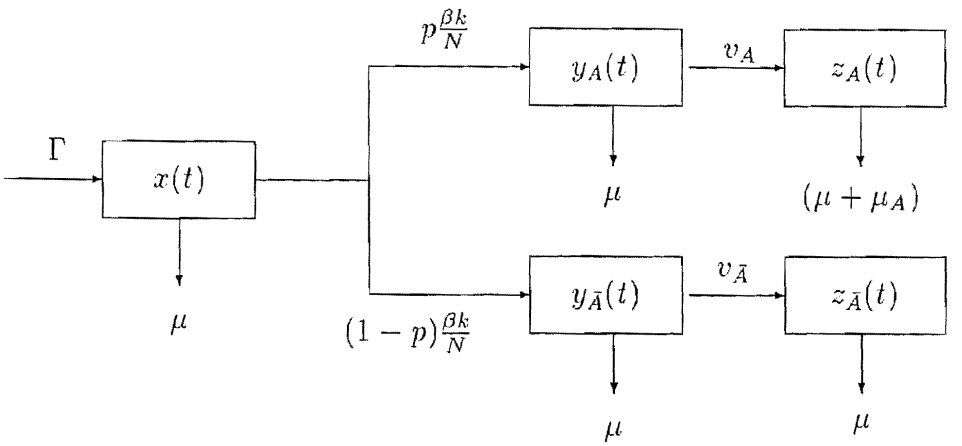

Figure 4.4.1: *A flow diagram illustrating the model for two infected groups.*

The additional parameters considered for this model are as follows:

p: the proportion of the infected individuals who finally develop AIDS,

$\frac{1}{v_A}$: the mean of incubation period for infected who develop AIDS,

$\frac{1}{v_{\bar{A}}}$: the mean of infectious period of seropositives who do not develop AIDS.

Moreover, the additional variables are

$y_A(t)$: the number of infected who ultimately develop AIDS up to time t,

$y_{\bar{A}}(t)$: the number of infected who do not develop AIDS up to time t,

$z_A(t)$: the number of AIDS cases up to time t,

$z_{\bar{A}}(t)$: the number of non-infectious seropositives up to time t.

The system of ordinary differential equations for a deterministic approximation of the Figure 4.4.1 is as follows:

$$\begin{cases} \frac{dx(t)}{dt} \equiv f_1(x, y_A, y_{\bar{A}}, z_A, z_{\bar{A}}) = \Gamma - \beta k x(t) \frac{y_A(t)+y_{\bar{A}}(t)}{N(t)} - \mu x(t), \\ \frac{dy_A(t)}{dt} \equiv f_2(x, y_A, y_{\bar{A}}, z_A, z_{\bar{A}}) = p\beta k x(t) \frac{y_A(t)+y_{\bar{A}}(t)}{N(t)} - (\mu + v_A) y_A(t), \\ \frac{dy_{\bar{A}}(t)}{dt} \equiv f_3(x, y_A, y_{\bar{A}}, z_A, z_{\bar{A}}) = (1-p)\beta k x(t) \frac{y_A(t)+y_{\bar{A}}(t)}{N(t)} - (\mu + v_{\bar{A}}) y_{\bar{A}}(t), \\ \frac{dz_A(t)}{dt} \equiv f_4(x, y_A, y_{\bar{A}}, z_A, z_{\bar{A}}) = v_A y_A(t) - (\mu + \mu_A) z_A(t), \\ \frac{dz_{\bar{A}}(t)}{dt} \equiv f_5(x, y_A, y_{\bar{A}}, z_A, z_{\bar{A}}) = v_{\bar{A}} y_{\bar{A}}(t) - \mu z_{\bar{A}}(t), \\ \qquad\qquad t > 0 \\ x(0) = x^0, \;\; y_A(0) = y_A^0, \;\; y_{\bar{A}}(0) = y_{\bar{A}}^0, \;\; z_A(0) = z_A^0, \;\; z_{\bar{A}}(0) = z_{\bar{A}}^0 \end{cases} \tag{4.4.24}$$

where $N(t) = x(t) + y_A(t) + y_{\bar{A}}(t) + z_A(t) + z_{\bar{A}}(t)$ seems most appropriate.

So far, the population has been taken to be closed, with attention being concentrated on the initial stage of the spread of the infection.

4.4.1 Model analysis

The system of equations under investigation given by (4.4.24) will be analysed to ensure that it does not predict chaos or divergence in the system, when chaos or divergence are not features of the system.

The steady state of the system (4.4.24), occurs when the time derivatives vanish (2.2.1), that is, $\frac{dx}{dt} = \frac{dy_A}{dt} = \frac{dy_{\bar{A}}}{dt} = \frac{dz_A}{dt} = \frac{dz_{\bar{A}}}{dt} = 0$ giving the critical points

$$x^* = \tfrac{\Gamma}{\mu}, \;\; y_A^* = 0, \;\; y_{\bar{A}}^* = 0, \;\; z_A^* = 0, \;\; z_{\bar{A}}^* = 0 \tag{4.4.25}$$

and

$$x^* = \frac{\Gamma(\mu+v_{\bar{A}})[\mu(\mu+\mu_A)+v_A[\mu+\mu_A(1-p)]]}{\mu[v_A[\mu_A[k\beta(1-p)-p(\mu+v_{\bar{A}})]+k\beta\mu(1-p)]+k\beta(\mu+\mu_A)(\mu+pv_{\bar{A}})]},$$

$$y_A^* = \frac{\Gamma p(\mu+\mu_A)[\mu(\mu-k\beta)+v_A[\mu-k\beta(1-p)]+v_{\bar{A}}(\mu+v_A-k\beta p)]}{(\mu+v_A)[v_A[\mu_A[p(\mu+v_{\bar{A}})-k\beta(1-p)]-k\beta\mu(1-p)]-k\beta(\mu+pv_{\bar{A}})(\mu+\mu_A)]},$$

$$y_{\bar{A}}^* = \frac{\Gamma(1-p)(\mu+\mu_A)[\mu(\mu-k\beta)+v_A[\mu-k\beta(1-p)]+v_{\bar{A}}(\mu+v_A-k\beta p)]}{(\mu+v_{\bar{A}})[v_A[\mu_A[p(\mu+v_{\bar{A}})-k\beta(1-p)]-k\beta\mu(1-p)]-k\beta(\mu+pv_{\bar{A}})(\mu+\mu_A)]}, \tag{4.4.26}$$

$$z_A^* = \frac{\Gamma pv_A[\mu(\mu-k\beta)+v_A[\mu-k\beta(1-p)]+v_{\bar{A}}(\mu+v_A-kp\beta)]}{(\mu+v_A)[v_A[\mu_A[k\beta(1-p)-p(\mu+v_{\bar{A}})]+k\beta\mu(1-p)]+k\beta(\mu+\mu_A)(\mu+pv_{\bar{A}})]},$$

$$z_{\bar{A}}^* = \frac{\Gamma(1-p)(\mu+\mu_A)v_{\bar{A}}[\mu(\mu-k\beta)+v_A[\mu-k\beta(1-p)]+v_{\bar{A}}(\mu+v_A-k\beta p)]}{\mu(\mu+v_{\bar{A}})[v_A[\mu_A[k\beta(1-p)-p(\mu+v_{\bar{A}})]+k\beta\mu(1-p)]+k\beta(\mu+\mu_A)(\mu+pv_{\bar{A}})]},$$

the first equilibrium/critical point (4.4.25) is trivial, as there are no infectious individuals at the steady state.

The stability of the critical points (4.4.25) and (4.4.26) will be examined. This is achieved by generating the Jacobian of the form (2.2.3), evaluated at the trivial critical point. The Jacobian associated with (4.4.24) at the trivial critical point (4.4.25) is given by

$$J_1^* = \begin{bmatrix} -\mu & -k\beta & -k\beta & 0 & 0 \\ 0 & k\beta p-\mu-v_A & k\beta p & 0 & 0 \\ 0 & k\beta(1-p) & k\beta(1-p)-\mu-v_{\bar{A}} & 0 & 0 \\ 0 & v_A & 0 & -\mu-\mu_A & 0 \\ 0 & 0 & v_{\bar{A}} & 0 & -\mu \end{bmatrix}.$$

The determinant of the Jacobian vanishes when

$$k = k^* = \frac{(\mu+v_A)(\mu+v_{\bar{A}})}{\beta[\mu+v_A(1-p)+v_{\bar{A}}p]} \tag{4.4.27}$$

This unique value of k (4.4.27) is regarded as the bifurcation parameter of the model equations.

Therefore, the total reproductive rate of the form (2.3.8) is given by

$$R = \frac{k}{k^*} = \frac{k\beta[\mu + v_A(1-p) + v_{\bar{A}}p]}{(\mu + v_A)(\mu + v_{\bar{A}})}$$

Note that this model involves with two groups of infectives known as y_A, $y_{\bar{A}}$. Therefore the total reproductive rate is

$$R = R_A + R_{\bar{A}}.$$

Investigation shows that

$$R = \frac{k\beta[\mu(1-p+p) + v_A(1-p) + v_{\bar{A}}p]}{(\mu + v_A)(\mu + v_{\bar{A}})} = \frac{k\beta[(\mu + v_A)(1-p) + (\mu + v_{\bar{A}})p]}{(\mu + v_A)(\mu + v_{\bar{A}})}$$

followed by

$$R = p\frac{\beta k}{\mu + v_A} + (1-p)\frac{\beta k}{\mu + v_{\bar{A}}}.$$

Therefore, $R_A = p\frac{\beta k}{\mu + v_A}$: is the reproductive rate of infected who ultimately develop AIDS, and

$R_{\bar{A}} = (1-p)\frac{\beta k}{\mu + v_{\bar{A}}}$: is the reproductive rate of the infected group who do not develop AIDS.

The actual balance between the two terms of the overall reproductive rate will depend on p. It is possible to allow the infectivity parameter β to differ between two groups of infected, which also affects the balance.

Overall, both critical points of the system (4.4.24) exchange their stability properties as R passes through unity which has been summarised in Table 4.12.

Assuming $p = 0.7$ meaning that 70% of the HIV positive individuals develop full blown AIDS, $\beta = 0.23$ is the probability of a susceptible individual catching the virus per sexual partner. Moreover, $v_A = \frac{1}{4.75}$ means that the average incubation period of the infected individuals who ultimately develop

Table 4.12: *Stability properties of the critical points*

	Trivial critical point	Non-trivial critical point
$R < 1$	stable	unstable
$R = 1$	neutrally stable	neutrally stable
$R > 1$	unstable	stable

Table 4.13: *Steady state solutions for double-infected model*

R	k	x^*	y_A^*	$y_{\bar{A}}^*$	$y_A^* + y_{\bar{A}}^*$	z_A^*	$z_{\bar{A}}^*$	$z_A^* + z_{\bar{A}}$
50.0	36.5	353	3828	4051	7879	782	8643	9425
20.0	14.6	899	3779	3999	7778	771	8531	9302
15.0	11.0	1211	3750	3969	7720	766	8468	9234
10.0	7.3	1854	3693	3908	7601	754	8336	9090
5.0	3.6	3958	3502	3706	7208	715	7907	8622
2.0	1.4	12384	2740	2899	5639	559	6185	6744
1.0	0.7	42667	0	0	0	0	0	0
0.8	0.6	42667	0	0	0	0	0	0

AIDS is 4.75 years. $v_{\bar{A}} = \frac{1}{15}$ means that the infected population who do not develop AIDS are sexually active for 15 years. The value $\Gamma = \frac{4000}{3}$ means that about 1333 individuals join the pool of sexually active homosexual population every year and $\mu = \frac{1}{32}$ means that on average homosexual people are sexually active for 32 years. Finally $\mu_A = 1$ is the life expectancy of a full-blown AIDS patient.

Critical points for various reproductive rates R, are summarised in the Table 4.13.

Whenever $R = 1$ at least one of the eigenvalues of the Jacobian is equal to zero. Therefore, the non-trivial and trivial critical points coincide, which is neutrally stable.

Table 4.13 indicates that as R increases the total number of HIV and AIDS cases increases and the number of susceptibles decreases. The high impact of the infection appears as soon as the infectious moves from static ($R = 1$) to development stage ($R > 1$).

4.4.2 Numerical method *I*

Replacing the derivatives in (4.4.24) by their first-order, forward-difference approximations given by (3.2.1) and considering the right hand side at the base time level (Euler's method) gives

$$\begin{cases} \frac{x^{n+1}-x^n}{h} = \Gamma - \beta k x^n \frac{y_A^n + y_{\bar{A}}^n}{x^n + y_A^n + y_{\bar{A}}^n + z_A^n + z_{\bar{A}}^n} - \mu x^n, \\ \frac{y_A^{n+1}-y_A^n}{h} = p\beta k x^n \frac{y_A^n + y_{\bar{A}}^n}{x^n + y_A^n + y_{\bar{A}}^n + z_A^n + z_{\bar{A}}^n} - (\mu + v_A) y_A^n, \\ \frac{y_{\bar{A}}^{n+1}-y_{\bar{A}}^n}{h} = (1-p)\beta k x^n \frac{y_A^n + y_{\bar{A}}^n}{x^n + y_A^n + y_{\bar{A}}^n + z_A^n + z_{\bar{A}}^n} - (\mu + v_{\bar{A}}) y_{\bar{A}}^n, \\ \frac{z_A^{n+1}-z_A^n}{h} = v_A y_A^n - (\mu + \mu_A) z_A^n, \\ \frac{z_{\bar{A}}^{n+1}-z_{\bar{A}}^n}{h} = v_{\bar{A}} y_{\bar{A}}^n - \mu z_{\bar{A}}^n, \end{cases} \tag{4.4.28}$$

for $n = 0, 1, 2, 3, \cdots$.

Rearranging the above equations explicitly gives

$$\begin{cases} x^{n+1} \equiv g_1(x^n, y_A^n, y_{\bar{A}}^n, z_A^n, z_{\bar{A}}^n) = x^n + h[\Gamma - \beta k x^n \frac{y_A^n + y_{\bar{A}}^n}{x^n + y_A^n + y_{\bar{A}}^n + z_A^n + z_{\bar{A}}^n} - \mu x^n], \\ y_A^{n+1} \equiv g_2(x^n, y_A^n, y_{\bar{A}}^n, z_A^n, z_{\bar{A}}^n) = y_A^n + h[p\beta k x^n \frac{y_A^n + y_{\bar{A}}^n}{x^n + y_A^n + y_{\bar{A}}^n + z_A^n + z_{\bar{A}}^n} - (\mu + v_A) y_A^n], \\ y_{\bar{A}}^{n+1} \equiv g_3(x^n, y_A^n, y_{\bar{A}}^n, z_A^n, z_{\bar{A}}^n) = y_{\bar{A}}^n + h[(1-p)\beta k x^n \frac{y_A^n + y_{\bar{A}}^n}{x^n + y_A^n + y_{\bar{A}}^n + z_A^n + z_{\bar{A}}^n} - (\mu + v_{\bar{A}}) y_{\bar{A}}^n], \\ z_A^{n+1} \equiv g_4(x^n, y_A^n, y_{\bar{A}}^n, z_A^n, z_{\bar{A}}^n) = z_A^n + h[v_A y_A^n - (\mu + \mu_A) z_A^n], \\ z_{\bar{A}}^{n+1} \equiv g_5(x^n, y_A^n, y_{\bar{A}}^n, z_A^n, z_{\bar{A}}^n) = z_{\bar{A}}^n + h(v_{\bar{A}} y_{\bar{A}}^n - \mu z_{\bar{A}}^n), \end{cases} \tag{4.4.29}$$

for $n = 0, 1, 2, 3, \cdots$.

The numerical method is stable if, after n iterations, the numerical solution converge to a fixed point which means $x^{n+1} = x^n = x$, $y_A^{n+1} = y_A^n = y_A$, $y_{\bar{A}}^{n+1} = y_{\bar{A}}^n = y_{\bar{A}}$ and $z_A^{n+1} = z_A^n = z_A$, $z_{\bar{A}}^{n+1} = z_{\bar{A}}^n = z_{\bar{A}}$. Therefore, the system of equations

$$\begin{cases} x - g_1(x, y_A, y_{\bar{A}}, z_A, z_{\bar{A}}) = 0 \\ y_A - g_2(x, y_A, y_{\bar{A}}, z_A, z_{\bar{A}}) = 0 \\ y_{\bar{A}} - g_3(x, y_A, y_{\bar{A}}, z_A, z_{\bar{A}}) = 0 \\ z_A - g_4(x, y_A, y_{\bar{A}}, z_A, z_{\bar{A}}) = 0 \\ z_{\bar{A}} - g_5(x, y_A, y_{\bar{A}}, z_A, z_{\bar{A}}) = 0 \end{cases} \tag{4.4.30}$$

associated with (4.4.29) show that the fixed points of the numerical method are the same as the critical points of the system of ODEs (4.4.24).

The numerical method will converge to a fixed point if eigenvalues of the Jacobian of the form (3.2.4) at that particular fixed point do not exceed unity.

Applying the conditions (3.2.8) and (3.2.9) on the eigenvalues of the Jacobian of the form (3.2.4), expected h-boundaries for monotonic, oscillatory convergence and divergence for the system (4.4.24) are summarised in Table 4.14.

Choosing the initial values $x(0) = x^0 = 94300$, $y_A(0) = y_A^0 = 3500$, $y_{\bar{A}}(0) = y_{\bar{A}}^0 = 1500$, $z_A(0) = z_A^0 = 600$ and $z_{\bar{A}}(0) = z_{\bar{A}}^0 = 100$, the real (observed) h-boundaries for monotonic, oscillatory convergence and divergence are summarised in Table 4.15.

There are some non-significant differences between the columns of the Tables 4.14 and 4.15 representing h-boundaries.

Table 4.14: *Expected h-boundaries for the numerical method I*

R	k	Monotonic convergence	Oscillatory convergence	Divergence
50.0	36.5	$0 < h \leq 0.27$	$0.27 < h \leq 0.54$	$h > 0.54$
20.0	14.6	$0 < h \leq 0.81$	$0.81 < h \leq 1.62$	$h > 1.62$
15.0	11.0	$0 < h \leq 1.00$	$1.00 < h \leq 2.00$	$h > 2.00$
10.0	7.3	$0 < h \leq 0.97$	$0.97 < h \leq 1.94$	$h > 1.94$
5.0	3.6	$0 < h \leq 0.99$	$0.99 < h \leq 1.98$	$h > 1.98$
2.0	1.4	$0 < h \leq 0.97$	$0.97 < h \leq 1.94$	$h > 1.94$
1.0	0.7	$0 < h \leq 0.95$	$0.95 < h \leq 1.9$	$h > 1.9$
0.8	0.6	$0 < h \leq 0.96$	$0.96 < h \leq 1.92$	$h > 1.92$

4.4.3 Numerical method *II*

The development of the numerical method *II* will be based on the first order approximations (3.2.1), in which $t = t_n$ (see Section 3.3.2).

Approximating the derivatives in (4.4.24) by (3.2.1), and evaluating the variables on the right hand side of (4.4.24) as follows

$$\begin{cases} \frac{x^{n+1}-x^n}{h} = \Gamma - \beta k x^{n+1} \frac{y_A^n + y_{\bar{A}}^n}{x^n + y_A^n + y_{\bar{A}}^n + z_A^n + z_{\bar{A}}^n} - \mu x^{n+1}, \\ \frac{y_A^{n+1}-y_A^n}{h} = p\beta k x^{n+1} \frac{y_A^{n+1} + y_{\bar{A}}^n}{x^{n+1} + y_A^n + y_{\bar{A}}^n + z_A^n + z_{\bar{A}}^n} - (\mu + v_A) y_A^{n+1}, \\ \frac{y_{\bar{A}}^{n+1}-y_{\bar{A}}^n}{h} = (1-p)\beta k x^{n+1} \frac{y_A^{n+1} + y_{\bar{A}}^{n+1}}{x^{n+1} + y_A^{n+1} + y_{\bar{A}}^n + z_A^n + z_{\bar{A}}^n} - (\mu + v_{\bar{A}}) y_A^{n+1}, \\ \frac{z_A^{n+1}-z_A^n}{h} = v_A y_A^{n+1} - (\mu + \mu_A) z_A^{n+1}, \\ \frac{z_{\bar{A}}^{n+1}-z_{\bar{A}}^n}{h} = v_{\bar{A}} y_{\bar{A}}^{n+1} - \mu z_{\bar{A}}^{n+1} \end{cases} \tag{4.4.31}$$

Table 4.15: *Observed h-boundaries for the numerical method I*

R	k	Monotonic convergence	Oscillatory convergence	Divergence
50.0	36.5	$0 < h \leq 0.13$	$0.13 < h \leq 0.35$	$h > 0.35$
20.0	14.6	$0 < h \leq 0.39$	$0.39 < h \leq 0.86$	$h > 0.86$
15.0	11.0	$0 < h \leq 0.55$	$0.55 < h \leq 1.10$	$h > 1.10$
10.0	7.3	$0 < h \leq 0.97$	$0.97 < h \leq 1.65$	$h > 1.65$
5.0	3.6	$0 < h \leq 0.99$	$0.99 < h \leq 1.98$	$h > 1.98$
2.0	1.4	$0 < h \leq 1.30$	$1.30 < h \leq 1.90$	$h > 1.90$
1.0	0.7	$0 < h \leq 0.95$	$0.95 < h \leq 1.90$	$h > 1.90$
0.8	0.6	$0 < h \leq 0.96$	$0.96 < h \leq 1.92$	$h > 1.92$

after re-arranging gives

$$\begin{cases} x^{n+1} \equiv g_1(x^n, y_A^n, y_{\bar{A}}^n, z_A^n, z_{\bar{A}}^n) = \dfrac{\Gamma h + x^n}{1+\mu h + \frac{hk\beta(y_A^n + y_{\bar{A}}^n)}{x^n + y_A^n + y_{\bar{A}}^n + z_A^n + z_{\bar{A}}^n}}, \\ y_A^{n+1} \equiv g_2(g_1, y_A^n, y_{\bar{A}}^n, z_A^n, z_{\bar{A}}^n) = \dfrac{x^{n+1}(y_A^n + hk\beta p y_{\bar{A}}^n) + y_A^n(y_A^n + y_{\bar{A}}^n + z_A^n + z_{\bar{A}}^n)}{x^{n+1}[1+h(\mu - k\beta p + v_A)] + (1+h\mu+hv_A)(y_A^n + y_{\bar{A}}^n + z_A^n + z_{\bar{A}}^n)}, \\ y_{\bar{A}}^{n+1} \equiv g_3(g_1, g_2, y_{\bar{A}}^n, z_A^n, z_{\bar{A}}^n) = \dfrac{x^{n+1}(hk\beta(1-p)y_A^n + y_{\bar{A}}^n) + y_{\bar{A}}^n(y_A^{n+1} + y_{\bar{A}}^n + z_A^n + z_{\bar{A}}^n)}{x^{n+1}[1+h(\mu - k\beta(1-p) + v_{\bar{A}})] + (1+h\mu+hv_{\bar{A}})(y_A^{n+1} + y_{\bar{A}}^n + z_A^n + z_{\bar{A}}^n)}, \\ z_A^{n+1} \equiv g_4(g_1, g_2, g_3, z_A^n, z_{\bar{A}}^n) = \dfrac{z_A^n + hv_A y_A^{n+1}}{1+h(\mu+\mu_A)}, \\ z_{\bar{A}}^{n+1} \equiv g_5(g_1, g_2, g_3, g_4, z_{\bar{A}}^n) = \dfrac{z_{\bar{A}}^n + hv_{\bar{A}} y_{\bar{A}}^{n+1}}{1+h\mu}, \end{cases} \tag{4.4.32}$$

for $n = 0, 1, 2, \cdots$.

Substituting for g_1, g_2, g_3 and g_4 in the above equations gives a set of

equations used in the analysis detailed below.

It is possible to show that the fixed points of the numerical method *II*, using (3.2.3) are the same as critical points (4.4.25), (4.4.26) of the system of ODEs (4.4.24).

Whenever $k < k^*$ the eigenvalues of the Jacobian associated with the method at the trivial fixed point (4.4.25) are positive and less than unity regardless of h value. This means that the numerical method is expected to converge monotonically for large values of time step (h).

If $k = k^*$ then $\lambda_1 = 1$, which means that the numerical solution is neutrally stable.

Table 4.16 represents expected h-boundaries of the numerical method *II* for monotonic convergence, oscillatory convergence and divergence.

With the same initial values as used in Section 4.4.2, Table 4.17 represents real (observed) h-boundaries.

The difference between the columns of Tables 4.16 and 4.17 representing h-boundaries is not significant.

Table 4.16: *Expected h-boundaries for the numerical method II*

R	k	Monotonic convergence	Oscillatory convergence	Divergence
50.0	36.5	$0 < h \leq 3.3$	$3.3 < h \leq 271.5$	$h > 271.5$
20.0	14.6	$0 < h \leq 12.2$	$12.2 < h \leq 226.5$	$h > 226.5$
15.0	11.0	$0 < h \leq 13.8$	$13.8 < h \leq 223.0$	$h > 223.0$
10.0	7.3	$0 < h \leq 16.1$	$16.1 < h \leq 233.5$	$h > 233.5$
5.0	3.6	$0 < h \leq 21.6$	$21.6 < h \leq 380.5$	$h > 380.5$
2.0	1.4	$0 < h \leq 37.3$	$37.3 < h < \infty$	$h > 5000.0$
1.0	0.7	$0 < h < \infty$	—	—
0.8	0.6	$0 < h < \infty$	—	—

Table 4.17: *Observed h-boundaries for the numerical method II*

R	k	Monotonic convergence	Oscillatory convergence	Divergence
50.0	36.5	$0 < h \leq 0.2$	$0.2 < h \leq 270.0$	$h > 270.0$
20.0	14.6	$0 < h \leq 0.5$	$0.5 < h \leq 200.0$	$h > 200.0$
15.0	11.0	$0 < h \leq 0.7$	$0.7 < h \leq 220.0$	$h > 220.0$
10.0	7.3	$0 < h \leq 1.1$	$1.1 < h \leq 225.0$	$h > 225.0$
5.0	3.6	$0 < h \leq 3.2$	$3.2 < h \leq 370.0$	$h > 370.0$
2.0	1.4	$0 < h \leq 8.0$	$8.0 < h < \infty$	—
1.0	0.7	$0 < h < \infty$	—	—
0.8	0.6	$0 < h < \infty$	—	—

4.5 Conclusion and summary

The mathematical analysis presented in this chapter suggests that, whenever individuals in a population choose less than k^* (bifurcation parameter) number of sexual partners per unit of time then the disease will eventually disappear. The bifurcation parameter is a unique parameter, which leads to the calculation of the reproductive rate. The total population's reproductive rate is the sum of group's reproductive rates.

Comparing the two numerical methods used to solve presented models show that the numerical method *II* converges for much bigger values of time step (h). However, in some circumstances the accuracy and reliability of the numerical method *II* is suspected.

Whenever the eigenvalues of the Jacobian associated with the numerical method are less than unity the numerical method is convergent,. This does not mean that whenever eigenvalues the Jacobian associated with the numerical method are less than unity the numerical method is necessarily convergent.

Chapter 5

Mathematical modelling of the effect of heterogeneity in sexual behavioural in the transmission dynamics of HIV/AIDS

So far, mathematical modelling of the transmission dynamics of HIV/AIDS in human populations with homogeneous sexual behaviour has been studied studied. Heterogeneity in sexual behaviour serves to complicate maths and in general, acts to increase the endemic prevalence from that pertaining in a population with homogeneity in sexual behaviour (see Anderson and May [9], Garnett and Anderson [50]).

Grouping individuals of a population according to their level of sexual activity from the highest to the lowest, require some assumptions on the sexual contacts within and between groups. The aim is to obtain equations that are consistent with observed population sexual contacts and to

investigate the effect of heterogeneity in sexual behaviour on the transmission dynamics of HIV/AIDS.

Section 5.2 gives a brief review of the range of mixing functions currently used in mathematical models of sexually transmitted diseases, spread within human communities. Some results of the developing theory of mixing matrices is given proposing the need for further constraints. In addition to presenting constraints that ensure the description of the full range of mixing patterns in a given population, for defined population parameters in a specified time interval.

Section 5.4 examines how the new constraints may be applied in generating compatible mixing matrices. The meaning of the mixing extremes are examined in the light of the new constraints. Of particular importance in this context is the observation that the distribution of individuals by number of sex partners tend to be highly skewed in character where most individuals have few partners and a few have many. This implies that in a defined community the number of people in the highest sexual activity group tends to be small, which in turn limits the possibilities of partnership with individuals in this group.

Section 5.4.2 presents the characteristics and the definitions of a large population.

Section 5.5 presents mathematical modelling of the transmission dynamics of HIV/AIDS in a heterogeneous population. Finally, Section 5.6 concludes this chapter.

5.1 Introduction

Levels of sexual activity varies in populations and with time for a particular individual. Stratifying population according to the level of sexual activity, allows the effect of behavioural heterogeneity to be explored.

Sexual mixing patterns are described by mixing matrices whose elements satisfy certain constraints imposed by the nature of the problem (see Uche [108] and Anderson *et al.* [10]).

In this chapter the most general form of mixing matrices (see Castillo-Chavez and Blythe [28], Hyman and Stanley [62]) is introduced followed by an emphasis on obtaining mixing matrices that are consistent with observed population parameters.

Specifying simple and compact functions to define the elements of the mixing matrices has been the centre of past studies. Population parameters are used to define the elements of mixing matrices (see Blythe *et al.* [19]). Some commonly used forms of mixing matrices include the:

i) **Assortative matrix** (like with like): is the form of an identity matrix. It is used whenever sexual activity groups are totally isolated from one another. For instance, all the individuals from a certain sexual activity group choose sexual partners only from their own group (see Blythe *et al.* [19] and Anderson *et al.* [10]).

ii) **Partially assortative matrix** (random mixing): is used whenever sexual activity groups are mixed. For instance, individuals from a certain sexual activity group choose sexual partners randomly from any any other sexual activity groups (see Castillo-Chavez *et al.* [29] and [30]).

iii) **Dis-assortative matrix** (like with unlike): has elements equal to zero on the diagonal and is used whenever all the individuals only choose sexual partners from other groups (see Anderson *et al.* [10]).

iv) **Preferred matrix:** is the form of a convex linear combination of mixing matrices.

Overall, the developments of mathematical theory of mixing matrices paid very little attention to the counting process that is involved in the recording of partnerships. However, in practice it is usual for the understanding of sexual mixing patterns, to design sexual behaviour surveys, which record the number of partners of individuals in a defined population in a specified time interval (see Schmitz *et al.* [101]). A careful analysis of the surveys is necessary to examine how the current theory of mixing matrices can be developed to make full use of available surveys.

5.2 Necessary constraints of the elements of the mixing matrices

In order to discuss the conditions on the elements of the mixing matrices the following parameters of the population need to be defined,

N : the total population size,

s : the number of sexual activity groups,

N_i : the sizes of discrete activity groups, $i = 1, 2, \cdots, s$.

k_i : the mean number of new sexual partners acquired by group N_i per unit of time, $i = 1, 2, \cdots, s$.

ρ : the mixing matrix of size $s \times s$, representing the sexual mixing pattern within and between groups.

ρ_{ij} : represents the elements of the mixing matrix, specifying the proportion of sexual partners of activity group j acquired from activity group i.

All the elements of the mixing matrix necessarily satisfies the following set of conditions:

$$0 \leq \rho_{ij} \leq 1, \quad \forall i, j \in \{1, 2, \cdots, s\} \tag{5.2.1}$$

$$\sum_{j=1}^{s} \rho_{ij} = 1, \quad \forall i \in \{1, 2, \cdots, s\} \tag{5.2.2}$$

$$\frac{\rho_{ij}}{N_j k_j} = \frac{\rho_{ji}}{N_i k_i}, \quad for \quad i \neq j. \tag{5.2.3}$$

The constraint (5.2.3) is the balance equation ensuring that the number of new sexual partnerships of individuals in group i formed with individuals from group j, equals the number of new partnerships of individuals in group j taken from group i.

Later an example shows that equations (5.2.1-5.2.3) are just necessary conditions on the elements of the mixing matrices and are not necessarily sufficient.

The following functional forms satisfy conditions (5.2.1-5.2.3) therefore described as potential mixing matrices representing the sexual patterns such as:

i) **Assortative population:** elements of the assortative population mixing matrix are the form of

$$\rho_{ij} = I_{ij} = \begin{cases} 1, & if \quad i = j \\ 0, & if \quad i \neq j \end{cases} \tag{5.2.4}$$

in which the mixing matrix is the form of an $s \times s$ identity matrix,

$$\rho = \begin{bmatrix} 1 & 0 & \cdots & 0 \\ 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & 1 \end{bmatrix}.$$

ii) **Proportionate mixing population:** elements of the proportionate mixing matrix are presented by

$$\rho_{ij} = \frac{N_j k_j}{\sum_{m=1}^{s} N_m k_m} \tag{5.2.5}$$

Therefore proportionate mixing matrix is the form of

$$\rho = \begin{bmatrix} \frac{N_1 k_1}{\sum_{m=1}^{s} N_m k_m} & \frac{N_2 k_2}{\sum_{m=1}^{s} N_m k_m} & \cdots & \frac{N_s k_s}{\sum_{m=1}^{s} N_m k_m} \\ \frac{N_1 k_1}{\sum_{m=1}^{s} N_m k_m} & \frac{N_2 k_2}{\sum_{m=1}^{s} N_m k_m} & \cdots & \frac{N_s k_s}{\sum_{m=1}^{s} N_m k_m} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{N_1 k_1}{\sum_{m=1}^{s} N_m k_m} & \frac{N_2 k_2}{\sum_{m=1}^{s} N_m k_m} & \cdots & \frac{N_s k_s}{\sum_{m=1}^{s} N_m k_m} \end{bmatrix}.$$

5.2.1 Implications of the mixing matrices

Some implications of the constraints (5.2.1-5.2.3) are listed below:

i) **Linear combination:** linear combination of mixing matrices is a mixing matrix. Suppose ρ_1 and ρ_2 are two mixing matrices for a defined population then,

$$\rho = \wp\rho_1 + (1 - \wp)\rho_2, \quad 0 \leq \wp \leq 1 \tag{5.2.6}$$

is a mixing matrix.

Where $\wp$ is regarded as mixing parameter. Equation (5.2.6) is frequently used to construct a variety of mixing matrices for defined population parameters (see Busenberg and Castillo-Chavez [26]).

ii) **Biased matrix:** a very special form of the equation (5.2.6) is the linear combination of the assortative and proportionate matrices

$$\rho_{ij} = \wp I_{ij} + (1 - \wp)\frac{N_j k_j}{\sum_{m=1}^{s} N_m k_m}, \quad 0 \leq \wp \leq 1 \tag{5.2.7}$$

is regarded as a biased matrix. At $\wp = 0$, the biased matrix reduces to the proportionate, while at $\wp = 1$ it yields the assortative matrix. Therefore, biased matrix is, said to span the range from the proportionate to the assortative extremes.

iii) **Preferred matrix:** finally, preferred matrix with the elements

$$\rho_{ij} = \wp_i I_{ij} + \frac{(1 - \wp_i) N_j k_j}{\sum_{m=1}^{s} (1 - \wp_m) N_m k_m}, \quad 0 \leq \wp_i \leq 1 \tag{5.2.8}$$

Where $\wp_i$ denotes mixing parameter of sexual activity group i. $\wp_i = 0,\ \forall i \in \{1, 2, \cdots, s\}$ yields the proportionate matrix, while $\wp_i = 1,\ \forall i \in \{1, 2, \cdots, s\}$ gives the assortative matrix. As a result the preferred matrix is said to span the same range as the biased matrix (see Uche [108]).

5.3 Counting process

Developments of mathematical theory of mixing matrices paid very little attention to the counting process that is involved in the recording of partnerships. Sexual behaviour surveys, record the number of partners of individuals in a defined population in a specified time interval (see Schmitz *et al.* [101]).

Assuming that a, b and c are three individuals belong to a population of size N, the facts about the sexual relations among those individuals are:

i) **not reflexive:** an individual a cannot mix with himself,

ii) **symmetric:** if a mixes with b, then b also mixes with a,

iii) **non-transitive:** if individual a mixes with b and b mixes with c does not necessarily mean that a mixes with c.

The symmetric nature of the mixing relation implies that when two people form a partnership, the partnership is counted for each of them.

Within the unit of time, (most often chosen as one year), the partnerships of all individuals are counted. A distinction is made between the number of sexual contacts/acts and the number of partnerships. During the unit of time, partnership with an individual is counted once. For example, if the unit of time is one year (Jan. 1 - Dec. 31), and an individual a has sexual contacts with two individuals b (Feb. - Apr. and Jun. - Dec.) and c (Mar. - Jun.) therefore, individual a is said to form two partnerships within the time period even though there may be numerous sexual contacts in a partnership, breakage and reunion of sexual acquaintance.

Where interest lies in the number of sexual contacts, extensions can be made in a straight forward way by defining an appropriate unit of time and counting process.

In the following section, an example is used to examine the sufficiency of (5.2.1-5.2.3) constraints in defining the possible mixing patterns in populations of finite size, for specified population parameters.

5.3.1 Example 1 *"Insufficiency of the necessary constraints for populations of finite size"*

The constraints (5.2.1-5.2.3) have been employed in most published theoretical and numerical studies of the influence of different patterns of sexual contact between sexual activity groups on the spread of sexually transmitted

Table 5.1: *Sexual Activity Groups*

Activity group	Group index i	Group size N_i	Range of new sexual partnership	k_i
Low	1	8	1-3	2
Moderate	2	3	3-5	4
High	3	2	5-7	6
Total		13		

infections.

Figure 5.3.1 describes the pattern of new partnership formation in a closed population of 13 individuals in a defined time interval. The data of such a survey is tabulated in Table 5.1.

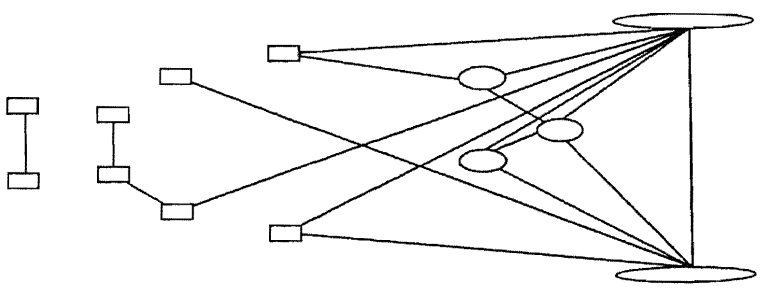

Figure 5.3.1: *Sexual partnership network in a population of 13 individuals.*

: High activity group of size 2, acquire 5-7 sexual partners per unit of time,

: Moderate activity group of size 3, acquire 3-5 sexual partners per unit of time,

: Low activity group of size 8, acquire 1-3 sexual partners per unit of time.

The population is stratified into three sexual activity groups low, moderate and high. The high activity group comprises of individuals with five or more new sexual partners per unit of time.

Therefore

$$N = \begin{bmatrix} 8 & 3 & 2 \end{bmatrix}^T, \; k = \begin{bmatrix} 2 & 4 & 6 \end{bmatrix}^T$$

give

$$Nk = \begin{bmatrix} 16 & 12 & 12 \end{bmatrix}^T$$

The mixing constraints (5.2.1-5.2.3) are insufficient in limiting the mixing matrices of this population to those that are possible. For instance, the assortative matrix given by the identity matrix

$$\rho = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

represents a possible mixing pattern for this population satisfying the constraints (5.2.1-5.2.3). However, if the assortative matrix is used as a possible mixing matrix, the number of new partnerships in the high activity group within their group is $N_3 k_3 = 12$. With the high activity group comprising only two individuals, the counting process allows them maximum 2 new partnerships amongst themselves.

With the counting process defined in section 5.3, two individuals cannot form 12 new partnerships between themselves. Therefore, the assortative matrix is not a possible mixing matrix for this population. The suggestion is that the other functional forms in the literature cannot be guaranteed to represent mixing matrices in populations of finite size and with specified population parameters.

The need is for a better method of characterising mixing matrices. This is reflected by an example in this section, that the size of an activity group can limit the number of possible new partnerships that an activity group can form within itself.

5.4 Sufficient constraints of the mixing matrices of homosexual populations

In this section sufficient constraints to developing true mixing matrices of a homosexual population are presented.

For a homosexual population of size N, stratified by sexual activity into s discrete activity groups of sizes N_i, with mean number of new partners k_i respectively in a specified time interval, sorted according to $k_{i-1} < k_i,\ i = \{1, 2, \cdots s\}$ the mixing matrix ρ is defined as a $s \times s$ matrix of the form of,

$$\rho = \begin{bmatrix} \frac{\alpha_{11}}{N_1 k_1} & \frac{\alpha_{12}}{N_1 k_1} & \cdots & \frac{\alpha_{1s}}{N_1 k_1} \\ \frac{\alpha_{21}}{N_2 k_2} & \frac{\alpha_{22}}{N_2 k_2} & \cdots & \frac{\alpha_{2s}}{N_2 k_2} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\alpha_{s1}}{N_s k_s} & \frac{\alpha_{s2}}{N_s k_s} & \cdots & \frac{\alpha_{ss}}{N_s k_s} \end{bmatrix} =$$

$$\begin{bmatrix} \frac{1}{N_1 k_1} \\ \frac{1}{N_2 k_2} \\ \vdots \\ \frac{1}{N_s k_s} \end{bmatrix} \cdot \begin{bmatrix} \alpha_{11} & \alpha_{12} & \cdots & \alpha_{1s} \\ \alpha_{21} & \alpha_{22} & \cdots & \alpha_{2s} \\ \vdots & \vdots & \ddots & \vdots \\ \alpha_{s1} & \alpha_{s2} & \cdots & \alpha_{ss} \end{bmatrix} \tag{5.4.9}$$

in which α_{ij}, is the number of individuals from activity group j among the new partners of individuals in activity group i, satisfying the following conditions,

1.

$$0 \leq \alpha_{ij} \leq \begin{cases} Min(N_i k_i, N_j k_j, N_i N_j), & \alpha_{ij} \in Z^+ \quad if \quad i \neq j \\ Min(N_i k_i, N_i(N_i - 1)), & \alpha_{ij} \in 2Z^+ \quad if \quad i = j \end{cases}, \tag{5.4.10}$$

2.

$$\alpha_{ij} = 0 \quad if \quad N_i k_i = 0, \tag{5.4.11}$$

3.

$$\sum_{j=1}^{s} \alpha_{ij} = N_i k_i, \quad \forall i \in \{1, 2, \cdots, s\}, \tag{5.4.12}$$

4.

$$\sum_{i=1}^{s} \alpha_{ij} = N_j k_j, \quad \forall j \in \{1, 2, \cdots, s\}, \tag{5.4.13}$$

5.

$$\alpha_{ij} = \alpha_{ji}, \quad \forall i, j \in \{1, 2, \cdots, s\}, \tag{5.4.14}$$

6.

$$\sum_{i=1}^{s} \sum_{j=1}^{s} \alpha_{ij} \leq Min\{N_i(N_i - 1), s(MaxN_i k_i)\}. \tag{5.4.15}$$

Equation (5.4.10) states that the number of sexual partners of the i^{th} group taken from group j group must be less than the total number of sexual partner changes made by group i and group j and $N_i N_j$ (i.e. the maximal number of partner changes possible between the two groups). The term $N_i(N_i - 1)$ is the maximal number of within-group partner changes for the i^{th} group. The term, $\rho_{ij} = 0$ in equation (5.4.11) represents the zero mixing matrix where no new partnerships are being formed; due to either the activity groups being empty or individuals in the population not choosing new sexual partner. Equations (5.4.12) and (5.4.13) state that the total number of new partners of individuals in activity groups i and j within and between groups are equal to the maximum possible number of new sexual partners that can be formed by the group and (5.4.14) follows the symmetrical nature of the mixing matrix.

5.4.1 Example 2 *"Sufficient constraints of the populations of finite size"*

By applying conditions (5.4.10-5.4.15) on the elements of mixing matrices of a homosexual population presented in Example 1, Section 5.3.1 the following mixing matrices are produced,

$$A = \begin{bmatrix} \frac{3}{4} & 0 & \frac{1}{4} \\ 0 & \frac{1}{2} & \frac{1}{2} \\ \frac{1}{4} & \frac{1}{2} & \frac{1}{4} \end{bmatrix},$$

$$B = \begin{bmatrix} \frac{2}{12} & \frac{3}{12} & \frac{7}{12} \\ \frac{3}{12} & \frac{6}{12} & \frac{3}{12} \\ \frac{7}{12} & \frac{3}{12} & \frac{2}{12} \end{bmatrix}.$$

Figures 5.4.1 and 5.4.2 represent the possible sexual network for mixing matrixes A and B.

It can be observed that equations (5.4.10-5.4.15) eliminate all the false mixing matrices such as assortative matrix.

5.4.2 Large populations

Generally the number of partnerships formed within a large population is enormous. Therefore

$$\rho_{ij} = \frac{\alpha_{ij}}{N_i k_i} \approx \frac{\alpha_{ij}+1}{N_i k_i}$$

which implies that α_{ij} may be either odd or even. For such population, the number of elements of the set of mixing matrices become enormously large making the listing of the set of mixing matrices difficult in practice. The adoption of a level of approximation to reduce the number of elements of the set, becomes necessary. This depends on the detail of the problem in which the matrices are developed to describe the sexual contact between individuals of the population.

A population of size N is said to be large if, changes of the order of the reciprocal of $Min\, N_i k_i$ in an element of a mixing matrix neither affect the mixing matrix nor the subject of application of the mixing matrix.

In models of the transmission dynamics of HIV/AIDS, a population is considered large if, only if, every matrix $\bar{\rho}$, such that

$$|\bar{\rho}_{ij} - \rho_{ij}| \leq \frac{1}{MinN_i k_i}, \quad \forall i,j \in \{1,2,\cdots,s\}$$

has the same effect as ρ on the magnitude of the force of infection in the sense that projected trends of incidence of HIV/AIDS populations are similar when either $\bar{\rho}_{ij}$ or ρ_{ij} is used.

5.5 Heterogeneous population

Mathematical models used in simulations, stratifies the population into s groups, according to their level of sexual activity. The population is also divided into, susceptibles $x_i(t) = x_i$, infected $y_i(t) = y_i$ and full-blown AIDS $z_i(t) = z_i$ groups, where $i = \{1, 2, \cdots, s\}$. Figure 5.4 is a flow diagram illustrating the model population.

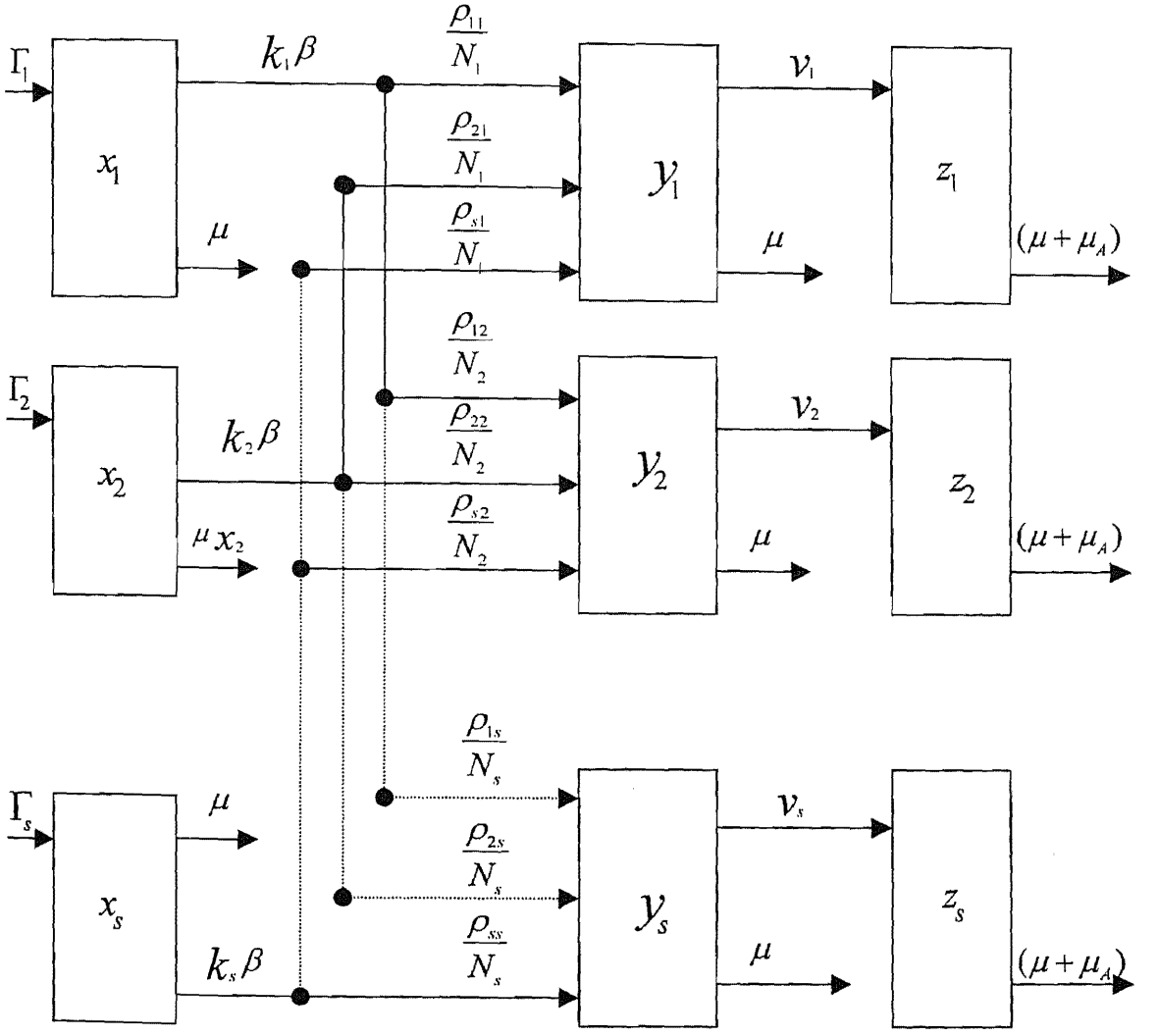

Figure 5.4: *A flow diagram illustrating the model used to simulate the HIV epidemic and the impact of different sexual mixing patterns.*

The model is defined by the following set of ordinary differential equations:

$$\begin{cases} \frac{dx_i}{dt} = \Gamma_i - x_i k_i \beta \sum_{j=1}^{s} (\rho_{ij} \frac{y_j}{N_j}) - \mu x_i, \\ \frac{dy_i}{dt} = x_i k_i \beta \sum_{j=1}^{s} (\rho_{ij} \frac{y_j}{N_j}) - (\mu + v) y_i \\ \frac{dz_i}{dt} = v y_i - (\mu + \mu_A) z_i \end{cases} \tag{5.5.16}$$

for $i = \{1, 2, \cdots, s\}$.

Where

N_j: is the total number of individuals in activity group j.

$i, j = \{1, 2, \cdots, s\}$: indicate the indexes of the sexual activity groups,

Γ_i: specify the immigration rate to the sexual activity group i,

k_i : represent the rate of sexual partner change of group i,

ρ_{ij}: denote the elements of mixing matrix satisfying the set of conditions represented by equations (5.4.10-5.4.15),

Section 2.3.1 shows that the trivial critical point is of the form of

$$x_i^* = \frac{\Gamma_i}{\mu}, \quad y_i^* = 0, \quad z_i^* = 0 \tag{5.5.17}$$

for $i = \{1, 2, \cdots, s\}$.

The effect of sexual behaviour changes (different level of mixing) on the transmission dynamics of HIV/AIDS is explored numerically by the following example.

5.5.1 Example 3 *"The effect of sexual behaviour changes on the transmission dynamics of HIV/AIDS"*

Assuming a population is stratified into three sexual activity groups ($s = 3$). Suppose $N_1 = 10000$, $N_2 = 4N_1 = 40000$, $N_3 = 5N_1 = 50000$, $\Gamma_1 = 100$, $\Gamma_2 = 2.5\Gamma_1 = 250$, $\Gamma_3 = 5\Gamma_1 = 500$, $\mu = 1/32$, $\mu_A = 1$, $\beta = 0.2$ and $v = 0.1$. Substituting $k_2 = k_1/6$ and $k_3 = k_1/36$ in the model equations (5.5.16) and choosing preferred matrix (5.2.8) with the elements

$$\rho_{ij} = \wp_i I_{ij} + \frac{(1-\wp_i)N_j k_j}{\sum_{m=1}^{s}(1-\wp_m)N_m k_m}, \quad 0 \leq \wp_i \leq 1, \ \forall i \in \{1, 2, \cdots, s\}$$

as mixing matrix covering from dis-assortative to random and assortative sexual mixing patterns.

i) **Dis-assortative mixing pattern:** assuming the above population with dis-assortative sexual mixing behaviour ($\wp_1 = \wp_2 = \wp_3 = 0.1$) gives the dis-assortative mixing matrix

$$\rho_d = \begin{bmatrix} 0.60 & 0.33 & 0.07 \\ 0.50 & 0.43 & 0.07 \\ 0.50 & 0.33 & 0.17 \end{bmatrix} \tag{5.5.18}$$

The determinant of the Jacobian associated with (5.5.16) at the trivial critical point (5.5.17) vanishes whenever,

$$k_1^* = 3.16$$

which is regarded as the bifurcation parameter. Assuming $k_1 = 12$, gives the total reproductive rate

$$R = \frac{k_1}{k_1^*} = 3.8$$

and the steady state solution

$$X_1^* = \begin{bmatrix} 726 & 8385 & 14768 & 589 & 1051 & 293 & 57 & 102 & 28 \end{bmatrix}^T$$

ii) **Random mixing pattern:** assuming the population with a random sexual mixing partner ($\wp_1 = \wp_2 = \wp_3 = 0.5$) the random mixing matrix is

$$\rho_r = \begin{bmatrix} 0.78 & 0.18 & 0.04 \\ 0.28 & 0.68 & 0.04 \\ 0.28 & 0.18 & 0.54 \end{bmatrix} \tag{5.5.19}$$

Therefore the bifurcation parameter associated with the model (5.5.16) is

$$k_1^* = 2.6$$

Assuming $k_1 = 12$, gives the total reproductive rate of the random mixing population is

$$R_r = \frac{k_1}{k_1^*} = 4.6$$

and the steady state solution

$$X_r^* = \begin{bmatrix} 646 & 9064 & 15256 & 608 & 889 & 177 & 59 & 86 & 17 \end{bmatrix}^T$$

iii) **Assortative mixing pattern:** assuming the population with an assortative sexual partner acquisition behaviour ($\wp_1 = \wp_2 = \wp_3 = 0.9$) gives the mixing matrix

$$\rho_a = \begin{bmatrix} 0.95 & 0.04 & 0.01 \\ 0.05 & 0.94 & 0.01 \\ 0.05 & 0.04 & 0.91 \end{bmatrix} \tag{5.5.20}$$

The bifurcation parameter of the assortative mixing population is

$$k_1^* = 2.1$$

Assuming $k_1 = 12$, gives the total reproductive rate

$$R_a = \frac{k_1}{k_1^*} = 5.7$$

and the steady state solution

$$X_a^* = \begin{bmatrix} 568 & 10746 & 15845 & 627 & 489 & 37 & 61 & 47 & 4 \end{bmatrix}^T$$

Comparing the total reproductive rates of the population with dis-assortative (R_d), random (R_r) and assortative (R_a) sexual mixing patterns indicate that $R_d < R_r < R_a$, meaning that the total reproductive rate for population with dis-assortative sexual mixing behaviour is grater than the total reproductive rate of a population with random mixing followed by the total reproductive rate of a population with assortative sexual mixing behaviour.

Figures 5.5.1-5.5.12 represent the graphical solution to the system of equations (5.5.16) simulating the transmission dynamics of HIV/AIDS in a population with from assortative to random and dis-assortative sexual mixing behaviour.

Figures 5.5.1-5.5.2 represent the susceptible population in three sexual activity groups ranging from 'assortative' to 'random' and 'dis-assortative' sexual mixing patterns. In general, at the steady state the total number of susceptibles for the assortative mixing pattern is shown to be higher than the random, which in turn is greater than a dis-assortative mixing pattern, for all sexual activity groups. The growths of the number of the susceptible population from dis-assortative to random is 6% and from dis-assortative to assortative 10%, for sexual activity group 1 as shown in Figure 5.5.1. In Figure 5.5.2, the growths from dis-assortative to random is 2% and from dis-assortative to assortative 4%, for sexual activity group 2. In Figure 5.5.3, the growth from dis-assortative to random is 16% and from dis-assortative to assortative 87%, for sexual activity group 3.

Figures 5.5.4-5.5.5 represent the HIV infection for sexual activity groups 1 and 2 which indicate that the mixing patterns have no significant impact on the steady state solution (less than 5%).

Figure 5.5.6 represents HIV infected population within sexual activity groups 3, indicating that at the steady state, HIV infected populations with an assortative mixing pattern declines to zero due to low levels of sexual partner acquisition and the total number of HIV infected with random mixing pattern "=1500" is lower than the dis-assortative mixing pattern "=1800".

Figures 5.5.7, 5.5.8 and 5.5.9 represent the total number of full-blown AIDS population in sexual activity groups 1, 2 and 3 according to the sexual mixing patterns. Figures 5.5.7 and 5.5.8 show that sexual mixing pattern has no significant impact on the total number of full-blown AIDS cases for sexual activity group 1 and 2 at steady state. Figure 5.5.9 shows that total number of full-blown AIDS population with assortative sexual mixing pattern vanishes at early stage. It also indicates that total number of full-blown AIDS cases with random mixing pattern is lower than dis-assortative mixing pattern at all the time.

Figures 5.5.10, 5.5.11 and 5.5.12 represent the total number of susceptible, HIV infected and full-blown AIDS cases in the population respectively. Figure 5.5.10 indicates that the growth of the number of susceptibles from dis-assortative to random sexual mixing pattern is 14% and to assortative mixing is 71%. Figure 5.5.11 indicates that the number of HIV infected from dis-assortative to random sexual mixing pattern decline by 6% and to as-

sortative mixing decline by 35%. Figure 5.5.12 indicates that the number of full-blown AIDS cases from dis-assortative to random sexual mixing pattern decline by 6% and to assortative mixing decline by 35%.

From the above it can be concluded that whenever the sexual mixing pattern varies from a range of assortative to random and dis-assortative the number of susceptibles decrease and the number of HIV infected and AIDS cases increase.

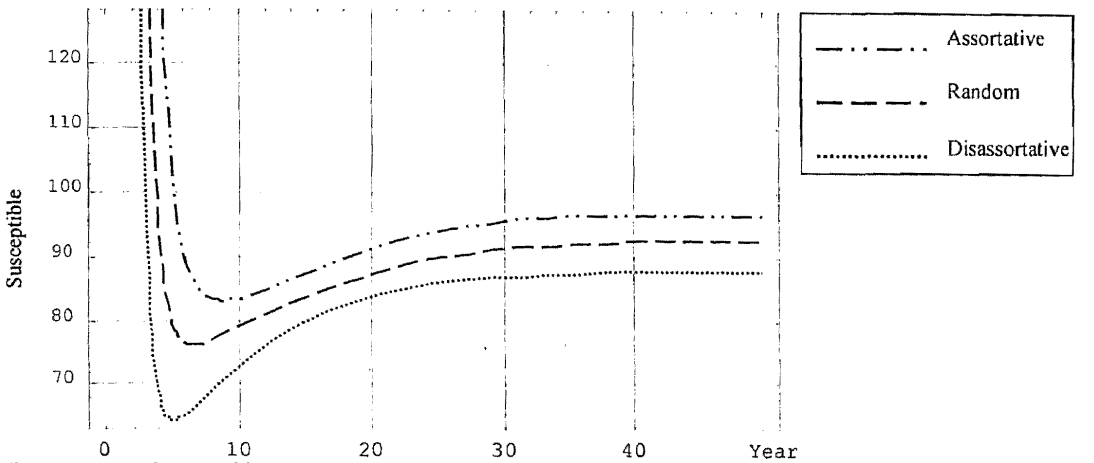

Figure 5.5.1: *Susceptibles in sexual activity group 1 with from assortative to random and disassortative sexual partner acquisition.*

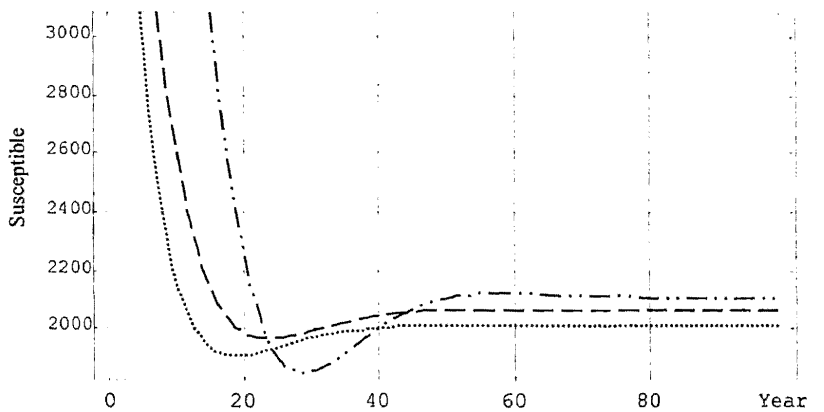

Figure 5.5.2: *Susceptibles in sexual activity group 2 with from assortative to random and disassortative sexual partner acquisition.*

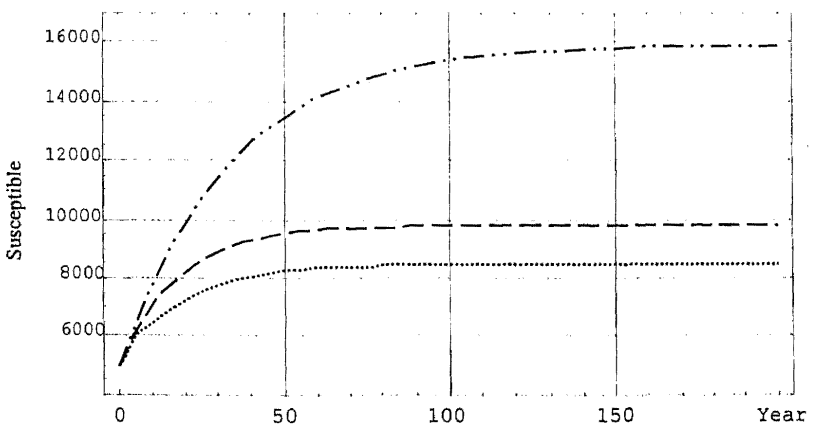

Figure 5.5.3: *Susceptibles in sexual activity group 2 with from assortative to random and disassortative sexual partner acquisition.*

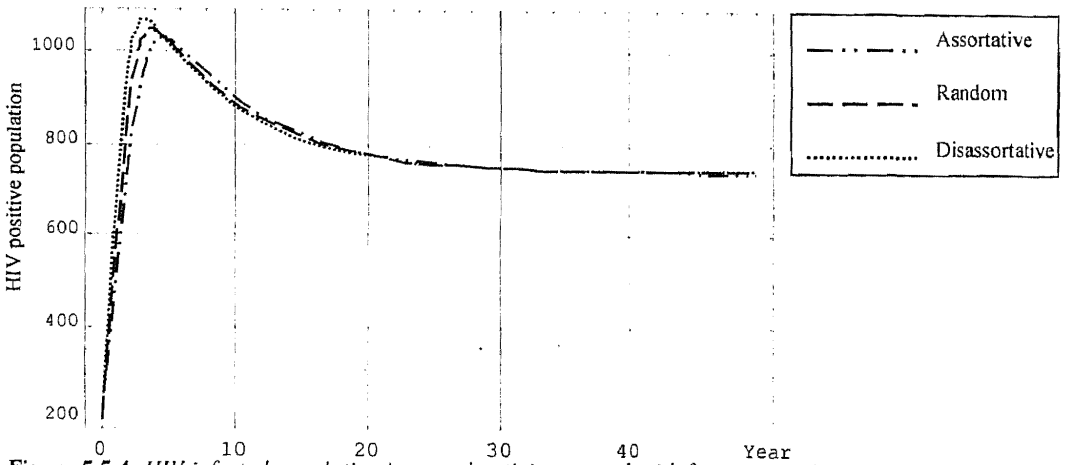

Figure 5.5.4: *HIV infected population in sexual activity group 1 with from assortative to random and disassortative sexual partner acquisition.*

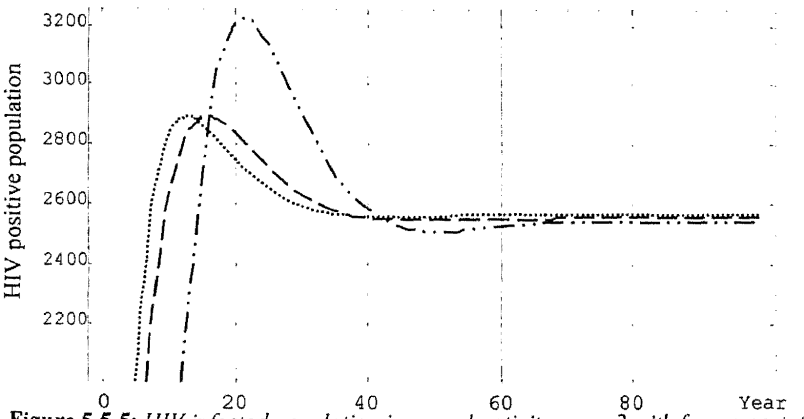

Figure 5.5.5: *HIV infected population in sexual activity group2 with from assortative to random and disassortative sexual partner acquisition.*

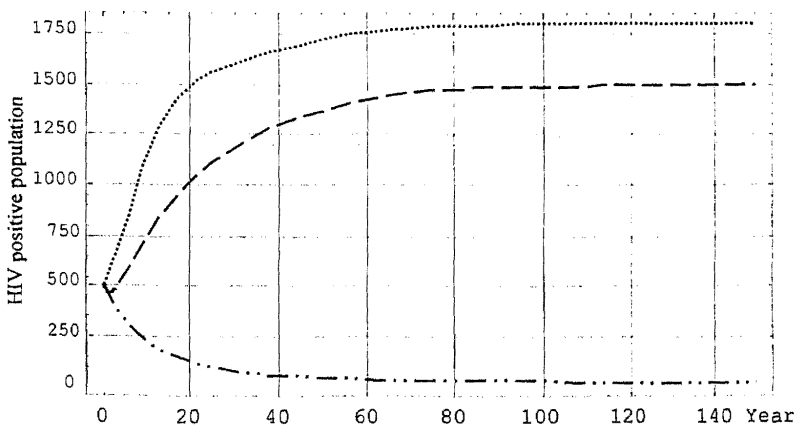

Figure 5.5.6: *HIV infected population in sexual activity group2 with from assortative to random and disassortative sexual partner acquisition.*

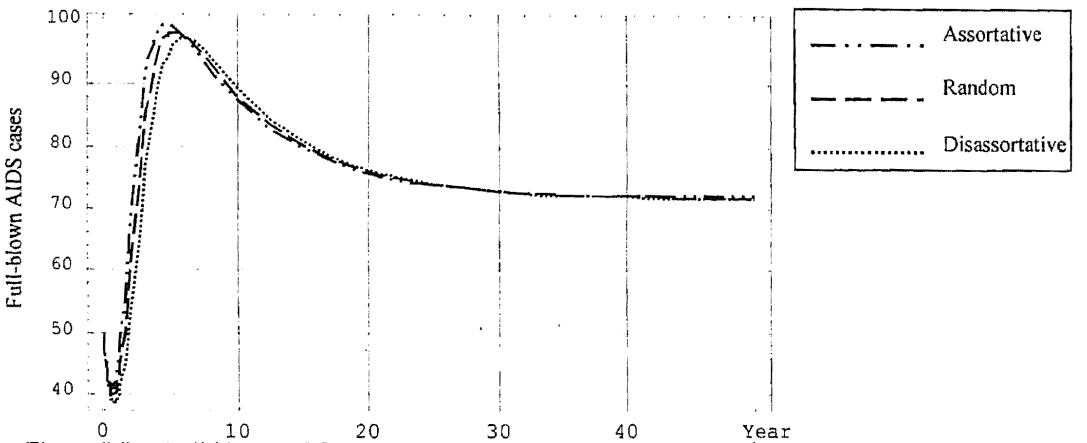

Figure 5.5.7: *Full-blown AIDS population in sexual activity group 1 with from assortative to random and disassortative sexual partner acquisition.*

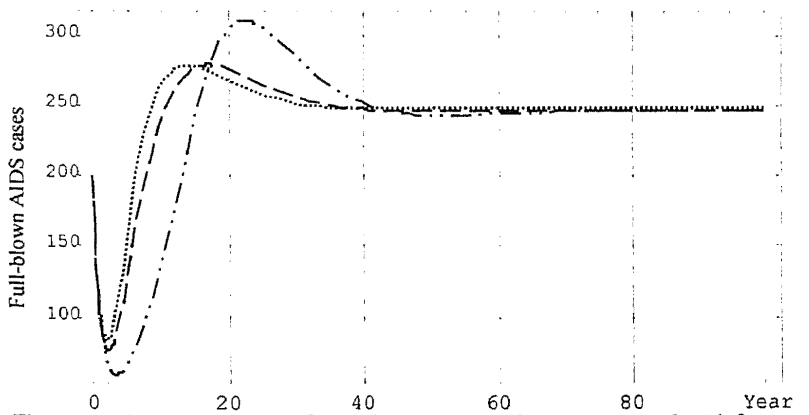

Figure 5.5.8: *Full-blown AIDS population in sexual activity group 2 with from assortative to random and disassortative sexual partner acquisition.*

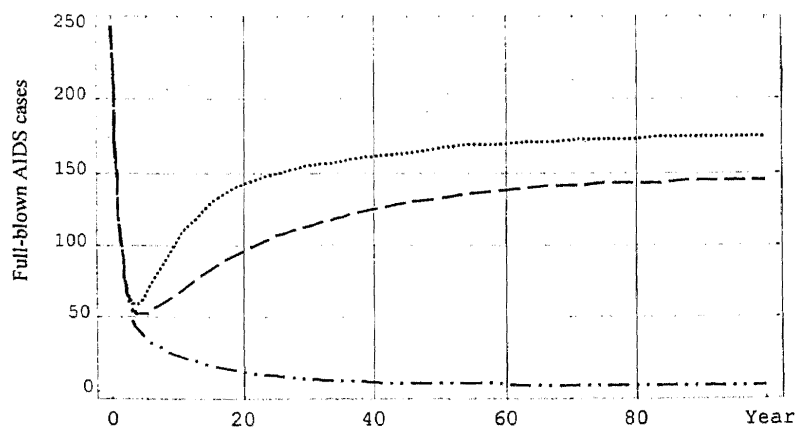

Figure 5.5.9: *Full-blown AIDS population in sexual activity group 3 with from assortative to random and disassortative sexual partner acquisition.*

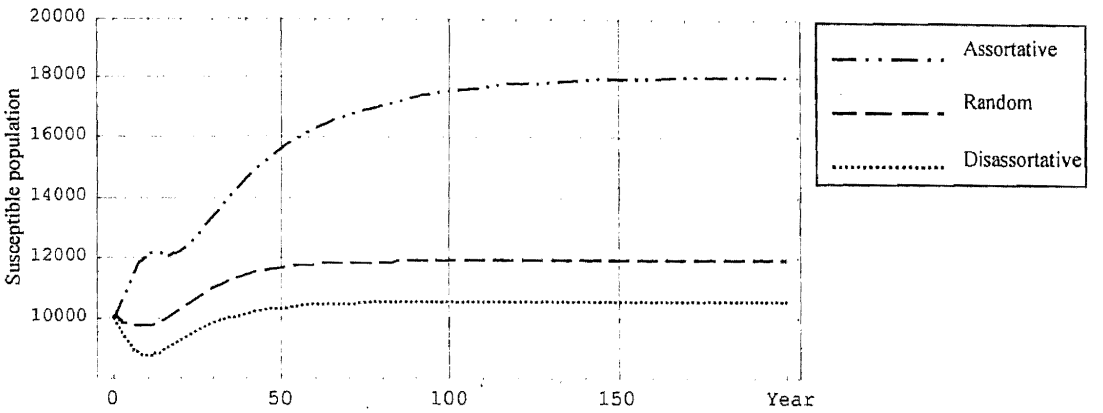

Figure 5.5.10: *Total Susceptibles in all sexual activity groups with from assortative to disassortative sexual partner acquisition.*

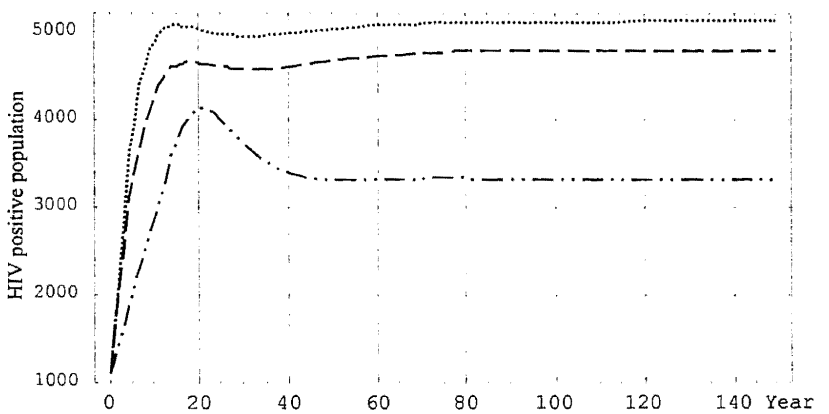

Figure 5.5.11: *Total HIV infected population in all sexual activity groups with from assortative to random and disassortative sexual partner acquisition.*

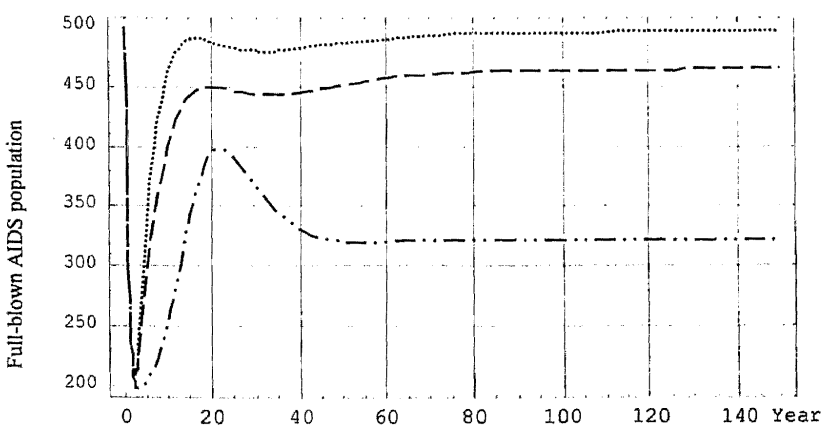

Figure 5.5.12: *Total full-blown AIDS population in all sexual activity groups with from assortative to random and disassortative sexual partner acquisition.*

5.6 Discussion

In this chapter numerical examples illustrate the insufficiency of the existing constraints on the elements of the mixing matrixes for a population of finite size. The major problem arises with the characteristics and nature of the sexual activity of individuals in a population that reports small number of individuals in high activity groups.

Some constraints are presented satisfying all the necessary and sufficient conditions on the elements of the mixing matrix of a finite size population of homosexual men to be a true mixing matrix.

Investigations showed that, assortative populations are less susceptible to the spread of HIV/AIDS than mixed or dis-assortative populations. In other words, whenever sexual mixing pattern varies from a range of assortative to random and dis-assortative the number of susceptibles decrease and the number of HIV infected and AIDS cases increase.

Chapter 6

Mathematical modelling of the effect of the antiviral therapies in the transmission dynamics of HIV/AIDS

With new age medicine and with discoveries in antiviral treatments administered to patients suffering from HIV and AIDS, it is inevitable to take the impact of such treatments into account when devising mathematical models of HIV/AIDS.

Treatment which acts to increase the incubation period before the onset of serious immunodeficiency, but has no impact on the infectiousness of a patient, is obviously beneficial to the individual. However, it can increase net morbidity and mortality when used on a community wide basis. When treatment prolongs the incubation period and reduces the infectiousness, community based chemotherapy is beneficial to both the individual and

community.

In this chapter the impact of anti-HIV treatments in a population with various sexual behaviour is investigated.

6.1 Introduction

Detection and treatment of the so called *cofactor sexually transmitted diseases* has begun to have an effect on the net rate of transmission of HIV in human population. However, the simplest methods to control HIV are condom use and education to encourage reduction in the rate at which individuals acquire new sexual partners. Although simple in concept, little is understood at present of how to induce behavioural changes in any given society or community.

Ideally vaccines will eventually be available, but if they have only moderate efficacy, or induce only short duration of protection, behavioural change will continue to be the desired intervention to limit HIV spread.

A further option in wealthy countries is the use of community wide programmes designed to treat all infected individuals with antiviral therapy. This obviously acts to the benefit of the individual who receives treatment (given the availability of a safe and efficacious drug), but it can also act to reduce net transmission within the community *if therapy reduces the infectiousness of a treated patient.* A number of antiviral agents are able to slow the replication rate of HIV, at least for periods of short to medium duration (i.e. 6 months to a year), and have therefore been able to slow the rate of progression to serious disease or to prolong the life expectancy of AIDS patients.

Examples of the, drugs currently or potentially of use are nucleoside reverse transcription inhibitors such as zidovudine *(ZDV)*, didanosine *(ddI)* and thiacytidine *(3TC)*, non-nucleoside reverse transcription inhibitors such as *L-697* and nevirapine, and protease inhibitors such as saquinavir (see Fischl *et al.*, [47]; Cooper, [33]; Volberding and Graham, [110]). The high mutation rate of HIV coupled with its very high replication rate within the host results in the rapid evolution of resistance to all the drugs in current use (see Richman *et al.*, [97]). After the initiation of therapy, viraemia often declines rapidly with a concomitant rise in CD4+ cells. However, the rapid emergence of resistant variants of the virus can lead to viraemia returning to its pre-treatment level within a few weeks of repeated exposure to the drug (see Ho *et al.*, [61]; Wei *et al.*, [111]).

As such most of the antiviral agents currently in use do not prolong the life expectancy of AIDS patients beyond a few months to a few years. The use of combinations of drugs holds out more promise for the long term suppression of viraemia (and hence the prevention of serious immunodeficiency), but current trials of various combinations have not been of sufficient duration to fully assess the benefits from combination therapy (Hammer *et al.*, [58]).

At present it is not clear that what different drugs combination could provide the best therapy. For example, is it best to administer three different drugs to the patient all at once or should use be staggered with sequential use of each drug? Since the object is to delay the onset of multiple drug resistance, much more thought needs to be given to the population genetics of viral replication under the selective pressures imposed by antiviral therapy.

In the absence of any behavioural change resulting from treatment and associated counselling, antiviral therapy that influences viral load within the treated patient is likely to reduce infectiousness to susceptible sexual part-

ners. The degree to which treatment of the individual will influence the transmission within a community is somewhat difficult to assess, in the absence of a mathematical framework mirroring the dynamics of viral transmission. In this chapter I examine the issue, (extending previous work of G. P. Garnett and R. M. Anderson [52], by the development and analysis of more detailed model) of the impact of antiviral treatment on the infectiousness of a treated patient, and of changes in CD4+ cell numbers during the incubation period of AIDS. Depending on the increase or decrease of the number of CD4+ cells the treated patients move back to the previous or next stage of the infection respectively.

Anderson, Gupta and May [9]; Gupta, Anderson and May [56]; Gupta and Anderson [55] have examined the impact of antiviral therapy at the community base with heterogeneous sexual activity and various patterns of mixing between sexual activity groups. This includes, the effect of antiviral therapy on the endemic prevalence of HIV infections and the associated mortality due to AIDS. One conclusion of these theoretical studies was that community wide treatment with antiviral drugs or immunotherapies that lengthen the incubation period of AIDS, without significantly reducing the infectiousness of treated individuals can increase the rate at which HIV-1 spreads in addition to increase the AIDS related death rate. This conclusion depends on the magnitude of transmission success in the community, the degree of heterogeneity in sexual activity, the pattern of mixing between sexual activity groups, and whether or not treatment is associated with changes in sexual behaviour (see Anderson *et al.*, [9]).

To examine these issues it is important to note that, the time scale and magnitude of an epidemic of an infectious disease depends on the magnitude of the basic reproductive rate (2.3.2).

6.2 Details of the mathematical model incorporating CD4+ cell density

In this section, I have extended the model described by G. P. Garnett and R. M. Anderson [52], which describes progression of an HIV infected patient from infection to AIDS by reference to the average CD4+ cells. I use this template within a broader framework to mirror the transmission dynamics of HIV and antiviral therapy. The choice of CD4+ cells is a simple consequence of the fact that this marker of progression is often used to decide whether or not to initiate antiviral therapy.

The broad structure of the extended model is represented diagrammatically in Figure 6.2.1. Susceptibles enter a primary infection class from which they progress at constant stage specific rates to further stages of infection, until they develop AIDS. The stages of infection represent different levels of CD4 count. At all stages those infected can be treated at a stage specific rate upon which they enter a treatment class, and from which they progress to further stages or go back to previous stage of infection at a different (slower) rate or back into the untreated class.

This framework is used to examine how treatment alters the pattern of an AIDS epidemic in a single sex community. In the model structure it is assumed that treated individuals can pass to an untreated class, to reflect both the termination of treatment due to adverse reactions to the drug and the failure of the drug to be effective, as a consequence of the emergence of drug resistant strains of the virus.

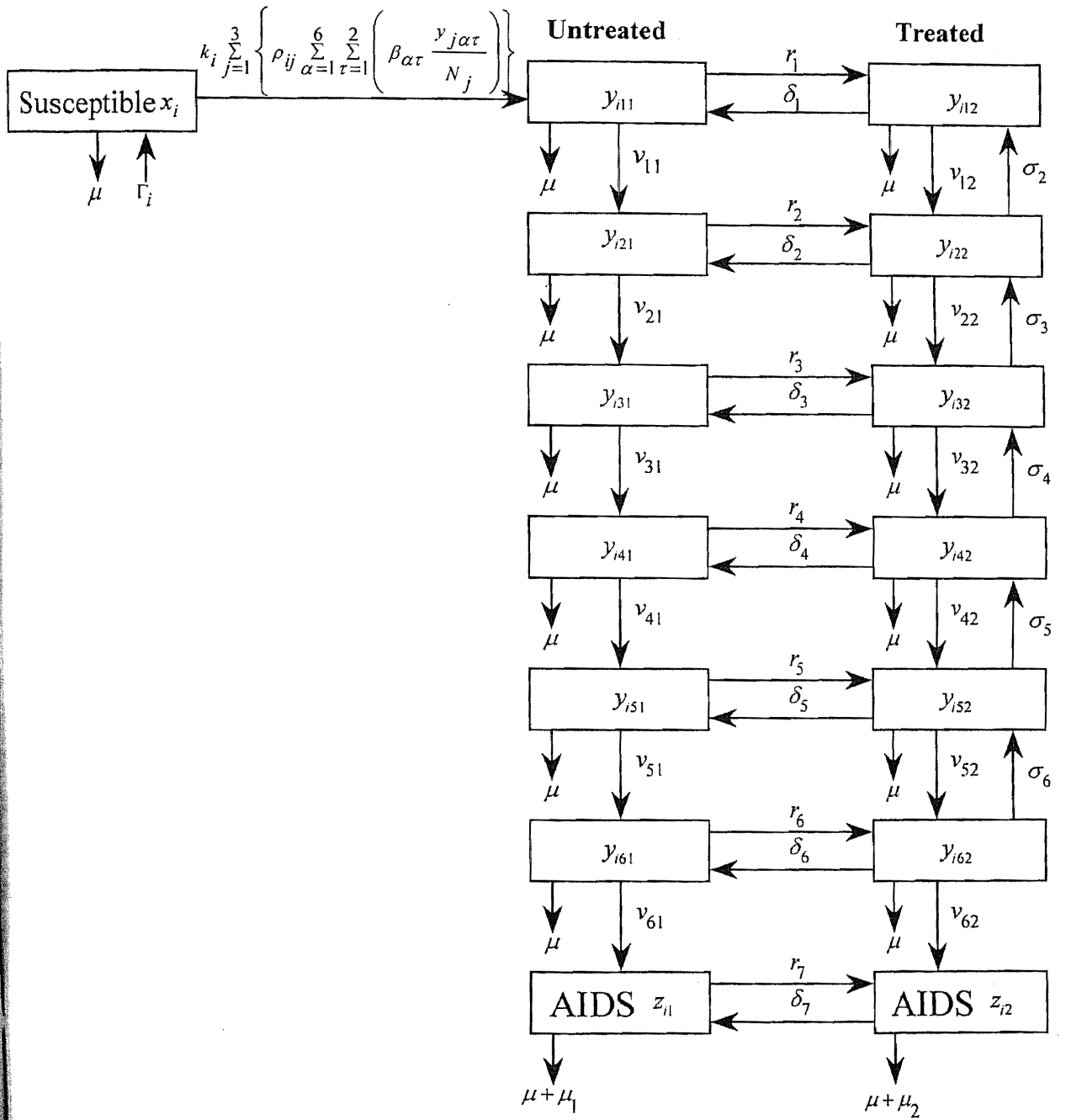

Figure 6.2.1. *A flow diagram illustrating the model used to simulate the HIV epidemic and the impact of antiviral therapy. Susceptibles enter a primary infection class from which they progress at constant stage specific rates to further stage of infection, until they develop AIDS. At all stages those infected can be treated at a stage specific rate upon which they enter a treatment class, and from which they progress to further stage of infection at a different (slower) rate or back into the untreated class or alternatively back into the previous stage of infection.*

Let:

i, j : specify sexual activity groups index, from the highest (sexual activity group 1) to the lowest (sexual activity group 3) range of sexual partner acquisition per unit of time.

α : denote the stage of infection, from primary HIV infection to full-blown AIDS, $\alpha = \{1, \cdots, 7\}$.

τ : represent the treatment status, $\tau = 1$ untreated and $\tau = 2$ denotes treated population.

In general, mathematical model used in simulations represents the population at risk of HIV infection divided into three groups $i, j = \{1, 2, 3\}$, with different levels of sexual activity according to rates of sexual partner change, k_i (see Figure 5.5.1, Section 5.5). The population is also divided into susceptibles x, infected y and full-blown AIDS z.

In particular, the susceptible group (x) is subdivided into $i_{max} = 3$ groups according to the level of sexual activity. The infected population (y) is subdivided into $i_{max} \times \alpha_{max} \times \tau_{max} = 36$ groups according to the level of sexual activity (i), stage of infection (α) and treatment status (τ). Also, full-blown AIDS population is subdivided into $i_{max} \times \tau_{max} = 6$ groups according to the level of sexual activity and treatment status. Therefore, total population is divided into $3 + 36 + 6 = 45$ groups. Constructing the model by a set of 45 non-linear ordinary differential equations gives,

$$
\begin{cases}
\frac{dx_i}{dt} = \Gamma_i - x_i k_i \sum_{j=1}^{3}\{\rho_{ij}\sum_{\alpha=1}^{6}\sum_{\tau=1}^{2}(\beta_{\alpha\tau}\frac{y_{j\alpha\tau}}{N_j})\} - \mu x_i \\
\frac{dy_{i11}}{dt} = x_i k_i \sum_{j=1}^{3}\{\rho_{ij}\sum_{\alpha=1}^{6}\sum_{\tau=1}^{2}(\beta_{\alpha\tau}\frac{y_{j\alpha\tau}}{N_j})\} - (\mu + v_{11} + r_1)y_{i11} + \delta_1 y_{i12} \\
\frac{dy_{i12}}{dt} = r_1 y_{i11} - (\mu + v_{12} + \delta_1)y_{i12} + \sigma_2 y_{i22} \\
\frac{dy_{i\alpha 1}}{dt} = v_{(\alpha-1)1}y_{i(\alpha-1)1} - (\mu + v_{\alpha 1} + r_\alpha)y_{i\alpha 1} + \delta_\alpha y_{i\alpha 2},\ (\alpha = 2,\cdots,6) \\
\frac{dy_{i\alpha 2}}{dt} = v_{(\alpha-1)2}y_{i(\alpha-1)2} + r_\alpha y_{i\alpha 1} + \sigma_{\alpha+1}y_{i(\alpha+1)2} - (\mu + v_{\alpha 2} + \delta_\alpha)y_{i\alpha 2},\ (\alpha = 2,\cdots,5) \\
\frac{dy_{i62}}{dt} = v_{52}y_{i52} + r_6 y_{i61} - (\mu + v_{62} - \delta_6)y_{i62}, \\
\frac{dz_{i1}}{dt} = v_{61}y_{i61} - (r_7 + \mu + \mu_1)z_{i1} + \delta_7 z_{i2} \\
\frac{dz_{i2}}{dt} = v_{62}y_{i62} + r_7 z_{i1} - (\mu + \mu_2)z_{i2} - \delta_7 z_{i2} \\
t > 0 \\
i = \{1,2,3\}
\end{cases}
\tag{6.2.1}
$$

where:

Γ_i : is the immigration rate to the group of susceptibles in sexual activity group i,

μ : specifies the natural mortality rate,

μ_τ : denote mortality rates due to AIDS related disease according to the treatment status,

$\beta_{\alpha\tau}$: indicates the probability that an infected partner transmits infection to

a susceptible partner which depends upon the stage of infection and treatment status,

ρ_{ij} : are the mixing parameters indicating the probability that a partner of someone from sexual activity group i is from sexual activity group j,

k_i : indicate rates at which sexual activity group i, acquire new sexual partners,

$v_{\alpha\tau}$: indicate the rate of movement from stage α to the next stage $(\alpha + 1)$ depending whether treated or not,

r_α : is the rate at which untreated individuals in stage α are diagnosed and join the treated group,

δ_α : is the rate at which treated individuals in stage α reject treatment due to adverse side effects,

σ_α : is the rate at which treated individuals in stage α return to previous stage of infection due to increasing the CD4+ cell count.

Sexual mixing patterns between individuals in different sexual activity groups has an important influence in the pattern of the epidemic (see Section 5.5). I define the pattern mixing on a scale from 'assortative' (like with like) to 'random' and 'dis-assortative' by using the preferred mixing matrix (5.2.8) with the elements of the form of

$$\rho_{ij} = \wp_i I_{ij} + \frac{(1 - \wp_i) N_j k_j}{\sum_{m=1}^{s} (1 - \wp_m) N_m k_m}, \quad 0 \leq \wp_i \leq 1,$$

Parameter values of the rates of progression to AIDS are presented in Table 6.1, derived from the work of Longini *et al.* [76] based on the San Francisco Men's Health Study (see also model developed by Jacquez *et al.* [64]). Assumptions made on the size of the population and its behavioural parameters used in implementations are summarised in Table 6.2.

Table 6.1: *Rates of progress through the seven stage of HIV infection*

α	CD4 cell count	r_α	$\beta_{\alpha 1}$	$\beta_{\alpha 2}$	$1/v_{\alpha 1}$	$1/v_{\alpha 2}$	σ_α	δ_α
1		0	0.2	0.1	NA	NA	0.75	0.3
2	>900	0.9	0.01	0.005	1.12	1.62	0.1	0.3
3	700-899	0.72	0.01	0.005	1.39	1.89	0.1	0.4
4	500-699	0.42	0.01	0.005	2.38	2.88	0.1	0.4
5	350-499	0.37	0.01	0.005	2.69	3.19	0.1	0.5
6	200-349	0.72	0.1	0.05	1.39	1.89	0.1	0.5
AIDS	<200	1.43	NA	NA	0.7	1.2	0.0	0.5

Table 6.2: *Demographic and behavioural parameters used for model simulations*

	Activity group 1	Activity group 2	Activity group 3
Γ_i	100	400	500
N_i	20000	80000	100000

I have made some minor alterations to these values to reflect the current understanding, such as an increase of 7 months in the duration of stay in the primary stage of infection with a corresponding decrease in the second stage.

[c]

Main interest is in the relative advantages and disadvantages of early treatment during the course of the incubation period. To examine the problem, for illustrative purposes, the impact of treatment on the duration of stay in any one class is defined. Antiviral therapy (for example, zidovudine) acts to suppress viraemia and concomitantly, CD4 cell counts increase. As such drugs tend to slow the progression to AIDS. An example is the study by Cooper *et al.* [34] which showed that induction of antiretroviral therapy in

subject with CD4 cell counts of over 400, significantly slowed the progression of disease and the decline in the CD4 cell count. In rough accord with the available data, it is assumed that treatment adds six months to the average duration of stay in each stage of infection.

The estimation of transmission probabilities during the course of infection to the development of AIDS is fraught with many problems. Transmission probability is defined per sexual partnership (as opposed to per sexual act) since this is the most frequently measured parameter in studies of discordant sexual partnership (initially one infected, one susceptible) (Garnett and Anderson, [50]). The relationship between the two measures (per partnership and per act) is unclear at present due to much heterogeneity in the available data. Heterogeneity in the likelihood of transmission over the incubation period of AIDS is known to occur, and the most reasonable assumption at present is that the likelihood is, in some manner, related to the level of viraemia (certainly the case for vertical transmission). This is an area of uncertainty since the quantity of virus in the blood may not reflect infectiousness and furthermore, the genetic constitution of the viral may be more important than viral load. However, in the absence of knowledge to the contrary, I assume that infectiousness is proportional to viraemia and that it is highest in the earliest stages of infection (Anderson, [6]; Jacques *et al.*, [64]).

The values recorded in Table 6.1 for changes in infectiousness in the different stages of infection, plus those assumed for the way treatment lengthens the duration of stay in any one group (i.e. 6 months for all groups) are purely illustrative at present. Their definition within a model framework highlights the need of the quantitative data in this area.

Other areas of uncertainty include the details of sexual behaviour. As defined the model framework includes heterogeneity in the rate of sexual

partner acquisition and variability in the pattern of mixing between sexual activity groups (random and assortative i.e. like with like (see Garnett and Anderson, [51])). The endemic prevalence of HIV infection in the absence of treatment is a function of transmission success as defined earlier. A key component of this success is the magnitude of the average transmission probability over the incubation period for assumptions of random or moderately assortative mixing between sexual activity groups. If the pre-treatment value of the transmission probability is low (but sufficient for $R > 1$) then small reductions in its value arising from the treatment of a fraction of the infected population will have a significant impact on HIV prevalence.

6.3 The analysis of the effect of antiviral therapies and sexual mixing patterns in transmission dynamics of HIV/AIDS

To examine the effect of the antiviral therapies and different sexual mixing patterns in the transmission dynamics of HIV/AIDS, mathematical model (6.2.1) is analysed (see Sections 2.3.1 and 2.3.2) and solved using alternative method (see Section 3.3.2) choosing optimum time step of $h = 0.127$ (see Section 3.2.3).

Mixing matrices representing sexual mixing patterns for the population detailed in Table 6.1, Section 6.2 from dis-assortative to random and assortative using preferred matrix (5.2.8) are presented as follow:

i) **Dis-assortative sexual mixing pattern:** substituting mixing parameters $\wp_1 = \wp_2 = \wp_3 = 0.1$ in the equation (5.2.8) gives the dis-

assortative mixing matrix

$$\rho_d = \begin{bmatrix} 0.60 & 0.33 & 0.07 \\ 0.50 & 0.43 & 0.07 \\ 0.50 & 0.33 & 0.17 \end{bmatrix}, \tag{6.3.2}$$

representing the population with dis-assortative sexual partner acquisition behaviour.

ii) **Random sexual mixing pattern:** substituting mixing parameters $\wp_1 = \wp_2 = \wp_3 = 0.5$, in equation (5.2.8) gives

$$\rho_r = \begin{bmatrix} 0.78 & 0.18 & 0.04 \\ 0.28 & 0.68 & 0.04 \\ 0.28 & 0.18 & 0.54 \end{bmatrix}, \tag{6.3.3}$$

representing the population with random sexual partner acquisition behaviour.

iii) **Assortative sexual mixing pattern:** substituting mixing parameters $\wp_1 = \wp_2 = \wp_3 = 0.9$, in equation (5.2.8) gives

$$\rho_a = \begin{bmatrix} 0.95 & 0.04 & 0.01 \\ 0.05 & 0.94 & 0.01 \\ 0.05 & 0.04 & 0.91 \end{bmatrix} \tag{6.3.4}$$

representing the population with assortative sexual acquisition behaviour.

The above mixing matrices are used to proceed with the following model analysis.

The trivial critical point of the system (6.2.1), is of the form of

$$X_1^* = [\frac{\Gamma_1}{\mu}, \frac{\Gamma_2}{\mu}, \frac{\Gamma_3}{\mu}, 0, \cdots, 0]^T \tag{6.3.5}$$

(see Section 2.3.1). This will be used later in computing reproductive rate.

6.3.1 Untreated population

In the implementations, system of equations (6.2.1) can be used to describe a population without treatment.

Parameter r_α for $\alpha = \{1, \cdots, 6\}$ represent the rate at which HIV infected population receive treatment at stage α, the seventh stage of infection is full-blown AIDS, therefore r_7 represent the proportion of full-blown AIDS population who receive treatment. Placing zero instead of r_α for $\alpha = \{1, \cdots, 7\}$ and the initial values of the treated population fixed at zero in model equations (6.2.1) give a set of equation simulating the population without treatment.

The population is stratified into three sexual activity groups, including susceptible, six stages of HIV infection and full-blown AIDS patients. Parameter values are presented in 6.1, Section 6.2.

i) **Dis-assortative sexual mixing pattern:** the determinant of the Jacobian associated with the model equation (6.2.1) of the form of (2.2.3), at the trivial critical point (6.3.5), after substituting dis-assortative mixing matrix (6.3.2) vanishes whenever,

$$k_1^* = 5.48$$

Assuming sexual activity group 1 with an average of $k_1 = 65$ new sexual partners per unit of time, gives the total reproductive rate of the population

$$R_d = \frac{k_1}{k_1^*} = 11.86 \tag{6.3.6}$$

ii) **Random sexual mixing pattern:** by substituting random mixing matrix (6.3.3) in model equation (6.2.1), the determinant of its Jacobian of the form of (2.2.3) at the trivial critical point (6.3.5) vanishes

whenever,

$$k_1^* = 4.29$$

Assuming sexual activity group 1 with an average of $k_1 = 65$ new sexual partners per unit of time, gives the total reproductive rate of the population

$$R_r = \frac{k_1}{k_1^*} = 15.15 \tag{6.3.7}$$

iii) **Assortative sexual mixing pattern:** finally by substituting assortative mixing matrix (6.3.4) in model equations (6.2.1), the determinant of its Jacobian of the form of (2.2.3) at the trivial critical point (6.3.5) vanishes whenever,

$$k_1^* = 3.39$$

Assuming sexual activity group 1 with an average of $k_1 = 65$ new sexual partners per unit of time, gives the total reproductive rate

$$R_a = \frac{k_1}{k_1^*} = 19.17 \tag{6.3.8}$$

Comparing the total reproductive rates of the population with dis-assortative (6.3.6), random (6.3.7) and assortative (6.3.8) sexual mixing patterns indicate that $R_d < R_r < R_a$, meaning that the total reproductive rate for dis-assortative sexual pattern is grater than the total reproductive rate of the random mixing followed by the total reproductive rate of the assortative mixing pattern.

In this section, Figures 6.3.1-6.3.21 represent the graphical solution of the system of equations (6.2.1) simulating the population without treatment.

Figures 6.3.1-6.3.3 represent the susceptible population in three sexual activity groups ranging from 'assortative' to 'random' and 'dis-assortative'

sexual mixing patterns. In general, at the steady state the total number of susceptibles for the assortative mixing pattern is shown to be higher than the random, which in turn is greater than a dis-assortative mixing pattern, for all sexual activity groups. The growths of the number of the susceptible population from dis-assortative to random is 10% and from dis-assortative to assortative 16%, for sexual activity group 1 as shown in Figure 6.3.1. In Figure 6.3.2, the growths from dis-assortative to random is 12% and from dis-assortative to assortative 25%, for sexual activity group 2. In Figure 6.3.3, the growth from dis-assortative to random is 14% and from dis-assortative to assortative 43%, for sexual activity group 3.

From the above therefore, it may be concluded that the growth of the number of susceptibles is shown to demonstrate a pattern; namely that the growth for sexual activity group 3 is higher than group 2 and group 2 higher than group 1. This means the effect of sexual mixing patterns on the number of susceptibles in populations with lower number of sexual partner acquisition is more considerable.

Figures 6.3.4-6.3.9 represent the six stages of HIV infection for sexual activity groups 1 and 2 which indicate that the mixing patterns have no significant impact on the steady state solution (less than 5%). Significantly, the transient state shows that the assortative mixing pattern contains the highest peaks occurring within a shorter period of time compared to those of a random and dis-assortative nature which occur at later periods of time at all stages respectively.

Figures 6.3.10, 6.3.11 and 6.3.12 represent the six stages of HIV infected population within sexual activity groups 3. Figure 6.3.10 shows that at the steady state, HIV infected populations with an assortative mixing pattern declines to zero due to low levels of sexual partner acquisition. In Figures

6.3.11 and 6.3.12, at the steady state, the total number of HIV infected with random mixing pattern "=400" is lower than the dis-assortative mixing pattern "=570". In the transient state the assortative mixing pattern contains the highest peaks occurring within a shorter period of time compared to those of a random and dis-assortative nature which occur at later periods of time at all stages.

Figures 6.3.13, 6.3.14 and 6.3.15 represent the total number of HIV infected population for sexual activity groups 1, 2 and 3 according to the sexual mixing patterns. Figures 6.3.13 and 6.3.14 show that sexual mixing pattern has no significant impact on the total number of HIV infected for sexual activity group 1 and 2 at steady state. Figure 6.3.15 shows that total number of HIV infected population with assortative sexual mixing pattern vanishes at early stage. It also indicates that total number of HIV infected population with random mixing pattern is lower than dis-assortative mixing pattern at all the time.

Figures 6.3.16, 6.3.17 and 6.3.18 represent the total number of full-blown AIDS population for sexual activity groups 1, 2 and 3 according to the sexual mixing patterns. Figures 6.3.16 and 6.3.17 show that sexual mixing pattern has no significant impact on the total number of full-blown AIDS cases for sexual activity group 1 and 2 at steady state. Figure 6.3.18 shows that total number of full-blown AIDS population with assortative sexual mixing pattern vanishes at early stage. It also indicates that total number of full-blown AIDS cases with random mixing pattern is lower than dis-assortative mixing pattern at all the time. In transient state of the solution, dis-assortative mixing pattern contains the highest pick followed by random and assortative mixing pattern at shorter period of time.

Figures 6.3.19, 6.3.20 and 6.3.21 represent the total number of suscept-

ible, HIV infected and full-blown AIDS cases in the population respectively. Figure 6.3.19 indicates that the growth of the number of susceptibles from dis-assortative to random sexual mixing pattern is 10% and to assortative mixing is 30%. Figure 6.3.20 indicates that the number of HIV infected from dis-assortative to random sexual mixing pattern decline by 10% and to assortative mixing decline by 29%. Figure 6.3.21 indicates that the number of full-blown AIDS cases from dis-assortative to random sexual mixing pattern decline by 3% and to assortative mixing decline by 6%.

From the above it can be concluded that for an untreated population whenever the sexual mixing pattern varies from a range of assortative to random and dis-assortative the number of susceptibles decrease and the number of HIV infected and AIDS cases increase.

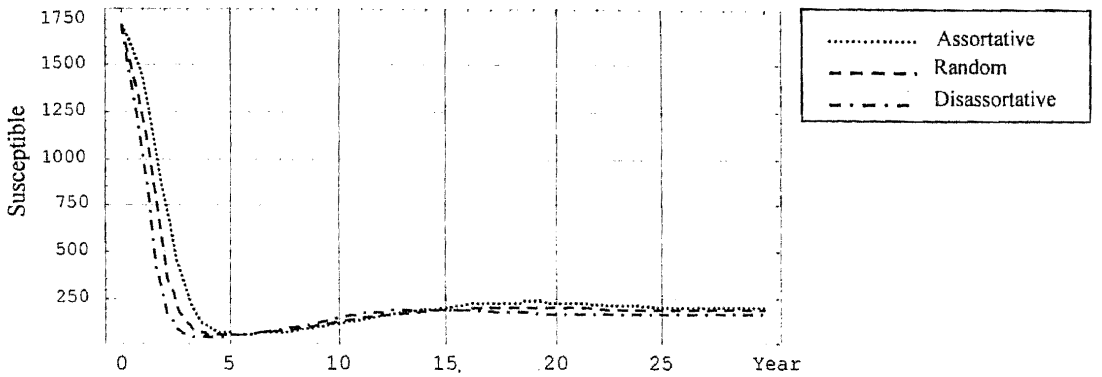

Figure 6.3.1: *Susceptibles in sexual activity group 1, from fully assortative to disassortative sexual partner acquisition.*

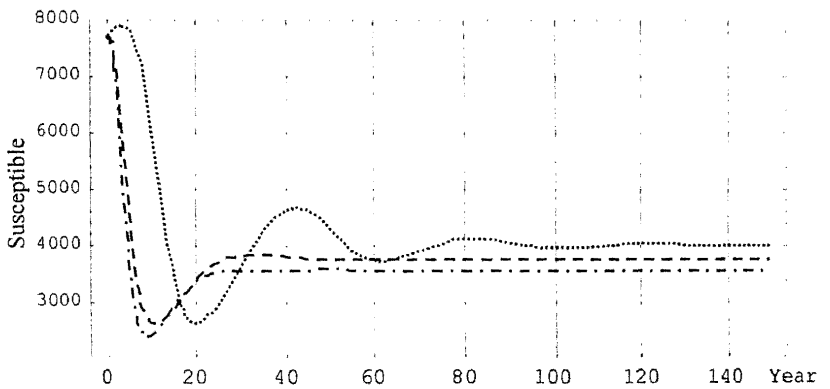

Figure 6.3.2: *Susceptibles in sexual activity group 2, from fully assortative to disassortative sexual partner acquisition.*

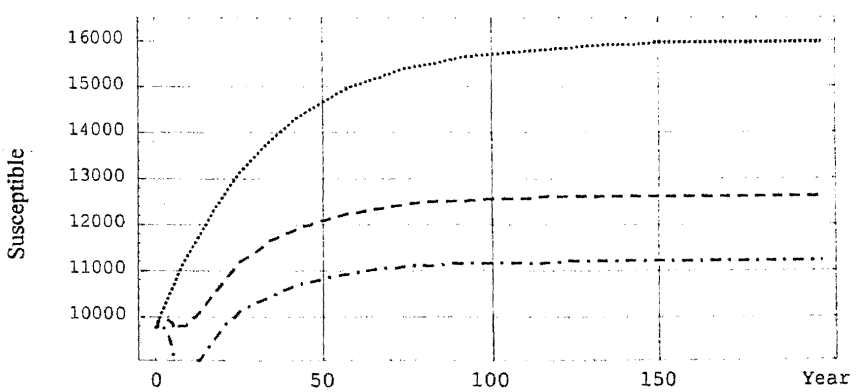

Figure 6.3.2: *Susceptibles in sexual activity group 2, from fully assortative to disassortative sexual partner acquisition.*

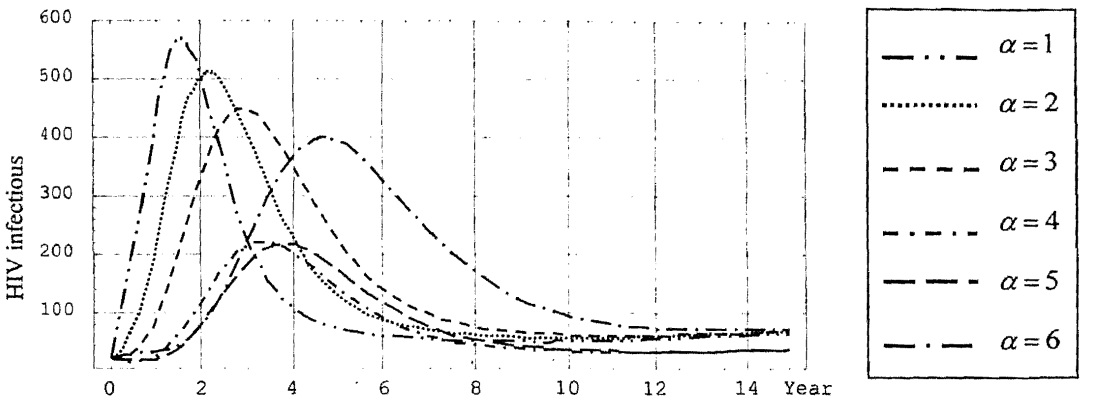

Figure 6.3.4: *Six stages of HIV infectious in sexual activity group 1, with fully assortative sexual partner acquisition.*

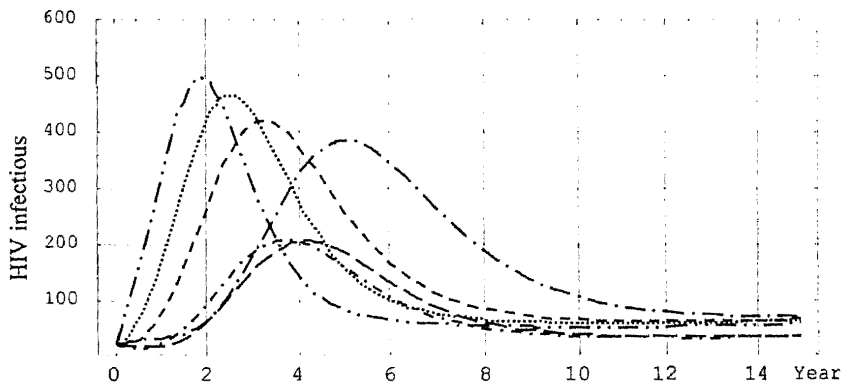

Figure 6.3.5: *Six stages of HIV infectious in sexual activity group 1, with random sexual partner acquisition.*

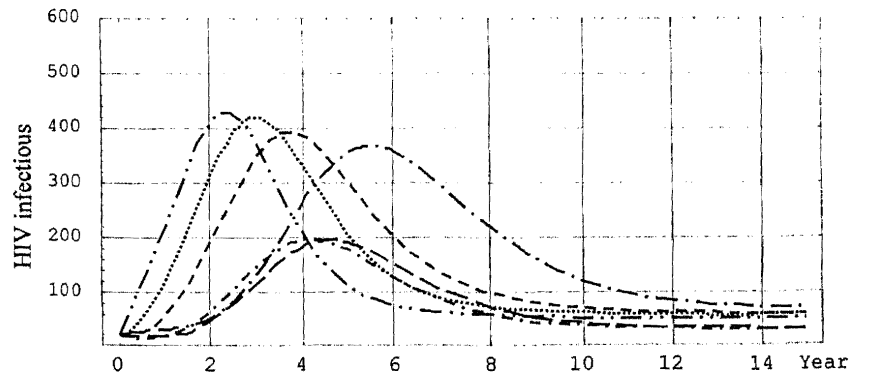

Figure 6.3.6: *Six stages of HIV infectious in sexual activity group 1, with disassortative sexual partner acquisition.*

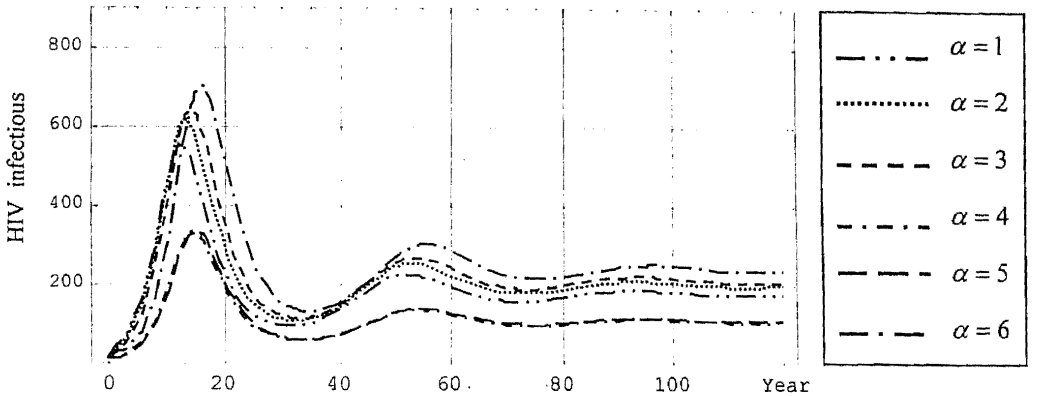

Figure 6.3.7: *Six stages of HIV infection in sexual activity group2, with assortative sexual partner acquisition.*

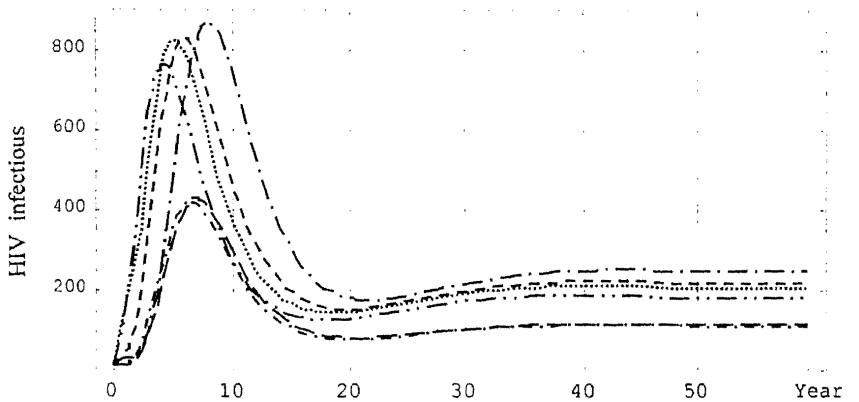

Figure 6.3.8: *Six stages of HIV infection in sexual activity group2, with random sexual partner acquisition.*

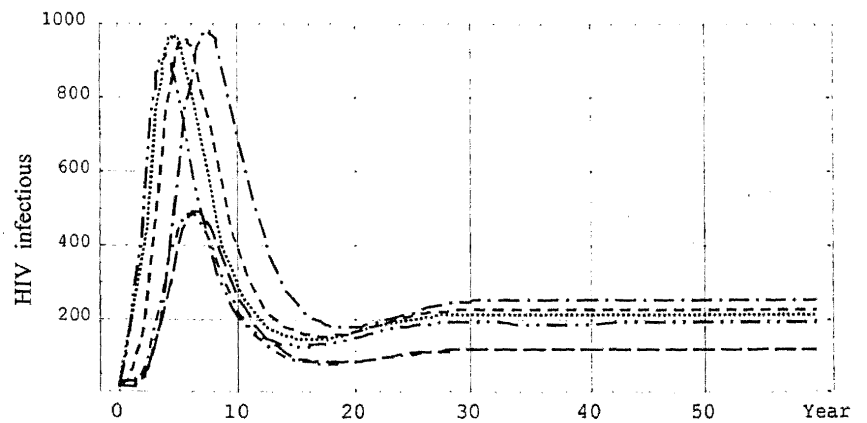

Figure 6.3.9: *Six stages of HIV infection in sexual activity group2, with disassortative sexual partner acquisition.*

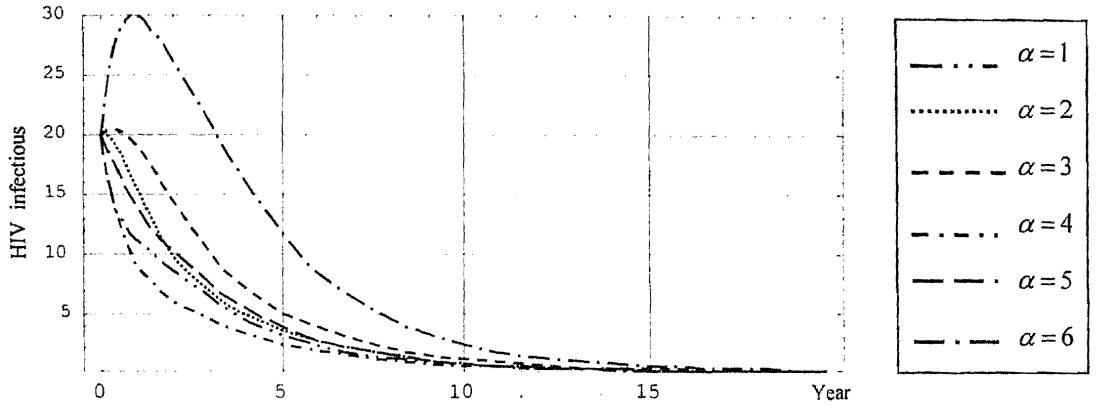

Figure 6.3.10: *Six stages of HIV infection in sexual activity group3, with assortative sexual partner acquisition.*

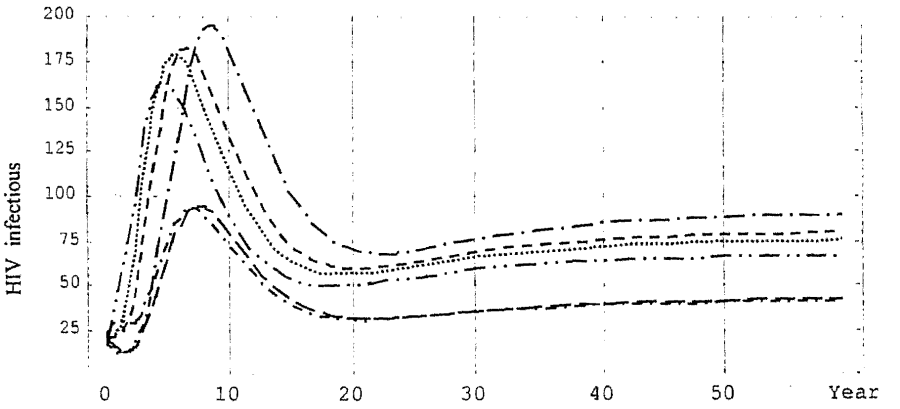

Figure 6.3.11: *Six stages of HIV infection in sexual activity group3, with random sexual partner acquisition.*

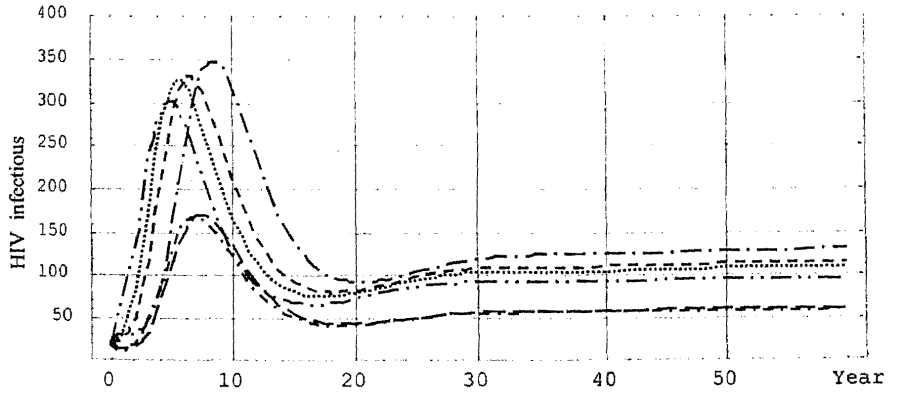

Figure 6.3.12: *Six stages of HIV infection in sexual activity group3, with disassortative sexual partner acquisition.*

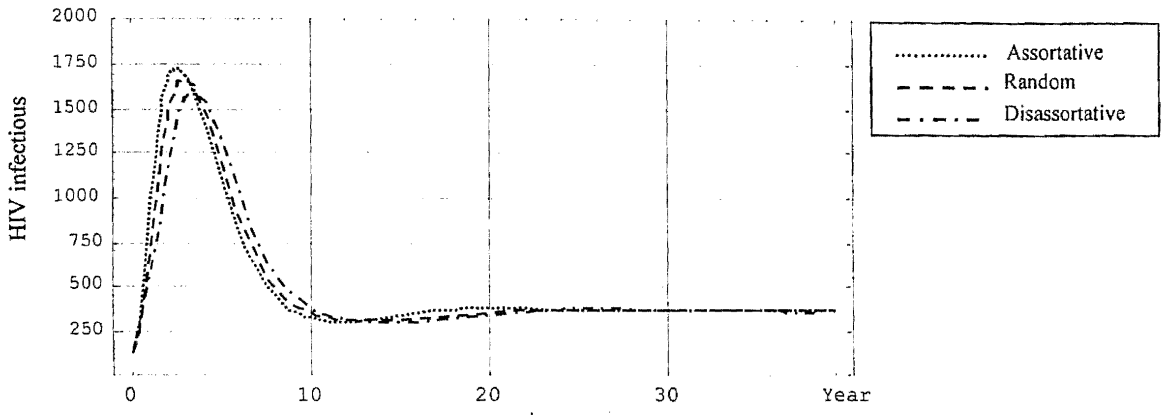

Figure 6.3.13: *Total HIV infected population in sexual activity group 1, with from assortative to random and disassortative sexual partner acquisition.*

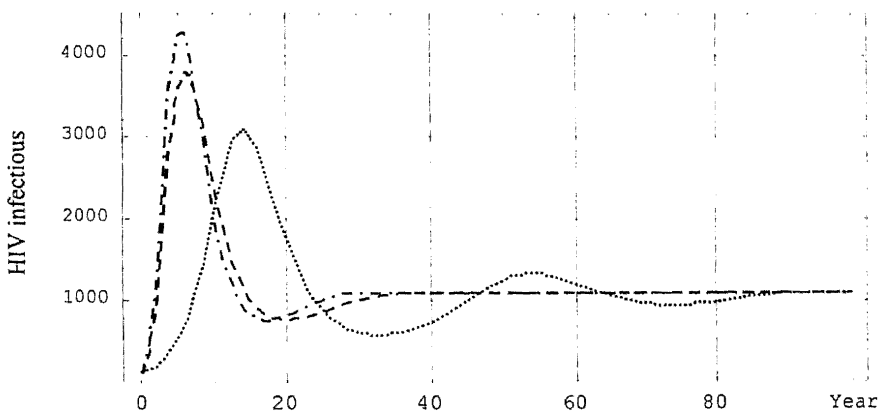

Figure 6.3.14: *Total HIV infected population in sexual activity group 2, with from assortative to random and disassortative sexual partner acquisition.*

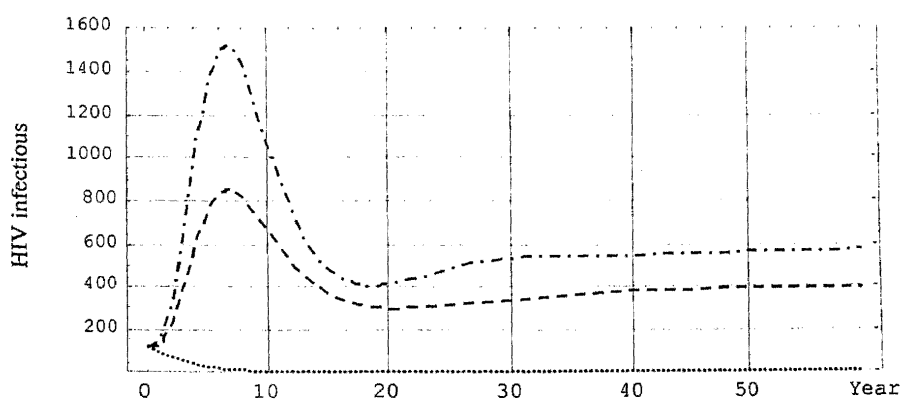

Figure 6.3.15: *Total HIV infected population in sexual activity group 3, with from assortative to random and disassortative sexual partner acquisition.*

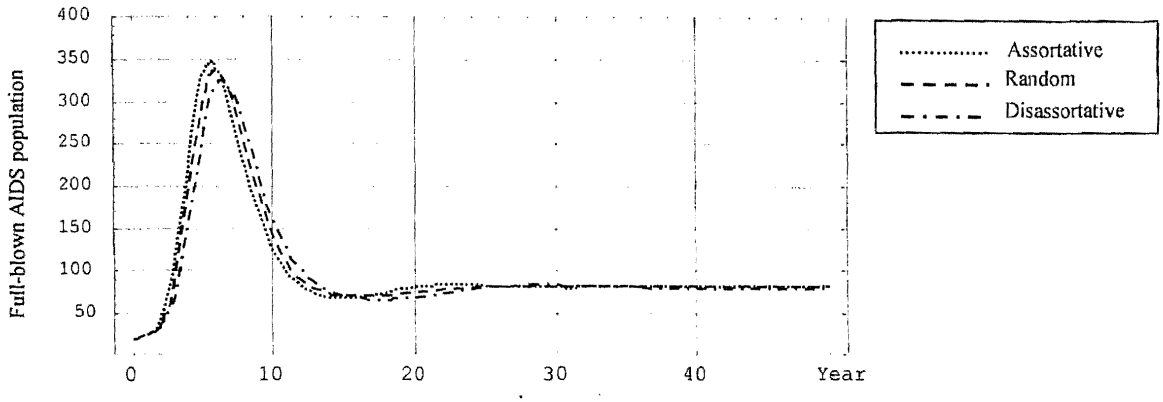

Figure 6.3.16: *Full blown AIDS population in sexual activity group 1, with from assortative to random and disassortative sexual partner acquisition.*

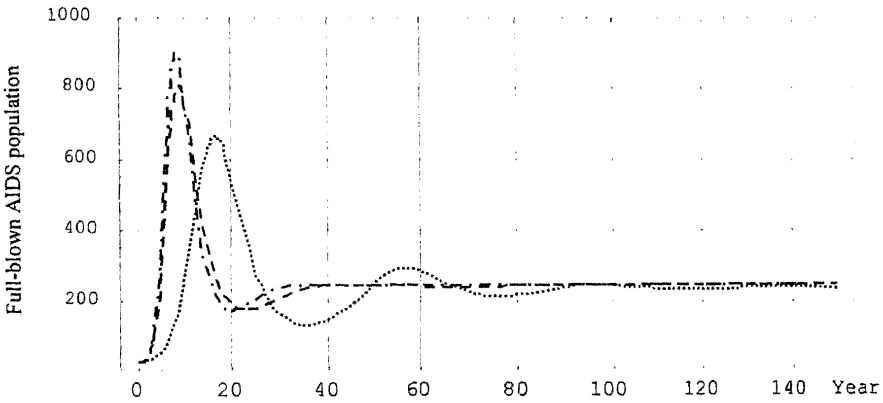

Figure 6.3.17: *Full blown AIDS population in sexual activity group 2, with from assortative to random and disassortative sexual partner acquisition.*

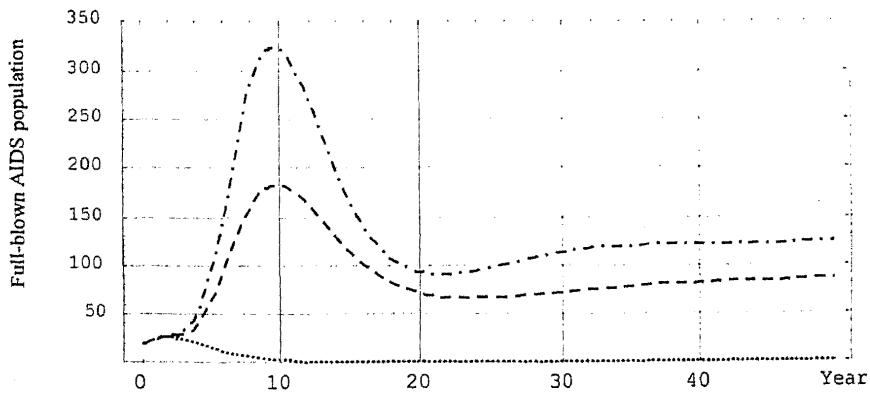

Figure 6.3.18: *Full blown AIDS population in sexual activity group 3, with from assortative to random and disassortative sexual partner acquisition.*

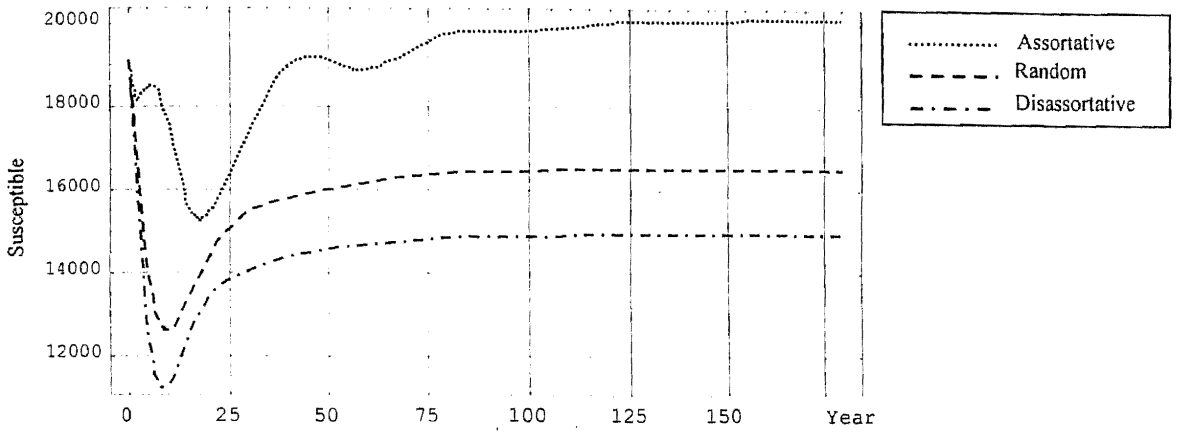

Figure 6.3.19: *Population's total susceptible with from assortative to random and disassortative sexual mixing behaviour.*

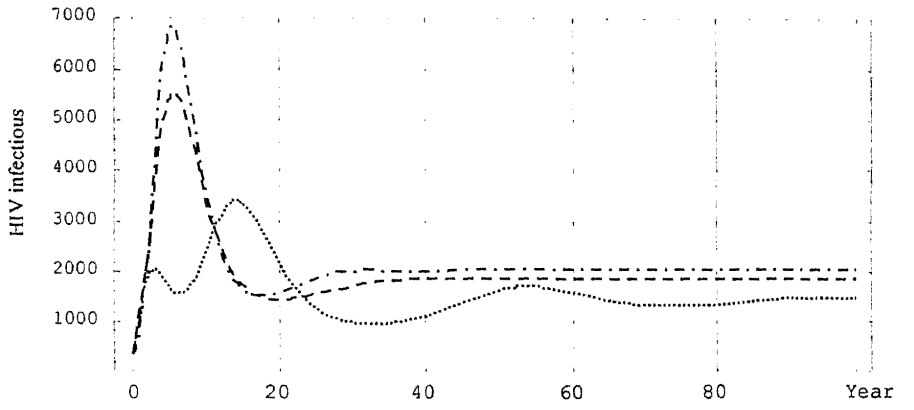

Figure 6.3.20: *Population's total HIV infectious with from assortative to random and disassortative sexual mixing behaviour.*

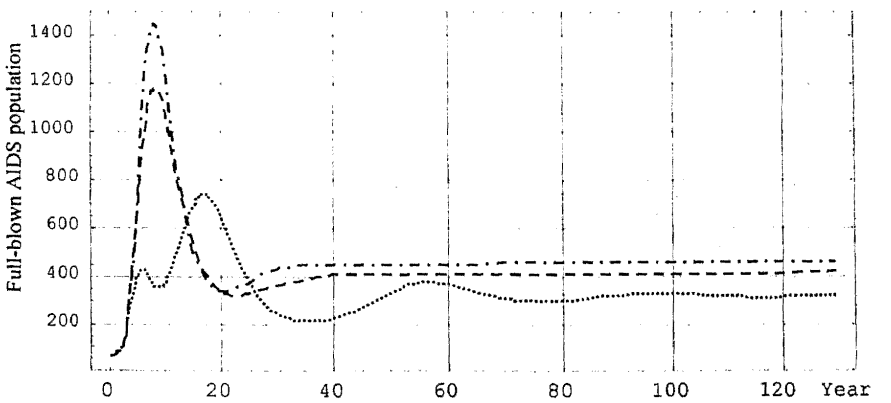

Figure 6.3.21: *Population's total full-blown AIDS cases with from assortative to random and disassortative sexual partner acquisition.*

6.3.2 Partially treated population, assuming treatment has no effect in infectiousness

Model equation (6.2.1) can be used to describe a partially treated population, assuming that treatment does not effect infectiousness. Parameters $\beta_{\alpha 2}$ represent infectiousness (transmission probability) of the treated population at stage α, $\alpha = \{1, \cdots, 6\}$. Placing $\beta_{\alpha 1} = \beta_{\alpha 2}$ for $\alpha = \{1, \cdots, 6\}$ in the model equations (6.2.1) gives a set of equation simulating a partially treated population in which treatment does not effect infectiousness. The population stratified into three sexual activities groups, including susceptible, six stages of HIV infection and full-blown AIDS patients. Parameter values are presented in 6.1, Section 6.2.

i) **Dis-assortative sexual mixing pattern:** by substituting dis-assortative mixing matrix (6.3.2) in the model equations (6.2.1), the determinant of the Jacobian of the form of (2.2.3) associated with the system at the trivial critical point (6.3.5) vanishes whenever,

$$k_1^* = 5.95$$

Assuming sexual activity group 1 with an average of $k_1 = 65$ new sexual partners per unit of time, gives the total reproductive rate

$$R_d = \frac{k_1}{k_1^*} = 10.92 \tag{6.3.9}$$

ii) **Random sexual mixing pattern:** by substituting random mixing matrix (6.3.3) in the model equations (6.2.1), the determinant of the Jacobian of the form of (2.2.3), associated with the model equation at the trivial critical point (6.3.5) vanishes whenever,

$$k_1^* = 4.65$$

Assuming sexual activity group 1 with an average of $k_1 = 65$ new sexual partners per unit of time, gives the total reproductive rate

$$R_r = \frac{k_1}{k_1^*} = 13.98 \tag{6.3.10}$$

iii) Assortative sexual mixing pattern: by substituting assortative mixing matrix (6.3.4) in the model equations (6.2.1), the determinant of the Jacobian of the form of (2.2.3), associated with the model equation at the trivial critical point (6.3.5) vanishes whenever,

$$k_1^* = 3.67$$

Assuming sexual activity group 1 with an average of $k_1 = 65$ new sexual partners per unit of time, gives the total reproductive rate

$$R_a = \frac{k_1}{k_1^*} = 17.71 \tag{6.3.11}$$

Comparing total reproductive rates with from dis-assortative (6.3.9), to random (6.3.10) and assortative (6.3.11) sexual mixing patterns indicate that $R_d < R_r < R_a$ meaning that the total reproductive rate for dis-assortative sexual pattern is grater than the total reproductive rate of the random mixing followed by the total reproductive rate of the assortative mixing pattern.

Figures 6.3.22-6.3.54 represent the graphical solution to the system of equations (6.2.1) simulating a partially treated population assuming that treatment does not effect infectiousness.

Figures 6.3.22-6.3.24 represent the susceptible population in three sexual activity groups ranging from 'assortative' to 'random' and 'dis-assortative' sexual mixing patterns. In general, the total number of susceptibles for the assortative pattern is shown to be higher than the random pattern, which in

turn is greater than a dis-assortative mixing pattern, for all sexual activity groups at the steady state.

At the steady state, the growths of the number of the susceptible population from dis-assortative to random is 25% and from dis-assortative to assortative 75%, for sexual activity group 1 as shown in Figure 6.3.22. In Figure 6.3.23, the growths from dis-assortative to random is 8% and from dis-assortative to assortative 16%, for sexual activity group 2. In 6.3.24, the growth from dis-assortative to random is 2% and from dis-assortative to assortative 5%, for sexual activity group 3.

From the above therefore, it may be concluded that the growth of the number of susceptibles is shown to demonstrate a pattern; namely that the growth for sexual activity group 1 is higher than group 2 and group 2 higher than group 3. This means the effect of sexual mixing patterns on the number of susceptibles in populations with higher number of sexual partner acquisition is more considerable.

Figures 6.3.25-6.3.36 represent six stages of treated and untreated HIV infectious population within sexual activity groups 1 and 2 which indicate that the mixing patterns have no significant impact on the steady state solution (less than 5%). However at, steady state the total number of treated HIV infectious population appear to be one third of the untreated HIV infectious population, this ratio depends on the rates at which infected population are diagnosed and receive treatment (r_α) for $\alpha = \{1, \cdots, 6\}$.

Significantly, the transient state shows that the dis-assortative mixing pattern contains the highest peaks occurring within a shorter period of time compared to those of a random and assortative nature which occur at later periods of time at all stages for both treated and untreated populations.

Figures 6.3.37-6.3.42 represent the six stages of treated and untreated HIV infectious population within sexual activity groups 3. Figures 6.3.37 and 6.3.40 show that at the steady state, treated and untreated HIV infectious populations with an assortative mixing pattern declines to zero due to sexual life style (assortative mixing). In Figures 6.3.38 and 6.3.39 at the steady state, the total number of untreated HIV infectious with random mixing pattern is lower than the dis-assortative mixing pattern. In Figures 6.3.41 and 6.3.42 at the steady state, the total number of treated HIV infectious with random mixing pattern is lower than the dis-assortative mixing pattern. Theses show an increase of 47% from random mixing pattern to dis-assortative mixing for both treated and untreated HIV infected population within sexual activity group 3. In the transient state the dis-assortative mixing pattern contains the highest peaks occurring within a shorter period of time compared to those of a random and assortative nature which occur at later periods of time at all stages.

Figures 6.3.43, 6.3.44 and 6.3.45 represent the treated and untreated AIDS population in sexual activity group 1, showing assortative, random and dis-assortative patterns respectively. At steady state no significant difference is observed according to sexual mixing patterns for both treated and untreated AIDS populations. However, the transient state shows that the assortative mixing pattern contains the highest peak occurring within a shorter period of time compared to those of a random and dis-assortative nature which occur at later periods.

Figures 6.3.46, 6.3.47 and 6.3.48 represent the treated and untreated AIDS population in sexual activity group 2, showing assortative, random and dis-assortative patterns respectively. At steady state no significant difference is observed according to the sexual mixing patterns for both treated

and untreated full-blown AIDS cases. However, the transient state shows that the dis-assortative mixing pattern contains the highest peak occurring within a shorter period of time compared to those of a random and assortative nature which occur at later periods of time at all stages.

Figures 6.3.49, 6.3.50 and 6.3.51 represent the treated and untreated AIDS population in sexual activity group 3. At steady state the number of treated and untreated AIDS cases with assortative sexual behaviour declines to zero. At steady state, the random pattern is lower than the dis-assortative pattern by a factor of 50% for both treated and untreated AIDS populations. In transient state of the solution, dis-assortative mixing pattern contains the highest pick followed by random and assortative mixing pattern at shorter period of time.

Figures 6.3.52, 6.3.53 and 6.3.54 represent the total number of susceptible, HIV infected and full-blown AIDS cases in a partially treated population respectively assuming that the treatment does not effect infectiousness. Figure 6.3.52 indicates that the growth of the number of susceptibles from dis-assortative to random sexual mixing pattern is 11% and to assortative mixing is 32%. Figure 6.3.53 indicates that the number of HIV infected from dis-assortative to random sexual mixing pattern decline by 16% and to assortative mixing decline by 31%. Figure 6.3.54 indicates that the number of full-blown AIDS cases from dis-assortative to random sexual mixing pattern decline by 10% and to assortative mixing decline by 31%.

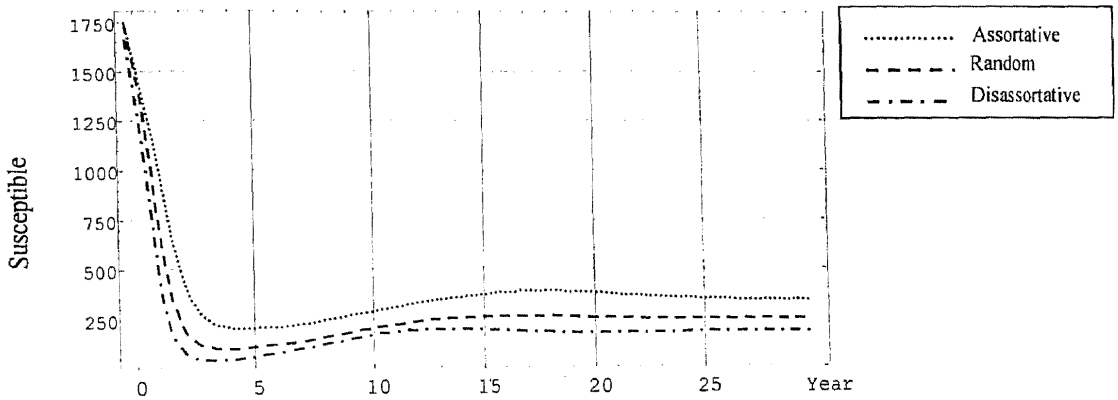

Figure 6.3.22: *Susceptibles in sexual activity group 1, with from assortative to random and disassortative sexual partner acquisition, assuming treatment does not effect infectiousness.*

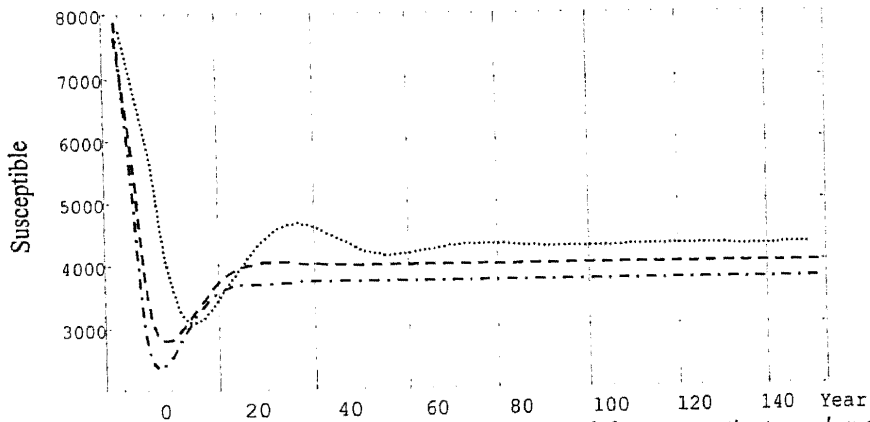

Figure 6.3.23: *Susceptibles in sexual activity group 2,with from assortative to random and disassortative sexual partner acquisition, assuming treatment does not effect infectiousness.*

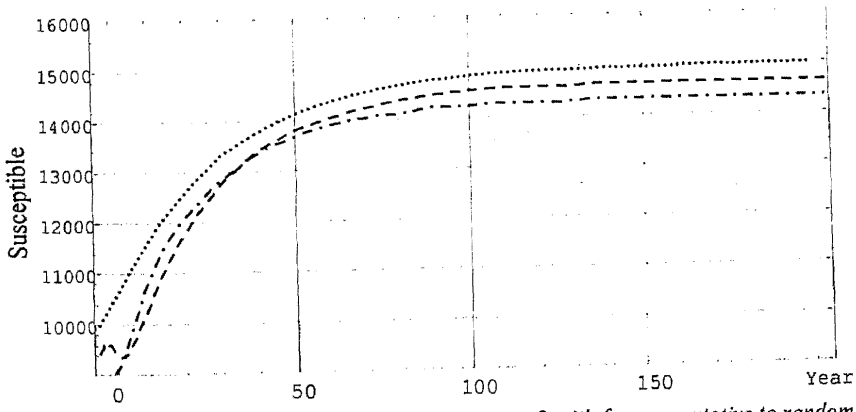

Figure 6.3.24: *Susceptibles in sexual activity group 3,with from assortative to random and disassortative sexual partner acquisition, assuming treatment does not effect infectiousness.*

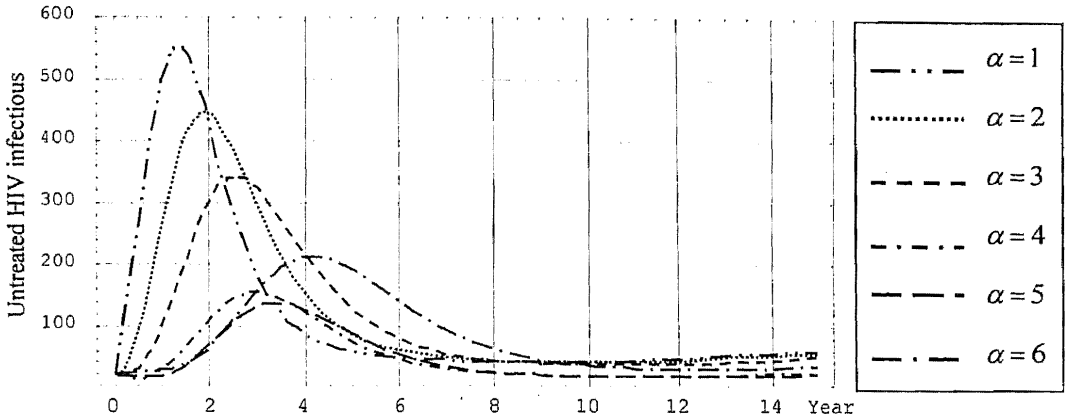

Figure 6.3.25: *Six stages of untreated HIV infectious in sexual activity group 1, with assortative sexual partner acquisition, assuming treatment does not effect infectiousness.*

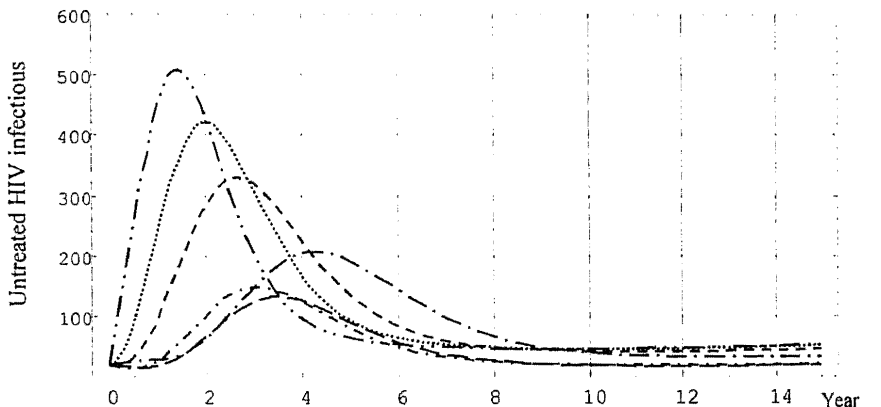

Figure 6.3.26: *Six stages of untreated HIV infectious in sexual activity group 1, with random sexual partner acquisition, assuming treatment does not effect infectiousness.*

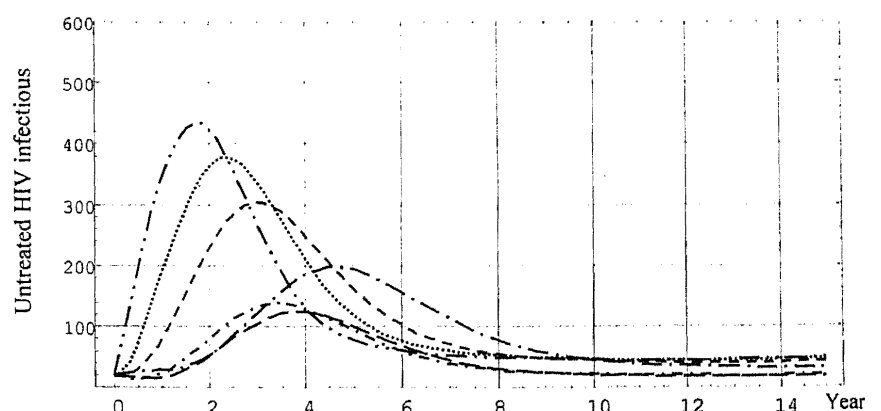

Figure 6.3.27: *Six stages of untreated HIV infectious in sexual activity group 1, with disassortative sexual partner acquisition, assuming treatment does not effect infectiousness.*

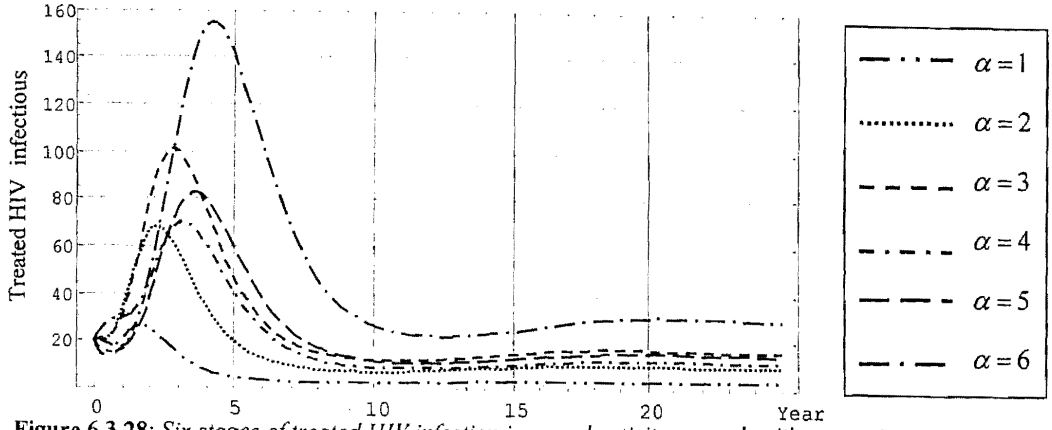

Figure 6.3.28: *Six stages of treated HIV infection in sexual activity group 1, with assortative sexual partner acquisition, assuming treatment does not effect infectiousness.*

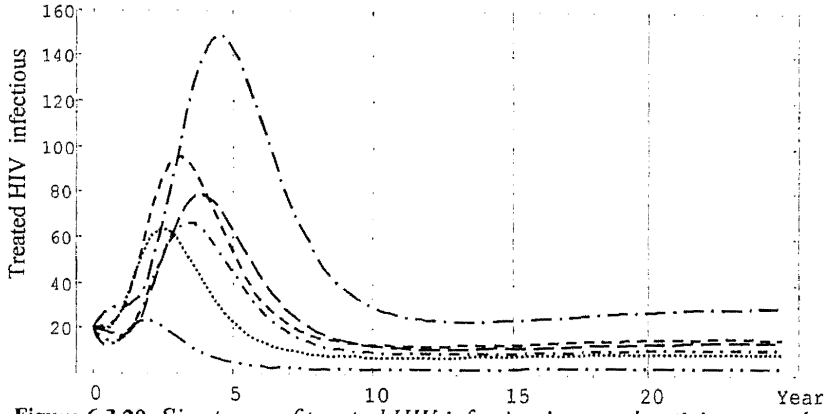

Figure 6.3.29: *Six stages of treated HIV infection in sexual activity group 1,with random sexual partner acquisition, assuming treatment does not effect infectiousness.*

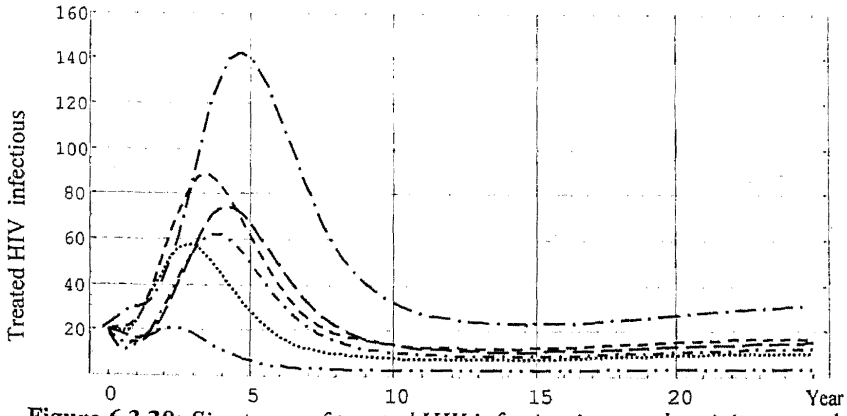

Figure 6.3.30: *Six stages of treated HIV infection in sexual activity group 1, with disassortative sexual partner acquisition, assuming treatment does not effect infectiousness.*

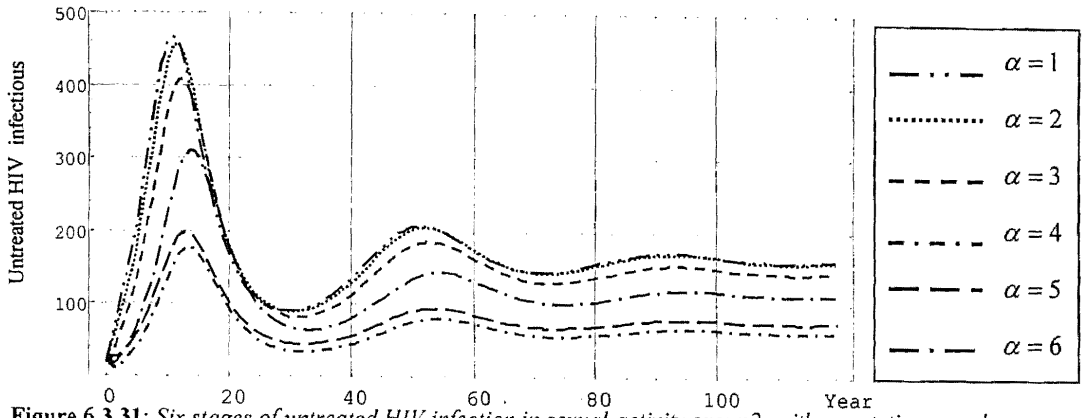

Figure 6.3.31: *Six stages of untreated HIV infection in sexual activity group2, with assortative sexual partner acquisition, assuming treatment does not effect infectiousness.*

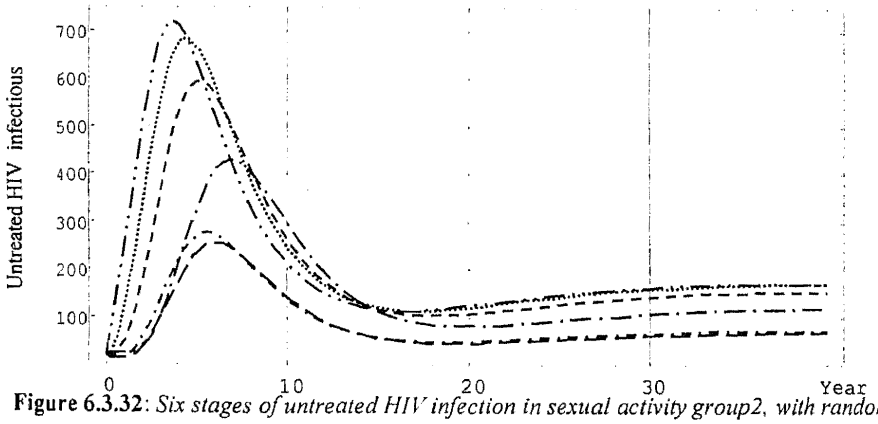

Figure 6.3.32: *Six stages of untreated HIV infection in sexual activity group2, with random sexual partner acquisition, assuming treatment does not effect infectiousness.*

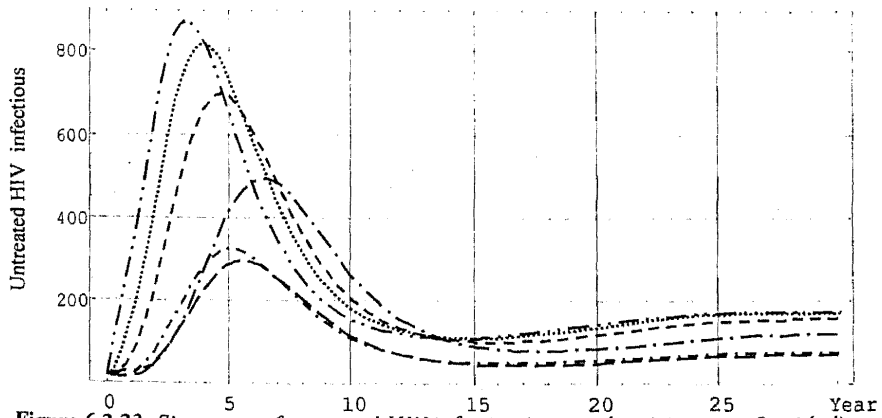

Figure 6.3.33: *Six stages of untreated HIV infection in sexual activity group2, with disassortative sexual partner acquisition, assuming treatment does not effect infectiousness.*

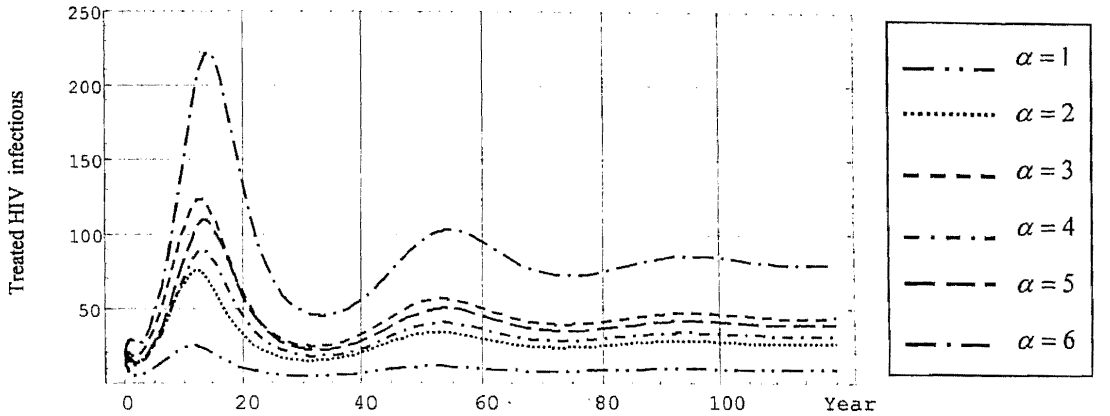

Figure 6.3.34: *Six stages of treated HIV infection in sexual activity group 2, with assortative sexual partner acquisition, assuming treatment does not effect infectiousness.*

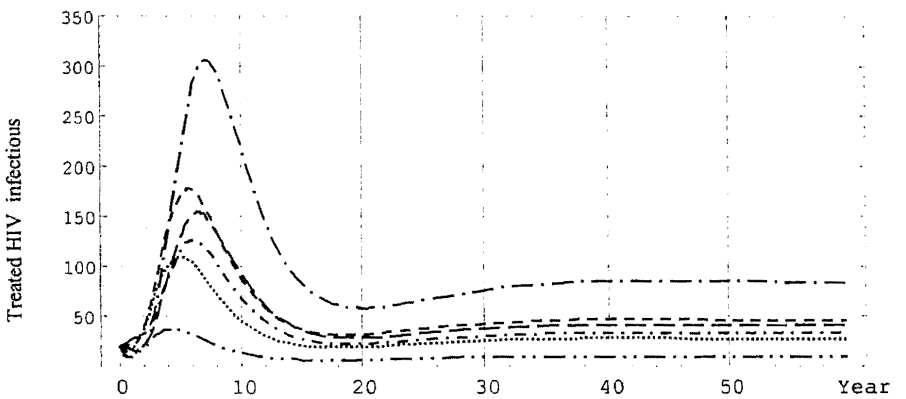

Figure 6.3.35: *Six stages of treated HIV infection in sexual activity group 2, with random sexual partner acquisition, assuming treatment does not effect infectiousness.*

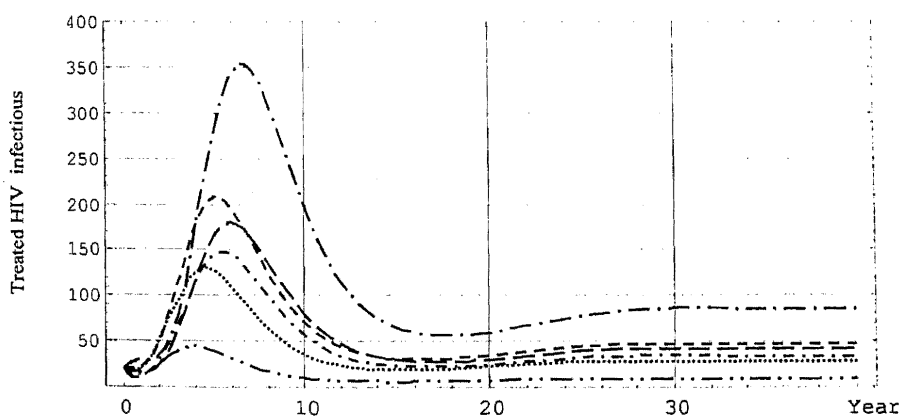

Figure 6.3.36: *Six stages of treated HIV infection in sexual activity group 2, with disassortative sexual partner acquisition, assuming treatment does not effect infectiousness.*

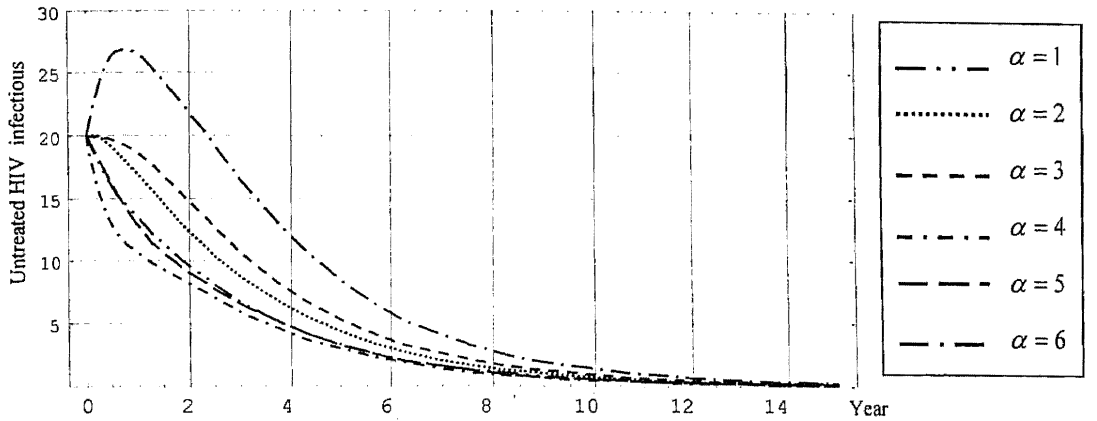

Figure 6.3.37: *Six stages of untreated HIV infection in sexual activity group3, with assortative sexual partner acquisition, assuming treatment does not effect infectiousness.*

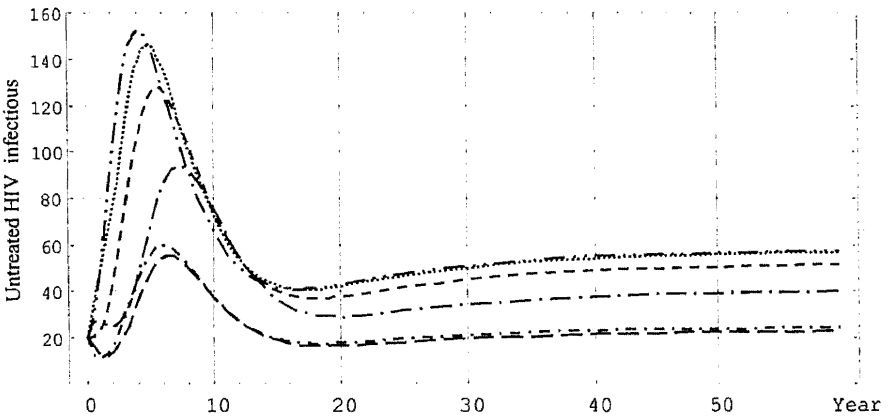

Figure 6.3.38: *Six stages of untreated HIV infection in sexual activity group3, with random sexual partner acquisition, assuming treatment does not effect infectiousness.*

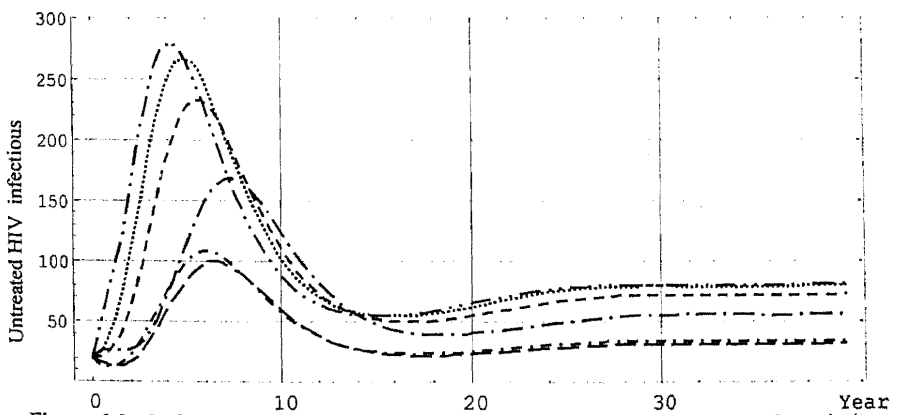

Figure 6.3.39: *Six stages of untreated HIV infection in sexual activity group3, with disassortative sexual partner acquisition, assuming treatment does not effect infectiousness.*

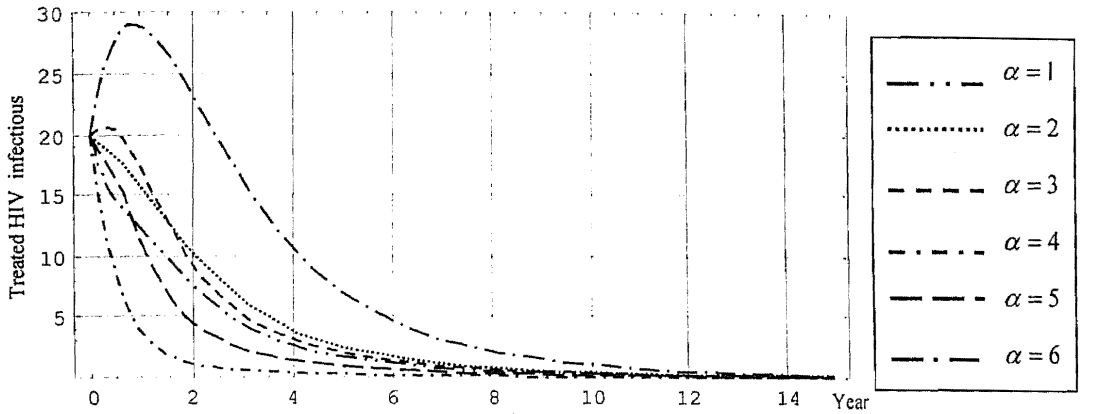

Figure 6.3.40: *Six stages of treated HIV infection in sexual activity group 3, with assortative sexual partner acquisition, assuming treatment does not effect infectiousness.*

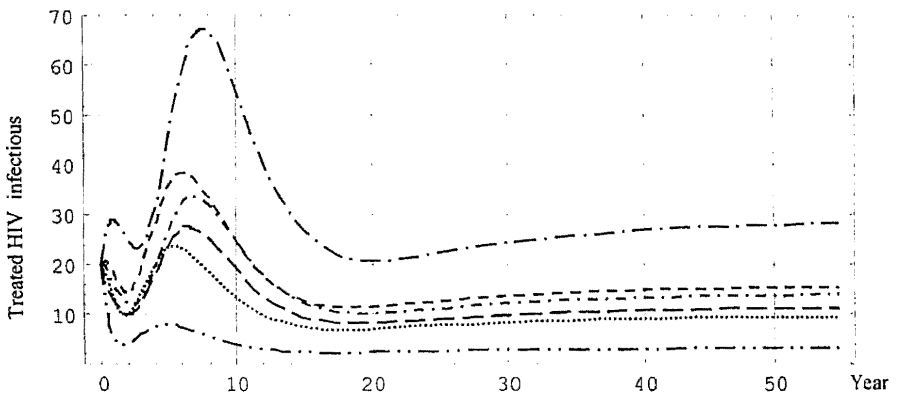

Figure 6.3.41: *Six stages of treated HIV infection in sexual activity group 3, with random sexual partner acquisition, assuming treatment does not effect infectiousness.*

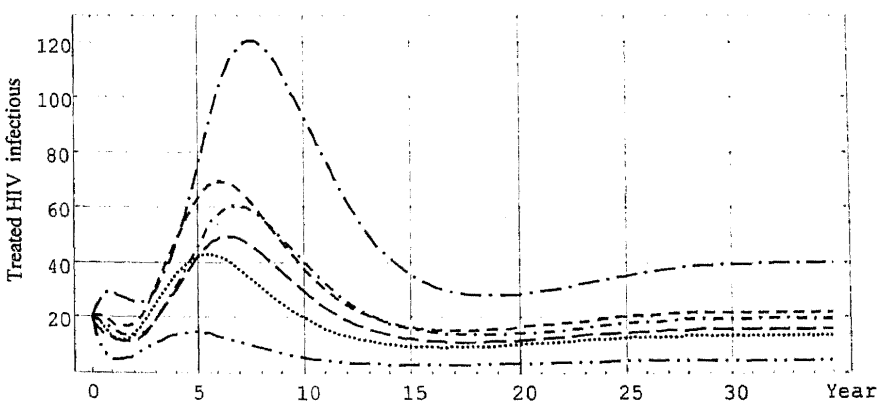

Figure 6.3.42: *Six stages of treated HIV infection in sexual activity group 3, with disassortative sexual partner acquisition, assuming treatment does not effect infectiousness.*

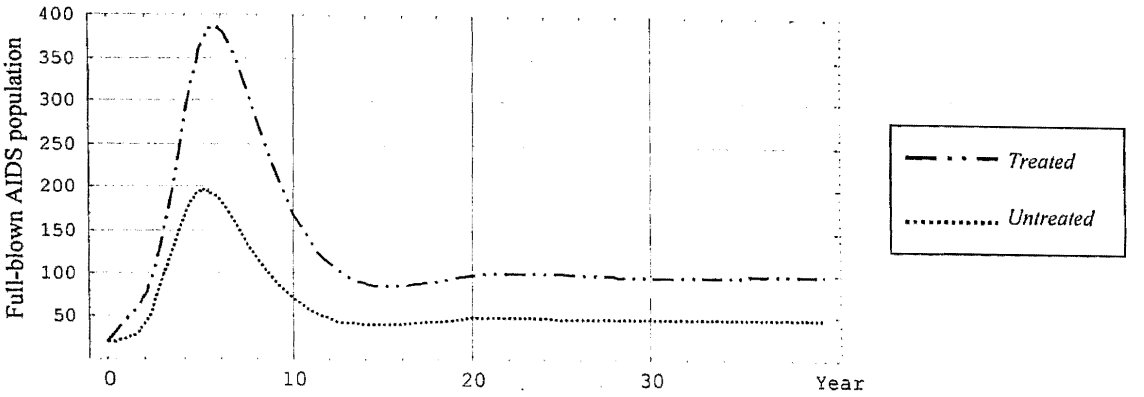

Figure 6.3.43: *Treated and untreated full blown AIDS population in sexual activity group 1, with assortative sexual partner acquisition, assuming treatment does not effect infectiousness.*

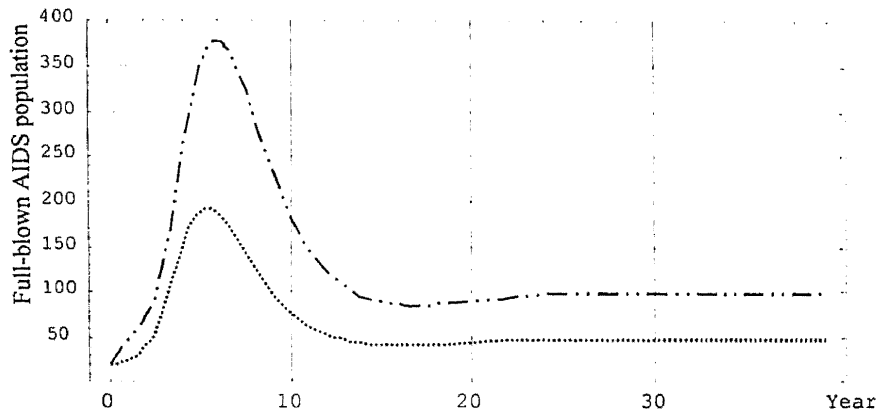

Figure 6.3.45: *Treated and untreated full blown AIDS population in sexual activity group 1, with random sexual partner acquisition, assuming treatment does not effect infectiousness.*

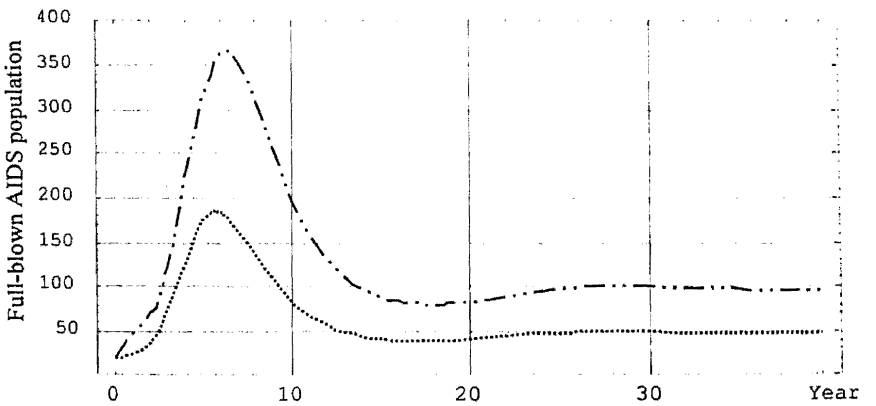

Figure 6.3.45: *Treated and untreated full blown AIDS population in sexual activity group 1, with disassortative sexual partner acquisition, assuming treatment does not effect infectiousness.*

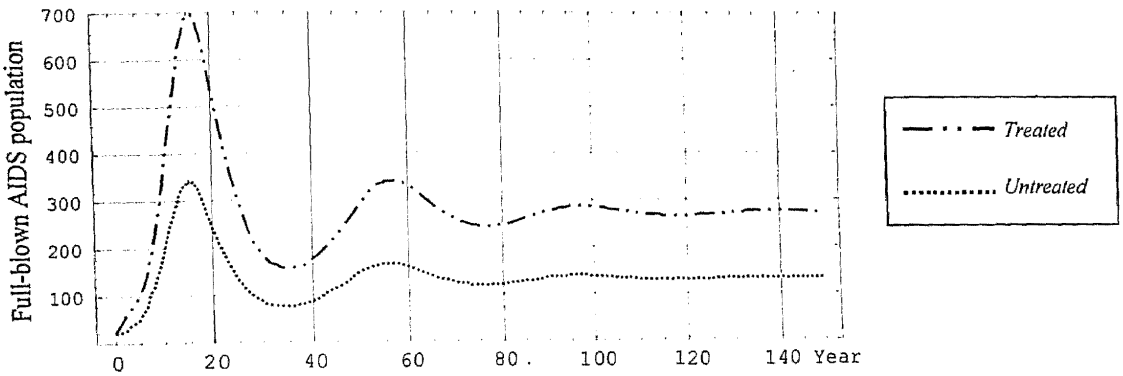

Figure 6.3.46: *Treated and untreated full-blown AIDS population in sexual activity group 2, with assortative sexual partner acquisition, assuming treatment does not effect infectiousness.*

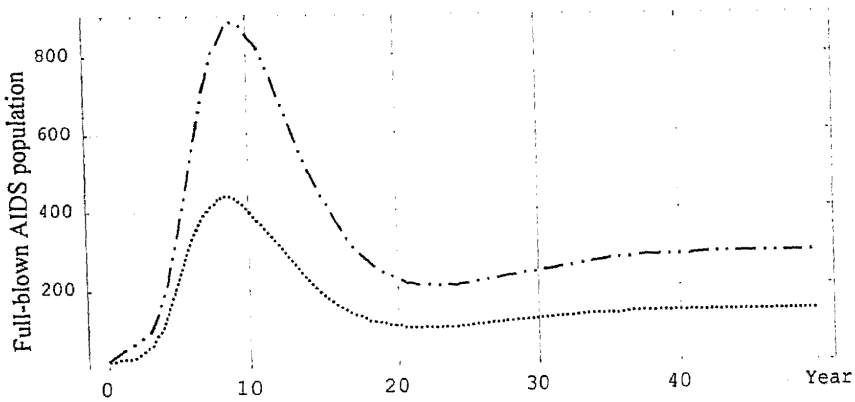

Figure 6.3.47: *Treated and untreated full blown AIDS population in sexual activity group 2, with random sexual partner acquisition, assuming treatment does not effect infectiousness.*

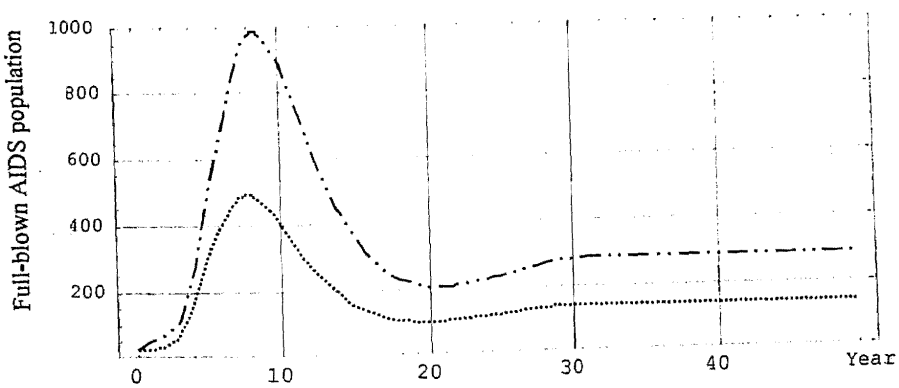

Figure 6. 48: *Treated and untreated full blown AIDS population in sexual activity group 2, with disassortative sexual partner acquisition, assuming treatment does not effect infectiousness.*

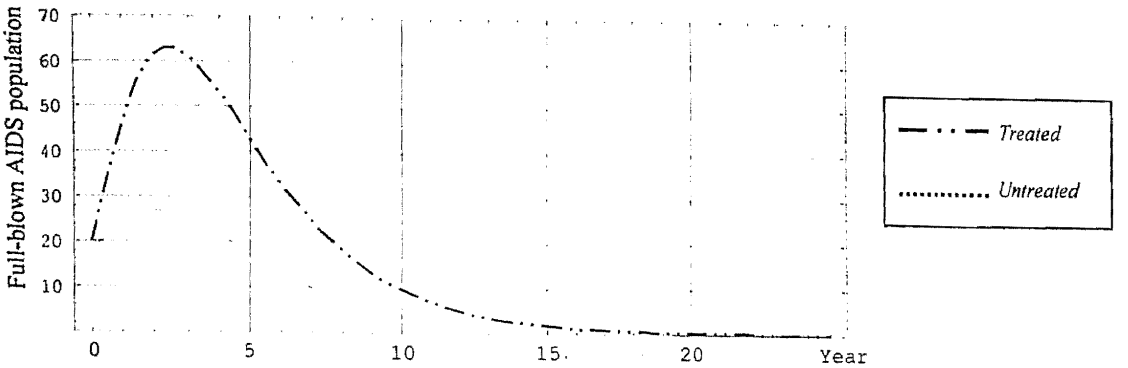

Figure 6.3.49: *Treated and untreated full blown AIDS population in sexual activity group 3, with assortative sexual partner acquisition, assuming treatment does not effect infectiousness.*

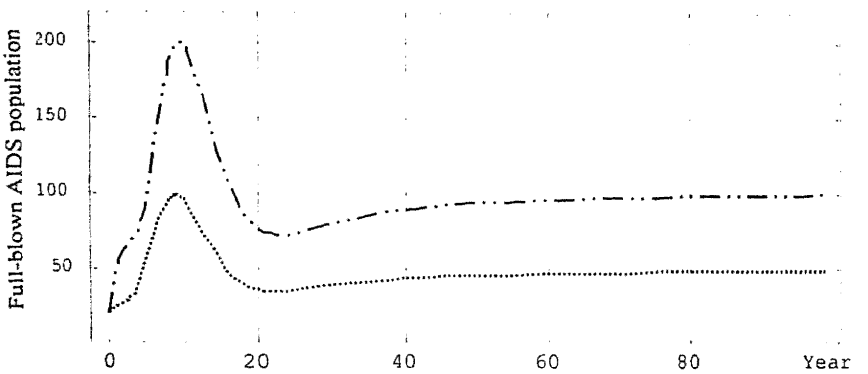

Figure 6.3.50: *Treated and untreated full blown AIDS population in sexual activity group 3, with random sexual partner acquisition, assuming treatment does not effect infectiousness.*

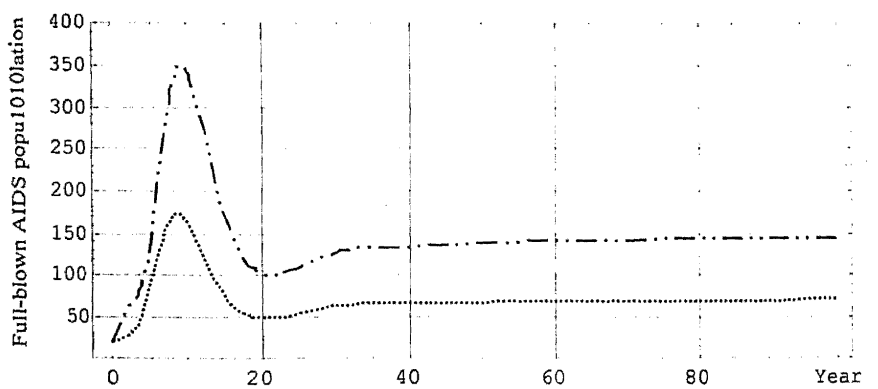

Figure 6.3.51: *Treated and untreated full blown AIDS population in sexual activity group 3, with disassortative sexual partner acquisition, assuming treatment does not effect infectiousness.*

6.3.3 Partially treated population, assuming treatment reduces the infectiousness by 50%

Model equation (6.2.1) can be used to describe a partially treated population Assuming that treatment reduces infectiousness by 50%. Parameters $\beta_{\alpha 2}$ represent infectiousness (transmission probability) of the treated population at stage α for $\alpha = \{1, \cdots, 7\}$. Placing $\beta_{\alpha 2} = 0.5\beta_{\alpha 1}$ for $\alpha = \{1, \cdots, 6\}$ in the model equations (6.2.1) gives a set of equation simulating a partially treated population in which treatment reduces the infectiousness by 50%. The population stratified into three sexual activities groups, including susceptible, six stages of HIV infection and full-blown AIDS patients. Parameter values are presented in 6.1, Section 6.2.

i) **Dis-assortative sexual mixing pattern:** by substituting dis-assortative mixing matrix (6.3.2) in model equations (6.2.1), the determinant of the Jacobian of the form of (2.2.3) associated with the model equation at the trivial critical point (6.3.5) vanishes whenever,

$$k_1^* = 6.89$$

Assuming sexual activity group 1 with an average of $k_1 = 65$ new sexual partners per unit of time, gives the total reproductive rate

$$R_d = \frac{k_1}{k_1^*} = 9.43 \tag{6.3.12}$$

ii) **Random sexual mixing pattern:** by substituting random mixing matrix (6.3.3) in model equations (6.2.1), the determinant of the Jacobian of the form of (2.2.3 associated with the model equation at the trivial critical point (6.3.5 vanishes whenever,

$$k_1^* = 5.38$$

Assuming sexual activity group 1 with an average of $k_1 = 65$ new sexual partners per unit of time, gives the total reproductive rate

$$R_r = \frac{k_1}{k_1^*} = 12.08 \tag{6.3.13}$$

iii) **Assortative sexual mixing pattern:** by substituting assortative mixing matrix (6.3.4) in model equations (6.2.1), the determinant of the Jacobian of the form of (2.2.3) associated with the model equation at the trivial critical point (6.3.5) vanishes whenever,

$$k_1^* = 4.25$$

Assuming sexual activity group 1 with an average of $k_1 = 65$ new sexual partners per unit of time, gives the total reproductive rate

$$R_a = \frac{k_1}{k_1^*} = 15.29 \tag{6.3.14}$$

Comparing total reproductive rates with from dis-assortative (6.3.12), to random (6.3.13) and assortative (6.3.14) sexual mixing patterns indicate that $R_d < R_r < R_a$ meaning that the total reproductive rate for dis-assortative sexual pattern is grater than the total reproductive rate of the random mixing followed by the total reproductive rate of the assortative mixing pattern.

Figures 6.3.22a-6.3.54a represent the graphical solution to the system of equations (6.2.1) simulating a partially treated population assuming that treatment reduces the infectiousness by 50% at all stages.

Figures 6.3.22a-6.3.24a represent the susceptible population in three sexual activity groups ranging from 'assortative' to 'random' and 'dis-assortative' sexual mixing patterns. In general, the total number of susceptibles for the assortative pattern is shown to be higher than the random pattern, which in

turn is greater than a dis-assortative mixing pattern, for all sexual activity groups at the steady state.

At the steady state, the growths of the number of the susceptible population from dis-assortative to random is 25% and from dis-assortative to assortative 75%, for sexual activity group 1 as shown in Figure 6.3.22a. In Figure 6.3.23a, the growths from dis-assortative to random is 8% and from dis-assortative to assortative 16%, for sexual activity group 2. In Figure 6.3.24a, the growth from dis-assortative to random is 13% and from dis-assortative to assortative 35%, for sexual activity group 3.

Figures 6.3.25a-6.3.36a represent six stages of treated and untreated HIV infectious population within sexual activity groups 1 and 2 which indicate that the mixing patterns have no significant impact on the steady state solution (less than 5%). However at steady state the total number of treated HIV infectious population appear to be one third of the untreated HIV infectious population, this ratio depends on the rates at which infected population are diagnosed and receive treatment (r_α). Significantly, the transient state shows that the assortative mixing pattern contains the highest peaks occurring within a shorter period of time compared to those of a random and dis-assortative nature which occur at later periods of time at all stages for both treated and untreated populations.

Figures 6.3.37a-6.3.42a represent the six stages of treated and untreated HIV infectious population within sexual activity groups 3. Figures 6.3.37a and 6.3.40a show that at the steady state, treated and untreated HIV infectious populations with an assortative mixing pattern declines to zero due to sexual mixing behaviour and low levels of sexual partner acquisition. In Figures 6.3.38a and 6.3.39a at the steady state, the total number of untreated HIV infectious with random mixing pattern is lower than the dis-assortative

mixing pattern. In Figures 6.3.41a and 6.3.42a at the steady state, the total number of treated HIV infectious with random mixing pattern is lower than the dis-assortative mixing pattern. Theses show an average increase of 52% from random mixing pattern to dis-assortative mixing for both treated and untreated HIV infected population. In the transient state the dis-assortative mixing pattern contains the highest peaks occurring within a shorter period of time compared to those of a random and assortative nature which occur at later periods of time at all stages.

Figures 6.3.43a-6.3.48a represent the treated and untreated AIDS population in sexual activity groups 1 and 2 showing assortative, random and dis-assortative mixing patterns. At steady state no significant difference is observed upon sexual mixing patterns for both treated and untreated AIDS populations (less than 5%). However, an increase of 100% on the total number of AIDS cases is observed from untreated and treated populations. In transient state assortative mixing pattern contains the highest peak occurring within a shorter period of time compared to those of a random and dis-assortative nature which occur at later periods of time at all stages.

Figures 6.3.49a, 6.3.50a and 6.3.51a represent the treated and untreated AIDS population in sexual activity group 3. At steady state the number of treated and untreated AIDS cases with assortative sexual behaviour declines to zero. At steady state, the random pattern is lower than the dis-assortative pattern by a factor of 100In transient state of the solution, dis-assortative mixing pattern contains the highest pick followed by random and assortative mixing pattern at shorter period of time.

Figures 6.3.52a, 6.3.53a and 6.3.54a represent the total number of susceptible, HIV infected and full-blown AIDS cases in a partially treated population respectively assuming that the treatment reduces infectiousness by

50%. Figure 6.3.52a indicates that the growth of the number of susceptibles from dis-assortative to random sexual mixing pattern is 10% and to assortative mixing is 30%. Figure 6.3.53a indicates that the number of HIV infected from dis-assortative to random sexual mixing pattern decline by 11% and to assortative mixing decline by 29%. Figure 6.3.54a indicates that the number of full-blown AIDS cases from dis-assortative to random sexual mixing pattern decline by 4% and to assortative mixing decline by 27%.

From the above it can be concluded that whenever the sexual mixing pattern varies from a range of assortative to dis-assortative for an untreated population the number of susceptibles decrease and the number of HIV infected and AIDS cases increase.

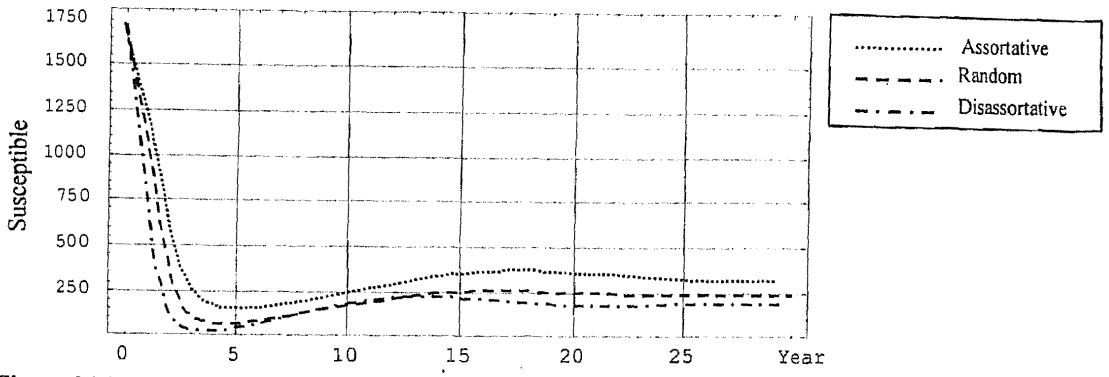

Figure 6.3.22a: *Susceptibles in sexual activity group 1,with from assortative to random and disassortative sexual partner acquisition, assuming treatment reduces infectiousness by 50%..*

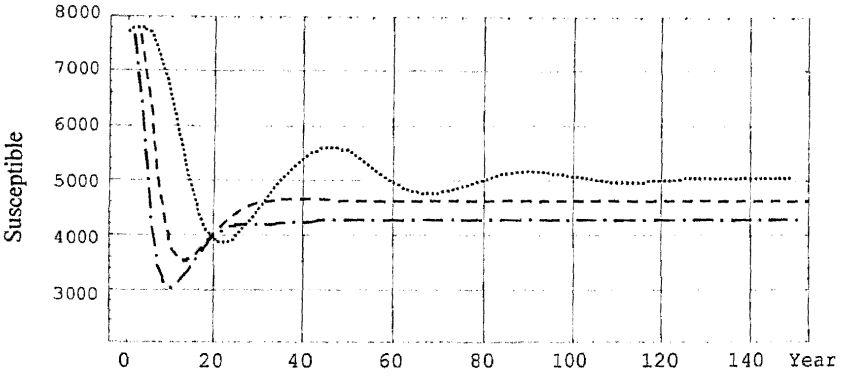

Figure 6.3.23a: *Susceptibles in sexual activity group 2,with from assortative to random and disassortative*
sexual partner acquisition, assuming treatment reduces infectiousness by 50%.

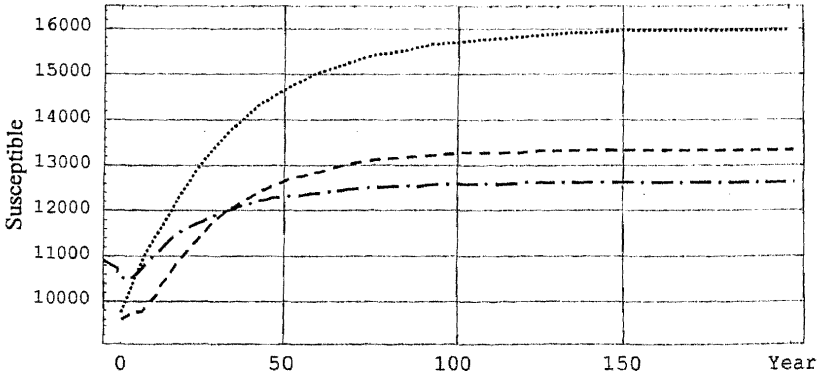

Figure 6.3.24a: *Susceptibles in sexual activity group 3,with from assortative to random and disassortative sexual partner acquisition, assuming treatment reduces infectiousness by 50%.*

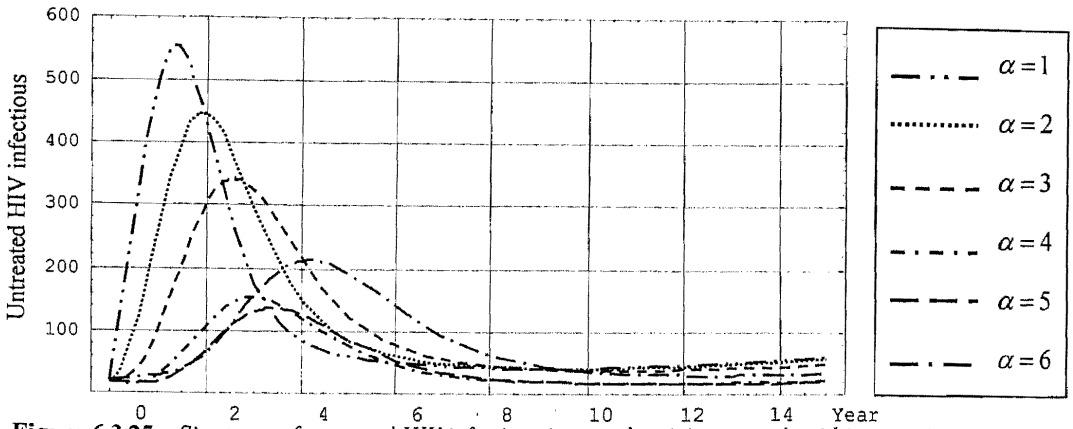

Figure 6.3.25a: *Six stages of untreated HIV infectious in sexual activity group 1, with assortative sexual partner acquisition, assuming treatment reduces infectiousness by 50%..*

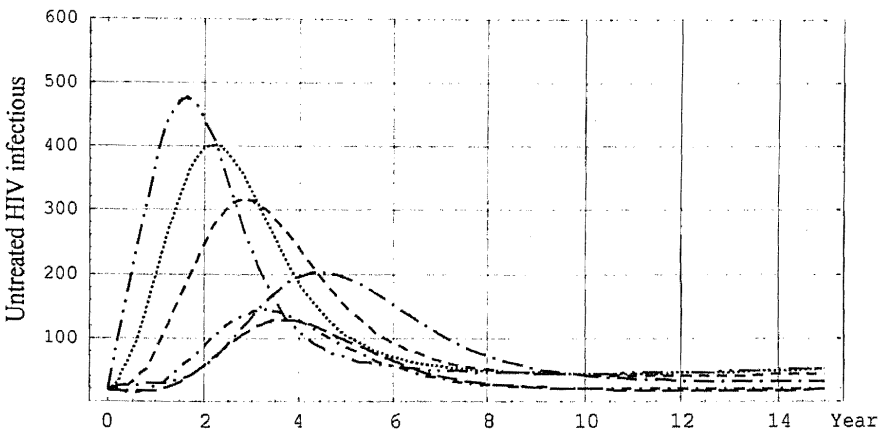

Figure 6.3.26a: *Six stages of untreated HIV infectious in sexual activity group 1, with random sexual partner acquisition, assuming treatment reduces infectiousness by 50%..*

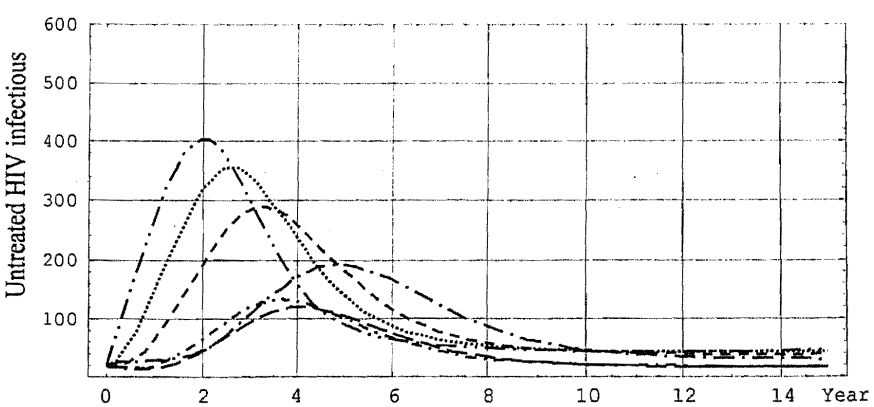

Figure 6.3.27a: *Six stages of untreated HIV infectious in sexual activity group 1, with disassortative sexual partner acquisition, assuming treatment reduces infectiousness by 50%..*

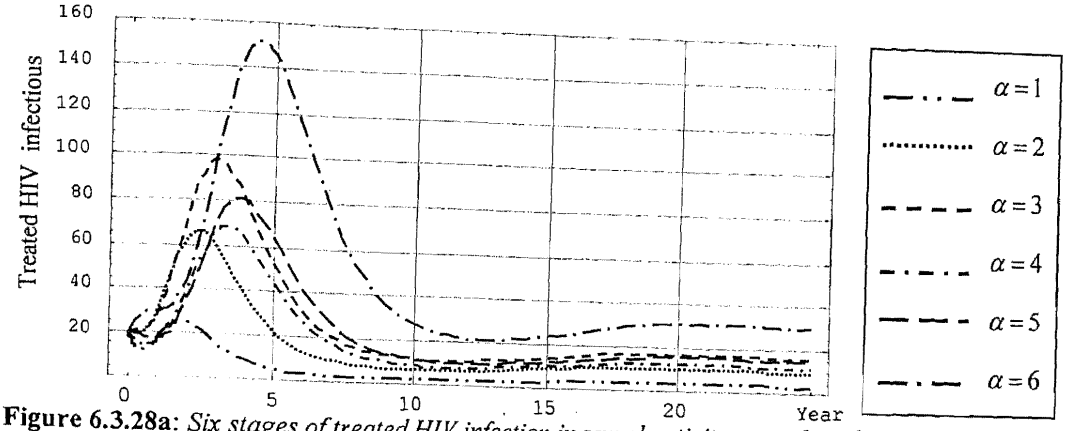

Figure 6.3.28a: *Six stages of treated HIV infection in sexual activity group 1, with assortative sexual partner acquisition, assuming treatment reduces infectiousness by 50%.*

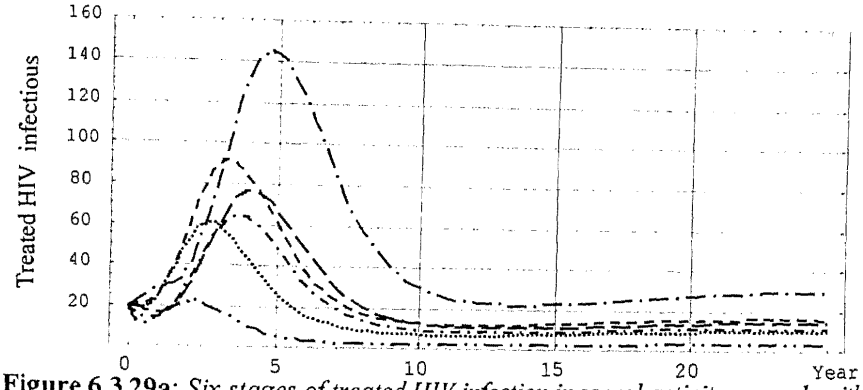

Figure 6.3.29a: *Six stages of treated HIV infection in sexual activity group 1, with random sexual partner acquisition, assuming treatment reduces infectiousness by 50%.*

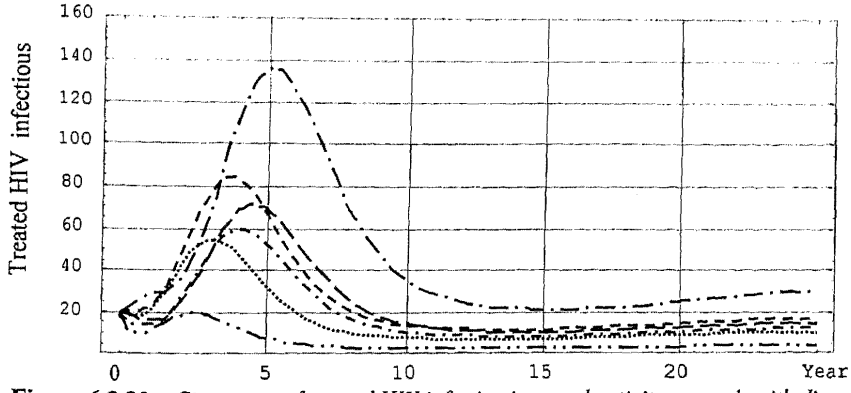

Figure 6.3.30a: *Six stages of treated HIV infection in sexual activity group 1, with disassortative sexual partner acquisition, assuming treatment reduces infectiousness by 50%.*

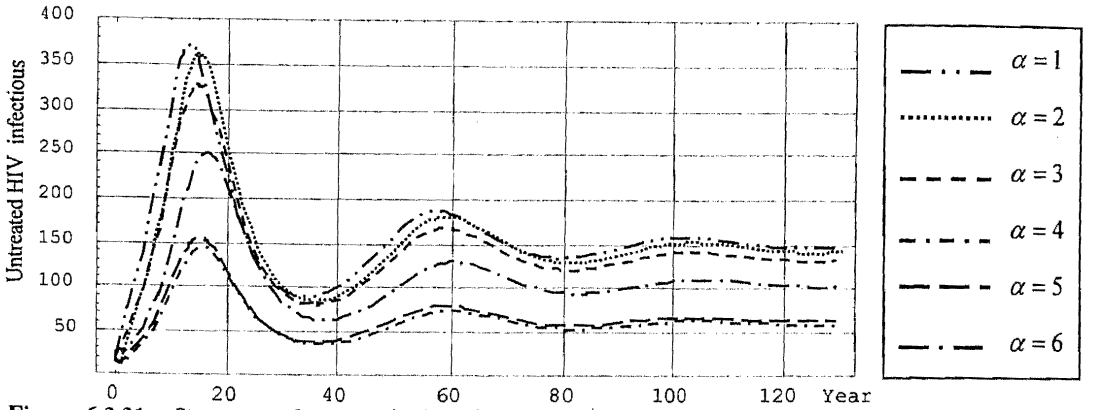

Figure 6.3.31a: *Six stages of untreated HIV infection in sexual activity group 2, with assortative sexual partner acquisition, assuming treatment reduces infectiousness by 50%.*

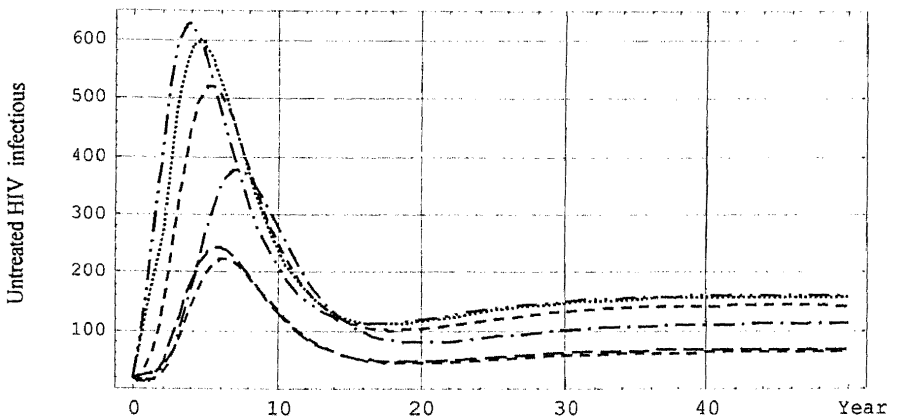

Figure 6.3.32a: *Six stages of untreated HIV infection in sexual activity group2, with random sexual partner acquisition, assuming treatment reduces infectiousness by 50%.*

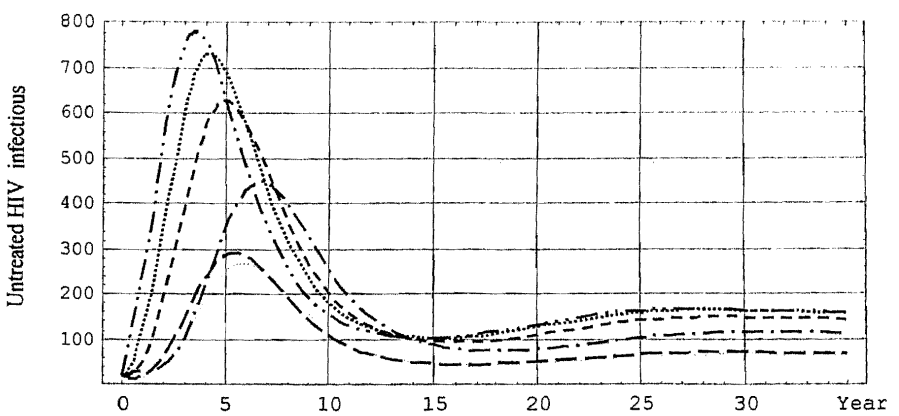

Figure 6.3.33a: *Six stages of untreated HIV infection in sexual activity group2, with disassortative sexual partner acquisition, assuming treatment reduces infectiousness by 50%.*

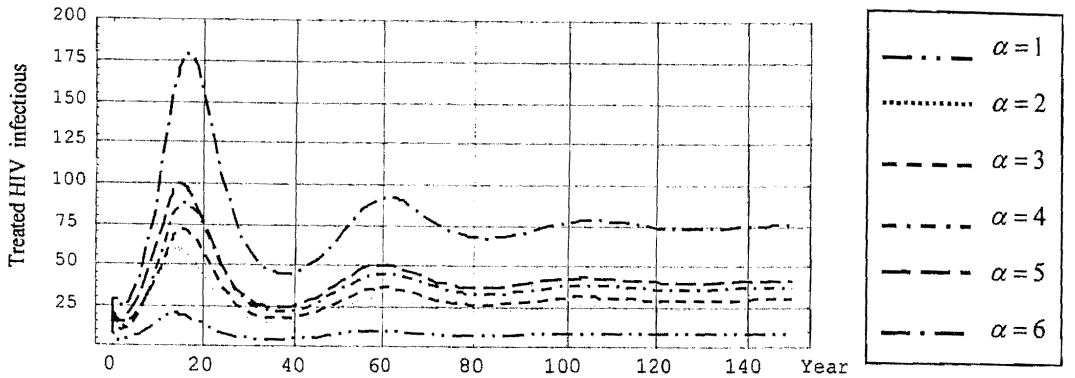

Figure 6.3.34a: *Six stages of treated HIV infection in sexual activity group 2, with assortative sexual partner acquisition, assuming treatment reduces infectiousness by 50%.*

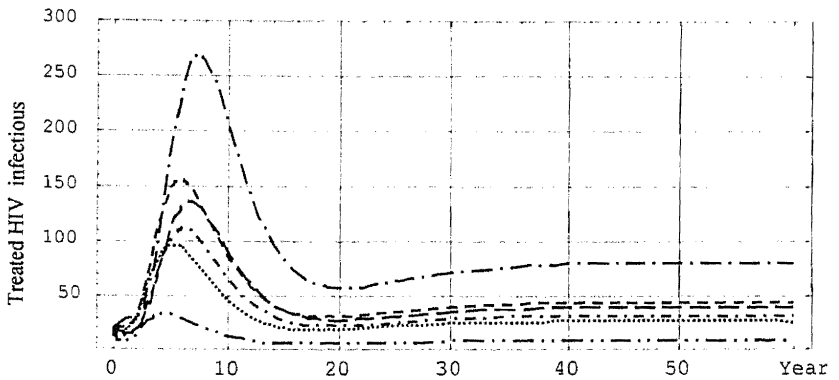

Figure 6.3.35a: *Six stages of treated HIV infection in sexual activity group 2, with random sexual partner acquisition, assuming treatment reduces infectiousness by 50%.*

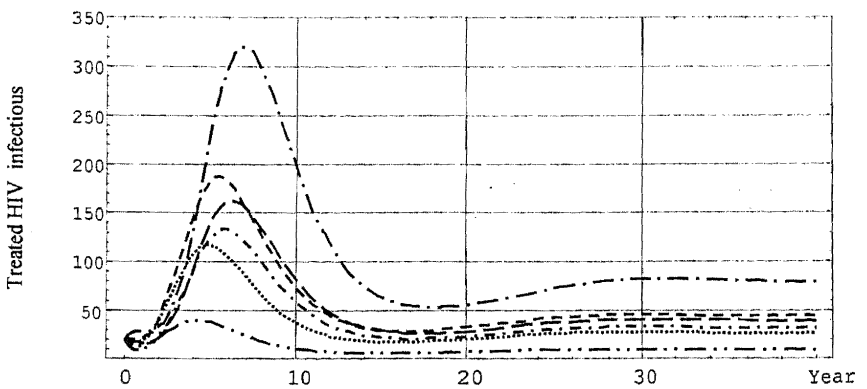

Figure 6.3.37a: *Six stages of treated HIV infection in sexual activity group 2, with disassortative sexual partner acquisition, assuming treatment reduces infectiousness by 50%.*

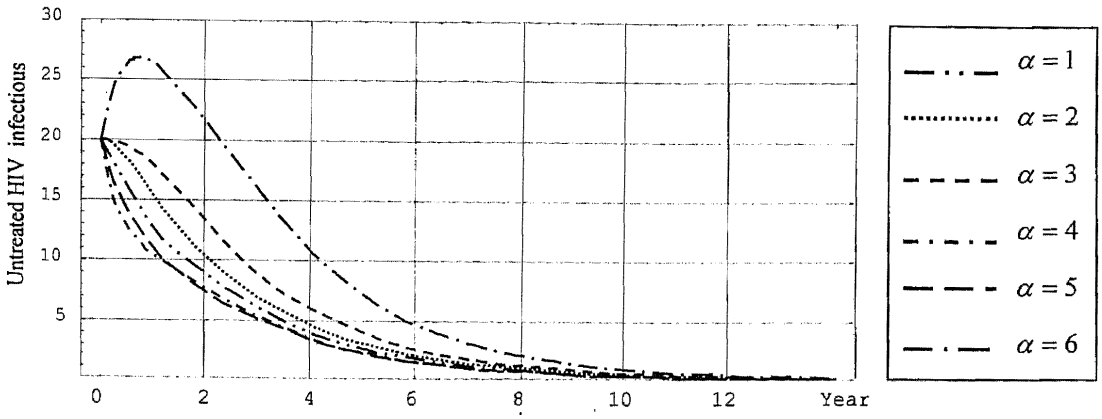

Figure 6.3.37a: *Six stages of untreated HIV infection in sexual activity group3, with assortative sexual partner acquisition, assuming treatment reduces infectiousness by 50%.*

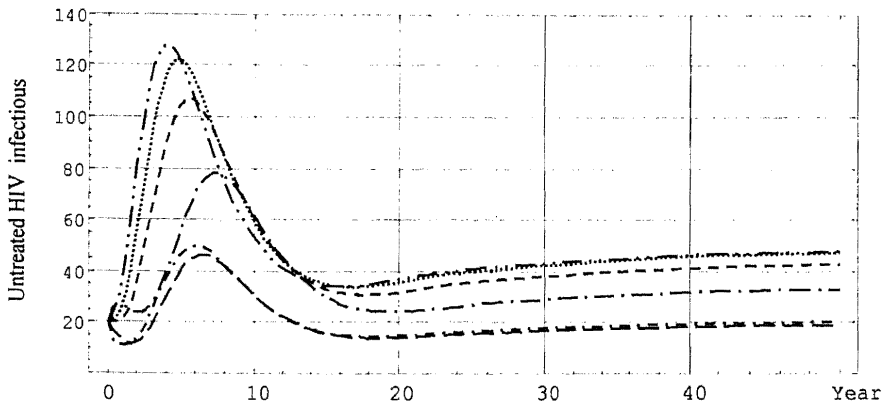

Figure 6.3.38a: *Six stages of untreated HIV infection in sexual activity group3, with random sexual partner acquisition, assuming treatment reduces infectiousness by 50%.*

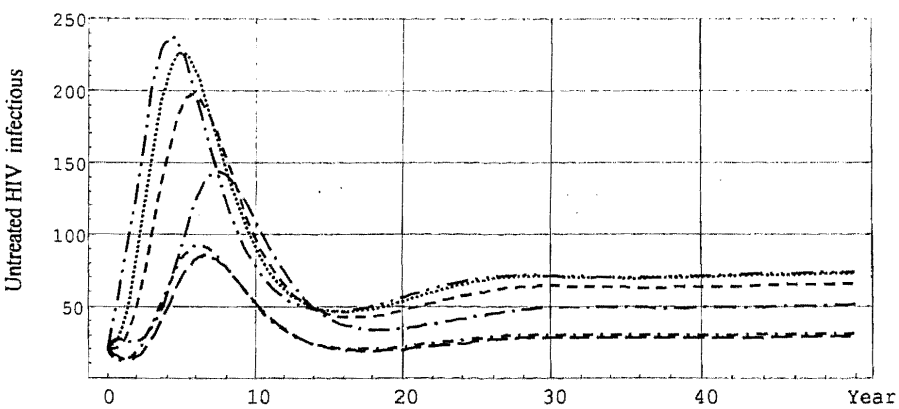

Figure 6.3.39a: *Six stages of untreated HIV infection in sexual activity group3, with disassortative sexual partner acquisition, assuming treatment reduces infectiousness by 50%..*

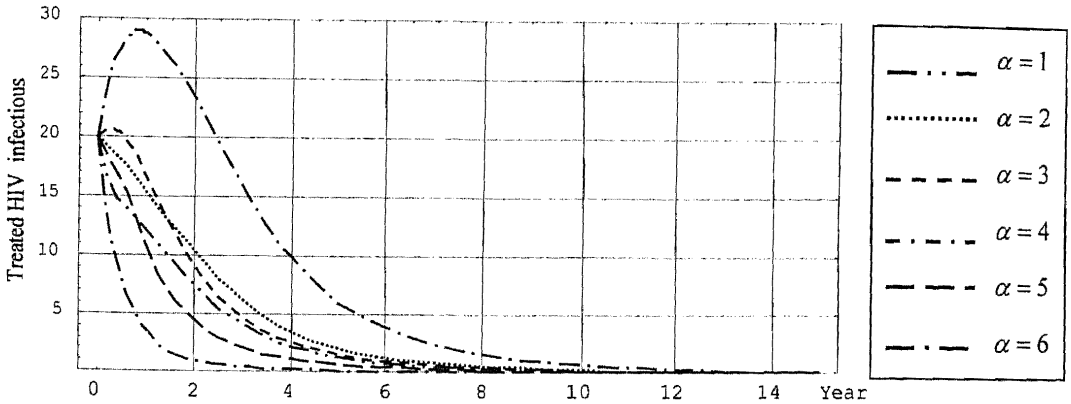

Figure 6.3.40a: *Six stages of treated HIV infection in sexual activity group 3, with assortative sexual partner acquisition, assuming treatment reduces infectiousness by 50%.*

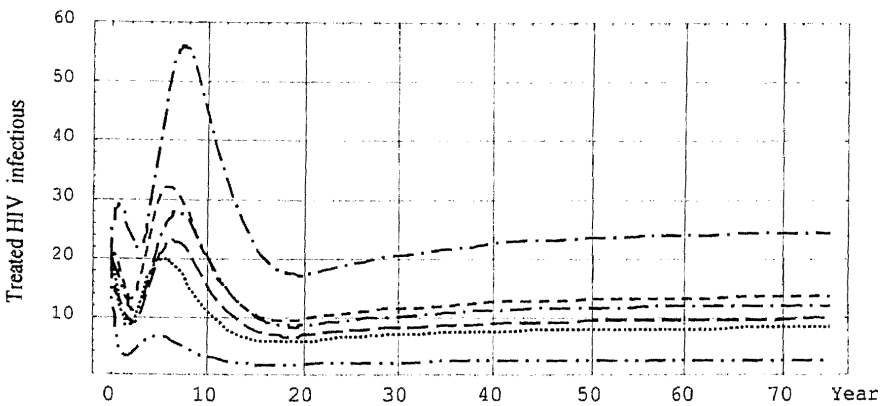

Figure 6.3.41a: *Six stages of treated HIV infection in sexual activity group 3, with random sexual partner acquisition, assuming treatment reduces infectiousness by 50%.*

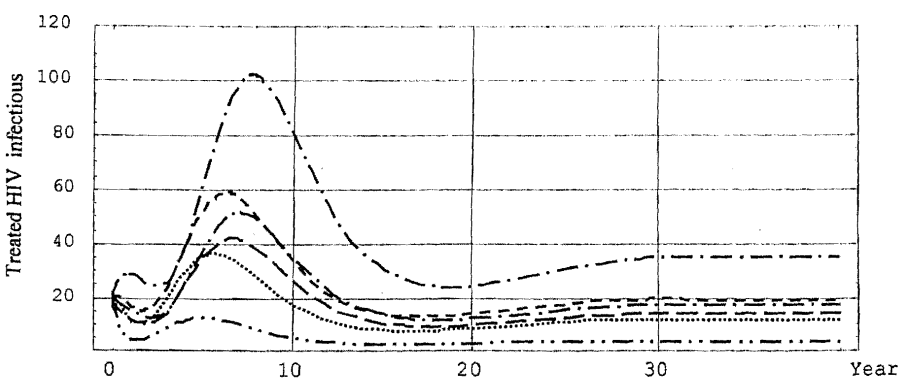

Figure 6.3.42a: *Six stages of treated HIV infection in sexual activity group 3, with disassortative sexual partner acquisition, assuming treatment reduces infectiousness by 50%.*

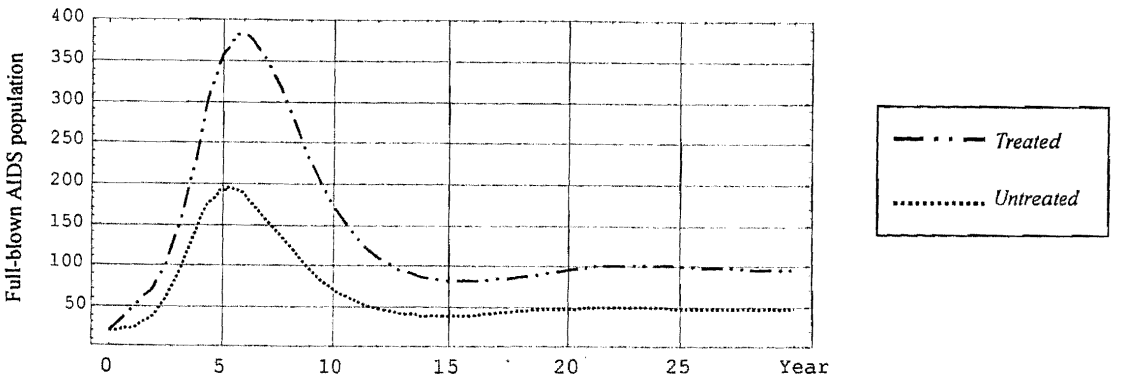

Figure 6.3.43a: *Treated and untreated full blown AIDS population in sexual activity group 1, with assortative sexual partner acquisition, assuming treatment reduces infectiousness by 50%.*

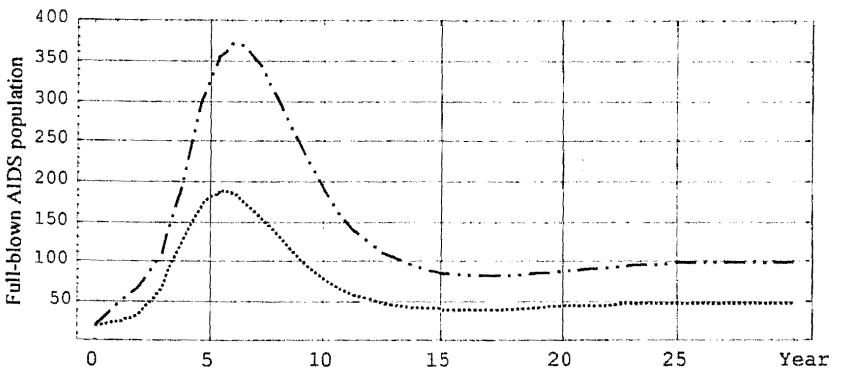

Figure 6.3.44a: *Treated and untreated full blown AIDS population in sexual activity group 1, with random sexual partner acquisition, assuming treatment reduces infectiousness by 50%.*

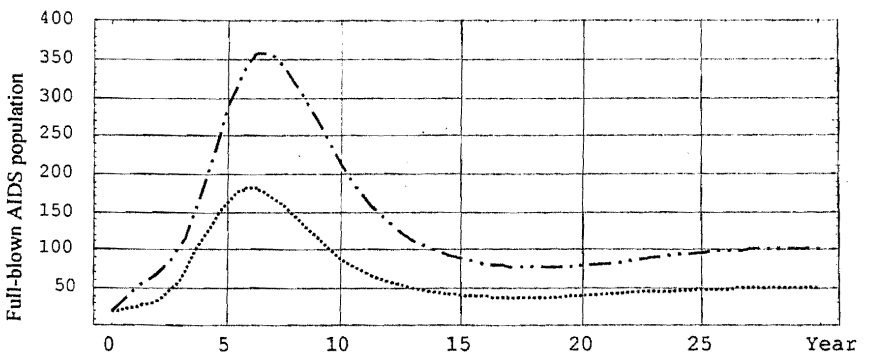

Figure 6.3.45a: *Treated and untreated full blown AIDS population in sexual activity group 1, with disassortative sexual partner acquisition, assuming treatment reduces infectiousness by 50%.*

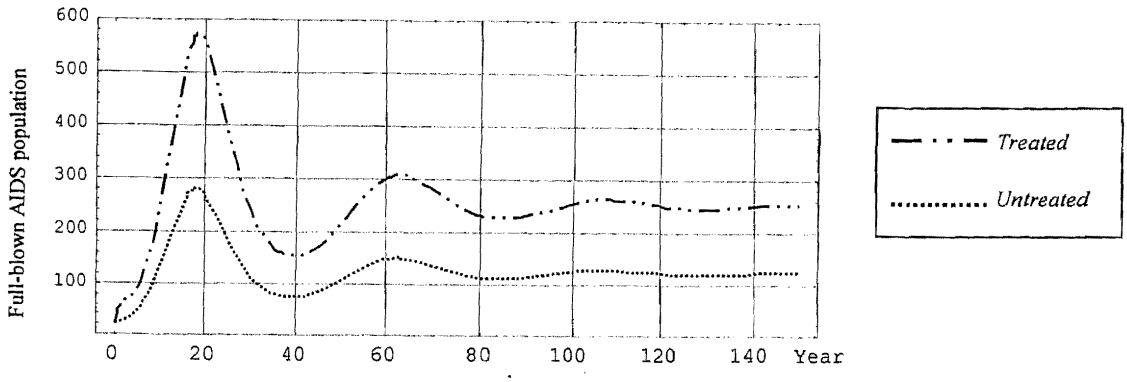

Figure 6.3.46a: *Treated and untreated full blown AIDS population in sexual activity group 2, with assortative sexual partner acquisition, assuming treatment reduces infectiousness by 50%.*

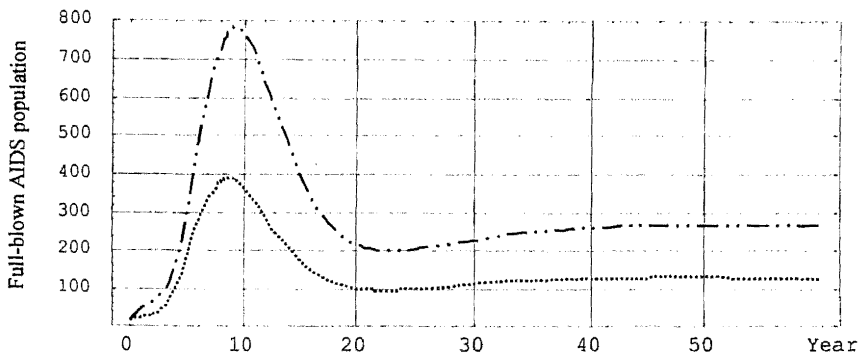

Figure 6.3.47a: *Treated and untreated full blown AIDS population in sexual activity group 2, with random sexual partner acquisition, assuming treatment reduces infectiousness by 50%.*

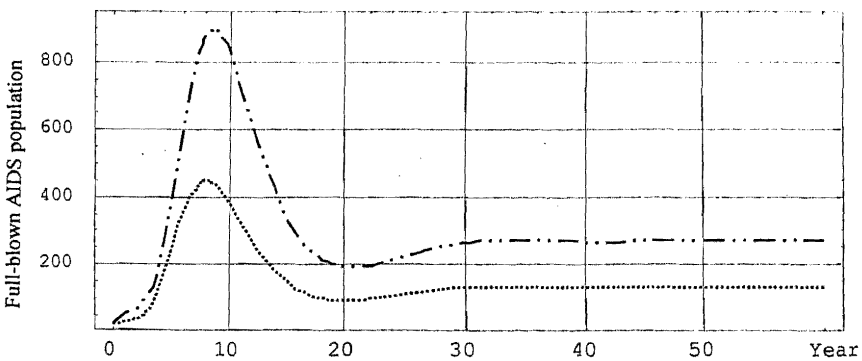

Figure 6.3.48a: *Treated and untreated full blown AIDS population in sexual activity group 2, with disassortative sexual partner acquisition, assuming treatment reduces infectiousness by 50%.*

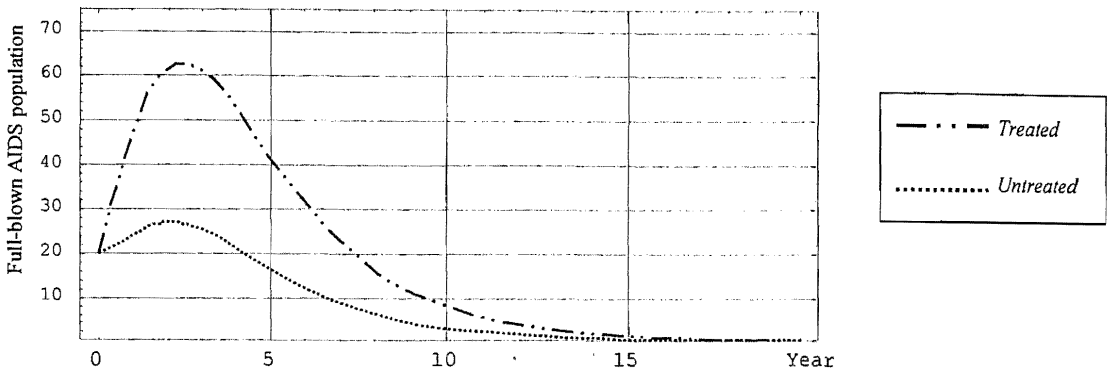

Figure 6.3.49a: *Treated and untreated full blown AIDS population in sexual activity group 3, with assortative sexual partner acquisition, assuming treatment reduces infectiousness by 50%.*

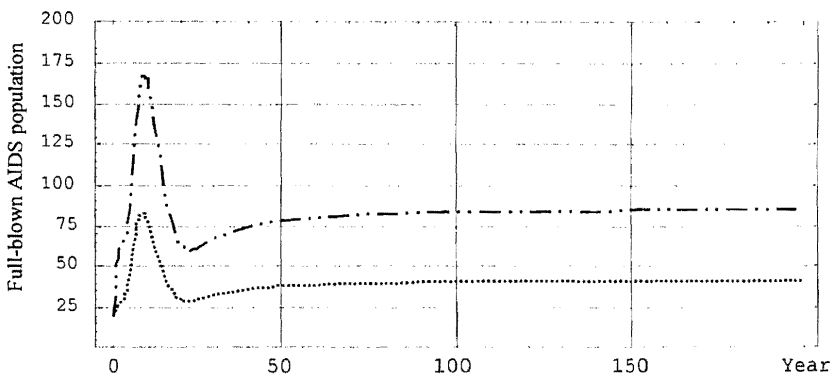

Figure 6.3.50a: *Treated and untreated full blown AIDS population in sexual activity group 3, with random sexual partner acquisition, assuming treatment reduces infectiousness by 50%.*

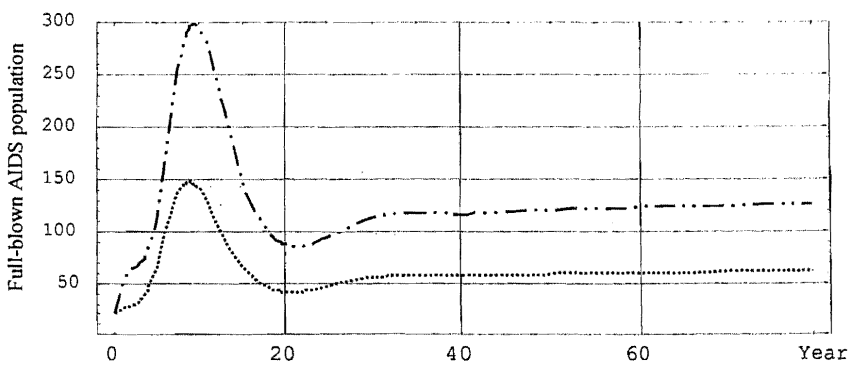

Figure 6.3.51a: *Treated and untreated full blown AIDS population in sexual activity group 3, with disassortative sexual partner acquisition, assuming treatment reduces infectiousness by 50%.*

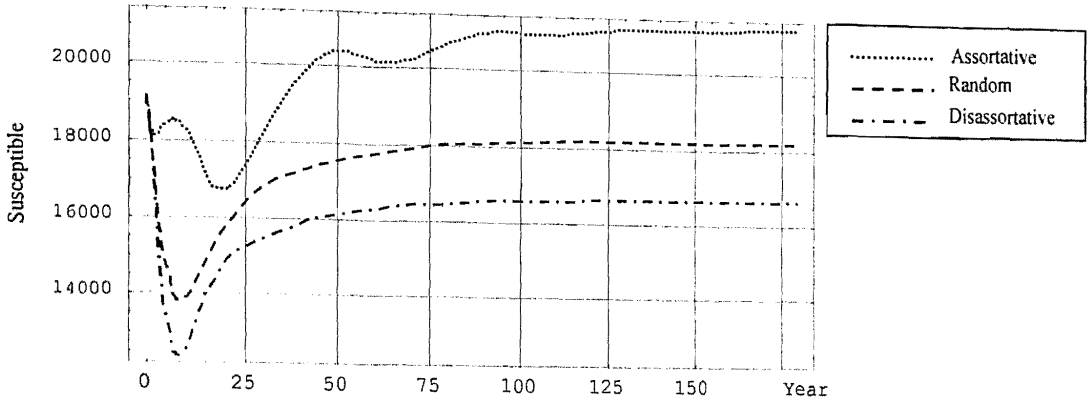

Figure 6.3.52a: *Population's total susceptible with from assortative to random and disassortative sexual mixing behaviour, assuming treatment reduces infectiousness by 50%.*

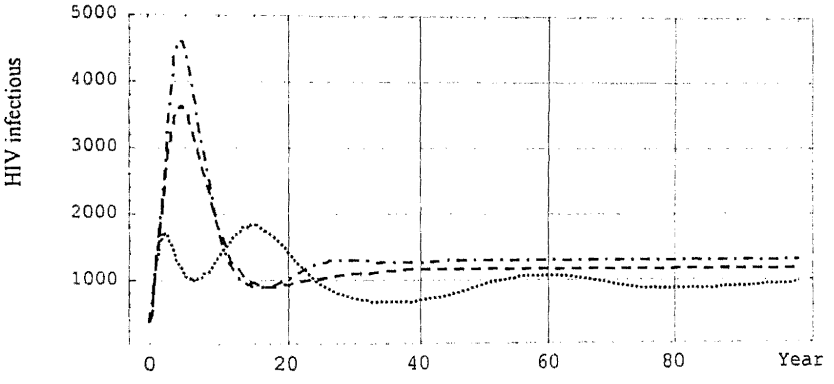

Figure 6.3.53a: *Population's total HIV infectious with from assortative to random and disassortative sexual mixing behaviour, assuming treatment reduces infectiousness by 50%.*

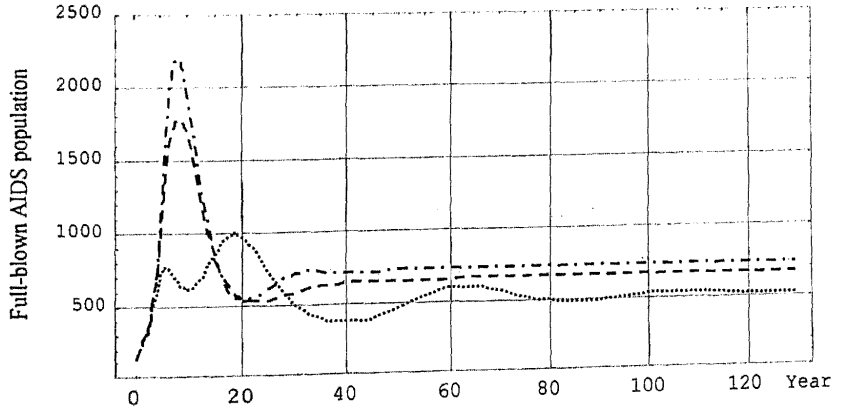

Figure 6.3.54a: *Population's total full-blown AIDS cases with from assortative to random and disassortative sexual partner acquisition, assuming treatment reduces infectiousness by 50%.*

6.4 Conclusion

This chapter has presented some results of the population level impact of antiviral therapy and sexual mixing patterns, based on the development and analysis of a complex model of the transmission dynamics of HIV in a male homosexual community. Antiviral therapy acts to increase life expectancy of the treated subjects (before the emergence and persistence of drug resistant strains of the virus (see Wei *et al.*, [111]) by slowing the rate of progression to AIDS. In most cases, particularly when the transmission intensity is high before community wide treatment, benefit to the individual is translated into net benefit to the community. However, graphical solution presented in Section 6.3.2 shows that lengthening the infectious period by increasing life expectancy can enhance the transmission success of the virus and, concomitantly, increase the net rate of AIDS induced mortality over that present before wide-scale treatment. Section 6.3.3 showed that likelihood of this perverse outcome arising is minimised by the use of drugs that suppress viraemia (assumed to equate with infectiousness) by 50% and by counselling of treated patients to impress upon them that treatment does not eliminate their infectiousness during unprotected sex.

The elimination of transmission with extensive treatment coverage of infected persons with a drug which suppresses infectiousness to zero will not be possible, because of the high infectiousness early in the incubation period coupled with the small probability of detection and treatment at the early stage of the disease. However, the benefits accruing from community wide use of drugs that effectively suppress infectiousness, even for periods of a few months to a few years, could be very significant if treatment reaches a high fraction of the infected population. These benefits in reducing transmission

are over and above those received by individual patients. However, at present this would be an expensive method for the community wide control of transmission, given the cheaper alternatives of inducing behavioural change and increased condom use. This is especially the case given uncertainties over the degree to which treatment reduces infectiousness, and the short duration of suppression of viraemia before drug resistant viral strains become dominant.

Studies of the population genetics and population dynamics of HIV in patients treated with antiviral drugs have revealed the rapidity with which drug resistance emerges (Wei *et al.*, [111]; Ho *et al.*, [61]).

How transmissible the resistant strains are, and how they compete with susceptible virus in the absence of treatment are key questions. Future work on the community wide implications of antiviral therapy to suppress HIV population growth in individual patients must begin to address the population genetics of the spread and persistence of drug resistant variants.

Chapter 7

Summary and concluding remarks

This thesis has mathematically modelled the transmission dynamics of HIV/AIDS considering a single sex community. The AIDS endemic has been characterised by the broad and complex range of epidemiological and sociological issues involved. Every endemic that occurs is in some way unique from others, even within the same city or community. Different risk groups like homosexual males can cause and maintain an epidemic within their own group, or interact with other risk groups like heterosexuals and injecting drug users.

Mathematical modellers are advised to direct their attention to specific questions, employing comparatively small models. In this way they can make valuable contributions to the understanding of the epidemiology of the disease, and assess the potential and actual impact of prevention and control measures. In addition to, identifying important issues, providing guidance on what additional data are critically needed from epidemiological and be-

havioural studies.

Chapter 1 is a broad discussion and review of the AIDS pandemic and the research efforts that has accompanied it. The knowledge of the human immune system is essential. The biggest obstacles facing collaborations is the inability of clinicians to understand advanced mathematics and on the mathematician's part, the lack of knowledge of the underlying medical problem. It can take years to come to terms with all the medical jargon, especially in a continually evolving area. This can be overcome through serious cross-training of interdisciplinary scientists whose goal will be doing good science, which in turn would advance knowledge in both disciplines.

The origin of AIDS epidemic in different regions across the globe has been dated back to the early Seventies although not clear. The most recent statistics is also given. Injecting drug use appears to be the main cause of the transmission of the disease in some regions. The implications of the pandemic for the social fabric as it effect regions (most notably sub-Sahara Africa).

In order to review the modelling of the epidemiology of HIV/AIDS, I first discuss the terminology of the AIDS modelling followed by difficulties encountered in modelling and natural history models. A glossary of the terminology used throughout this thesis finalises this chapter.

Chapter 2 discusses mathematical approach to the modelling of the transmission dynamics of HIV/AIDS epidemic. It also describes the mathematical structure of the transmission dynamics of HIV/AIDS models in form of deterministic approximation in the form of ordinary differential equations (ODEs). This is then followed by the stability analysis of the system of ordinary differential equations, used in the concept of AIDS dynamics mod-

elling. Also, this chapter introduces some novel algorithms used in analysis of the transmission dynamic models throughout this thesis. These include the computational methods and algorithms to reduce the size of the complexity of the problem by bypassing some standard algorithms involved in model analysis. An outline of the methods and novel techniques used in analysis of the system of ordinary differential equations devised to model transmission dynamics of HIV/AIDS throughout this thesis are presented.

Chapter 3 discusses solution techniques of the HIV/AIDS transmission models. These include algorithms and techniques used to solve system of ordinary differential equations. Also this chapter present a novel analytical approach in estimating boundary conditions on the numerical method's time step, covering a range from monotonically convergent to oscillatory convergence even divergence.

Two numerical methods including Euler's and an alternative method were employed as the solver engines in the implementations. In general, numerical method used to solve the mathematical model should not predict chaos or divergence when chaos and divergence are not features of the system. The efficiency of the numerical integration of the systems of non-linear differential equations over the largest possible time step, bearing in mind accuracy and stability, is of remarkable degree. The stability properties restrict the use of a large time step this is to avoid the presence of chaos or divergence in the solution of the model equations.

Choosing the suitable numerical method using maximum possible time step increases the speed and performance of the computational tools bearing in mind the accuracy and stability.

In order to eliminate the occurrence of the solution, which does not match

the stochastic nature of the problem choosing the appropriate time step is essential. This occurs whenever a large-scale model is to be analysed and solved. Computational experience shows that, solving large-scale problems are costly. As time step increase the number of iterations to converge to the steady state decreases. The theory of convergence and its extension are the keys to estimate the maximum time step.

Chapter 4 applies the algorithms and the techniques described previously in Chapters 2 and 3 on the three existing models. To direct the attention of this work to specific questions, three comparatively small models are investigated in details providing some valuable contributions to the understanding of the epidemiology of AIDS. Also the potential and actual impact of changing sexual behaviour in the transmission dynamics of HIV/AIDS.

The first mathematical model is a basic model stratifying the population into two groups of susceptible and infectives. The second one describes the mathematical model predicting transmission dynamics of AIDS for longer periods of time. This model stratifies the population into three groups of susceptible, infective and full-blown AIDS patients. Finally the third model stratifies population into five groups of susceptible, infectives who ultimately develop AIDS, and infectives who do not develop AIDS, full-blown AIDS patients and non-infectious seropositives.

Mathematical analysis presented in this chapter suggest that, whenever individuals in a population choose less than k^* (bifurcation parameter) number of sexual partners per unit of time then the disease will eventually disappear. The bifurcation parameter is a unique parameter, which leads to the calculation of the reproductive rate. Reproductive rate is the average total number of secondary HIV infected cases made by one primary infected case. Whenever an infected population is stratified into subpopulations the total

reproductive rate is the sum of infected subpopulation reproductive rates.

The aim of Chapter 5 is to obtain equations that are consistent with the observed population sexual contacts and to investigate the effect of heterogeneity in sexual behaviour on the transmission dynamics of HIV/AIDS. Heterogeneity in sexual behaviour increase the endemic prevalence from that pertaining in a population with homogeneity in sexual behaviour. Some results of the developing theory of mixing matrices is given proposing the need for further constraints. In addition to presenting constraints that ensure the description of the full range of mixing patterns of a given population, for defined population parameters in a specified time interval.

Also in this chapter the meaning of the mixing extremes are examined in the light of the new constraints. Distribution of individuals by number of sexual partners tend to be highly skewed in character where most individuals have few partners and a few have many. This implies that in a defined community the number of people in the highest sexual activity group tends to be small, which in turn limits the possibilities of partnership with individuals in this group. The effect of behavioural heterogeneity is explored by stratifying population according to the level of sexual activity.

In this chapter numerical examples illustrate the insufficiency of the existing constraints on the elements of the mixing matrixes for a population of finite size. The major problem arises with the characteristics and nature of the sexual activity of individuals in a population that reports small number of individuals in high activity groups. Some constraints are presented satisfying all the necessary and sufficient conditions on the elements of the mixing matrix of a finite size population of homosexual men to be a true mixing matrix.

Graphical solution to the mathematical modelling of a population with heterogeneous sexual behaviour shows that, assortative populations are less susceptible to the spread of HIV/AIDS than mixed or dis-assortative populations. In other words, whenever sexual mixing pattern varies from a range of assortative to random and dis-assortative the number of susceptibles decrease and the number of HIV infected and AIDS cases increase.

Finally, Chapter 6 discusses the mathematical modelling of the effect of the antiviral therapies in the transmission dynamics of HIV/AIDS within a population of homosexual male, with heterogeneous sexual behaviour. Anti-HIV treatments have begun to have an effect on the net rate of transmission of HIV in human population. Although simple in concept, little is understood at present of how to induce behavioural changes in any given society or community.

Behavioural change is the desired intervention to limit HIV spread. The simplest methods to control HIV are condom use and education to encourage reduction in the rate at which individuals acquire new sexual partners. A further option is the use of community wide programmes designed to treat all infected individuals with antiviral therapy. This obviously acts to the benefit of the individual who receives treatment (given the availability of a safe and efficacious drug), but it can also act to reduce net transmission within the community, if therapy reduces the infectiousness of a treated patient.

Some complex mathematical models are devised and studied with the assumptions made on the conditions of the treatment. These include a population with no treatment, treated population assuming that treatment does not effect the infectiousness of the treated individuals and finally, treated population assuming that treatment reduces the infectiousness by 50%. Comparing the graphical solutions indicate that whenever treatment does not effect the

infectiousness the anti-HIV treatment increase the net rate of HIV infection, full-blown AIDS and reduces the total number of susceptibles simultaneously. These rates increase according to the sexual mixing pattern from a range of assortative to random and dis-assortative respectively.

Reduction of the infectiousness by anti-HIV treatment is the key to eliminate the transmission in a population with extensive treatment coverage. However, suppressing the infectiousness to zero will not be possible, because of the high infectiousness early in the incubation period coupled with the small probability of detection and treatment at the early stage of the disease. The benefits accruing from community wide use of drugs that effectively suppress infectiousness, even for periods of a few months to a few years, could be very significant if treatment reaches a high fraction of the infected population. These benefits in reducing transmission are over and above those received by individual patients.

At present this would be an expensive method for the community wide control of transmission, given the cheaper alternatives of inducing behavioural change and increased condom use. This is especially the case given uncertainties over the degree to which treatment reduces infectiousness, and the short duration of suppression of viraemia before drug resistant viral strains become dominant.

How transmissible the resistant strains are, and how they compete with susceptible virus in the absence of treatment are key questions. Future work on the community wide implications of antiviral therapy to suppress HIV population growth in individual patients must begin to address the population genetics of the spread and persistence of drug resistant variants.

My work has contributed significantly to understanding the spread of

HIV/AIDS. This work can provide education and health authorities with the tools to plan effective strategies to fight the spread of the virus. This thesis suggests that sex education at early stages is more effective than antiviral therapies in controlling the spread of the HIV/AIDS.

As the Injecting Drug Use (IDU) is becoming a significant cause of the spread of HIV/AIDS in some areas in the world, a further research needs to be done to overcome this issue.

As away of comparing the results obtained in this work and the previous work by other researchers these findings show that novel numerical methods can be applied to a system of ordinary differential equations which incompases the administration of a cocktail of drugs to AIDS patients as well as the average number of sexual partners per year. This is a new work and has not been tackled by previous researchers in the same area.

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