# THE ASSOCIATION OF HIV-1 AND OTHER SEXUALLY TRANSMITTED DISEASES, AND ITS RELEVANCE TO INTERVENTION PROGRAMMES IN RURAL UGANDA: A SIMULATION MODELLING EXERCISE

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TO

ALMA AND LIONEL

WITH LOVE

## ABSTRACT

Since the heterosexual transmission of HIV may be enhanced in the presence of other sexually transmitted diseases (STDs), high STD prevalences in some African populations may contribute substantially to the HIV epidemic, but the magnitude of this effect is uncertain.

A stochastic simulation model, SimulAIDS, was extended, and used to simulate the transmission dynamics of HIV infection and of ulcerative and non-ulcerative STDs in an attempt to mirror the development of the HIV epidemic in a rural population cohort of 10,000 under study by the MRC Programme on AIDS in Uganda.

Three scenarios were compared, assuming different STD cofactor effects. Simulation results were most consistent with empirical data for a scenario that assumed enhancing effects on HIV transmission per sexual contact of 100 for ulcerative STDs and 5 for non-ulcerative STDs in females. A scenario assuming no STD cofactor effects was not consistent with results from the study population.

By sampling from the simulated population, it was possible to assess the influence of various factors on associations between HIV and other STDs in observational studies. The most important included type of study design, choice of study sample, prevalence of STDs, misclassification of STDs, period over which STD history is recorded, and sexual behaviour characteristics.

Further simulations were conducted to estimate the fraction of HIV infections in this population attributable to the cofactor effect of STDs, and to assess the relative effectiveness of differing intervention strategies. Results were consistent with STDs playing a critical role in establishing an HIV epidemic, their role decreasing as the epidemic progresses. Reducing the incidence of HIV infection in short-term sexual partnerships, through improved STD treatment, increased condom use, and a reduction in one-off sexual encounters, was found to have a substantial impact on HIV incidence in the general population.

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## PREFACE

I am delighted to acknowledge my supervisor, Richard Hayes, and collaborators Bertran Auvert and Daan Mulder whose contributions not only made this project feasible but also made these last years so rewarding.

I am grateful to Steve Bennett for facilitating an introduction to Bertran Auvert, author of SimulAIDS, in North Carolina in June 1991. By early 1992 Bertran and I had decided to pursue a collaboration. Over the next year or so, with assistance from Gianluca Buonamico, model developments, critical for the project, were addressed. I am indebted to Bertran for these contributions. I am delighted to be continuing my research with him in Paris.

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CHAPTER 1

# INTRODUCTION, AIMS AND OBJECTIVES

# 1. INTRODUCTION, AIMS AND OBJECTIVES

## 1.1 INTRODUCTION TO AIDS EPIDEMIOLOGY

HIV infection and AIDS are currently among the most pressing global public health issues (*World Bank 1993*). In Uganda, and other Central African countries, there has already been widespread infection (*Nkowane 1991*). The burden of disease and high mortality rates in some parts are already severe (*Mulder et al 1994a*), and forecasts suggest that the future impact will be immense (*Chin et al 1992*). The problem is not restricted to developing nations, but the magnitude of the epidemic in heterosexual populations in the industrialised world is much smaller, and is unlikely to ever reach the same proportions. This project has focused on the dynamics of infection in sub-Saharan Africa, and in particular a specific rural population in south-west Uganda (referred to here as the "Study Population") in which intensive epidemiological research is being carried out by the MRC Research Programme on AIDS in Uganda.

The role of the AIDS epidemiologist has been an evolving one. Initial studies were undertaken to assess the extent of HIV infection and AIDS in different population subgroups in sub-Saharan Africa. Risk factor studies were extensively carried out, and results from these have been used to assist in designing prevention programmes. In the absence of effective treatments or vaccines, which are unlikely to be widely available for many years, the main intervention efforts are now focused on control of the spread of the HIV infection.

There are, however, limitations with epidemiologic field data, in, for example, predicting the future course of HIV epidemics. This is where transmission models can prove useful. Their most widely perceived benefits are that they can assist in making future projections for the spread of HIV infection and AIDS, and can help to guide AIDS control activities. Policy decisions need to have a basis, and models can provide supporting evidence or otherwise for future decision making (*Brandt 1989*). Forecasts and predictions can subsequently be assessed for their fit (or lack of fit) to observed trends, which assists in highlighting areas of particular uncertainty and guiding further research. Models, however, are also useful in studying issues which prove particularly difficult to study empirically, in expressing explicit statements of assumptions, and in organising our thoughts in bringing together disparate

information to create a global picture.

As epidemiological information improves, so the structure of mathematical and simulation models can hope to provide a more accurate representation of reality. It is data from epidemiological studies that should drive model development. Results from modelling exercises can only ever be expected to be as reliable as the data that have been employed. With many uncertainties still surrounding important epidemiological and behavioural parameters, modelling exercises to date must be viewed exactly as that, and results must be treated with caution.

## 1.2 OBJECTIVES OF RESEARCH

### 1.2.1 SPECIFIC OBJECTIVES

The primary objectives of this exercise were to:

(1) Simulate the development of the HIV epidemic in a rural population cohort of 10000 in south-west Uganda, drawing on data collected by the MRC Programme on AIDS in Uganda in 1989-90;

(2) Investigate factors influencing statistical associations between HIV and other STDs observed in epidemiological studies;

(3) Estimate the proportion of HIV infections occurring in the study population that might be attributable to the presence of ulcerative & non-ulcerative STDs; and

(4) Investigate the likely impact on the HIV epidemic of STD treatment interventions compared with other control strategies.

These objectives have been addressed by application of SimulAIDS, a simulation model for the transmission dynamics of HIV infection.

### 1.2.2 BACKGROUND TO OBJECTIVES

#### STUDY POPULATION

A close collaboration with the MRC Programme on AIDS in Uganda provided a unique opportunity to develop HIV-1 transmission models around one of the most complete and extensive data sets generated from prospective follow-up of an entire population in a rural community in sub-Saharan Africa. Other modelling exercises have principally focused on typical urban populations in sub-Saharan Africa, where data have proved more readily available. Although HIV prevalence levels are usually higher in urban areas, the burden of

disease is also likely to be substantial in rural areas where over 70% of the population in sub-Saharan Africa resides (*World Bank 1990*).

The objectives of this exercise were clearly motivated by the needs of the study population in particular, but also with relevance to the wider population.

## GUIDING INTERVENTIONS

A core part of the remit of the MRC Programme on AIDS in Uganda was to evaluate the extent of HIV infection in the study area, investigate risk factors for infection, and subsequently develop intervention programmes to try to control the further spread of infection. Collaborating closely with the MRC programme, this modelling exercise provided an important opportunity to assist in guiding such intervention strategies. To facilitate this, it was necessary to develop a model incorporating the main features believed to be important in the dynamics of HIV infection in this community, and which could replicate observed characteristics of the study population reasonably well. If STDs were enhancing transmission of HIV infection, then treating other STDs could represent an important intervention strategy for reducing the incidence of HIV infection in the study population.

## STUDY OF OTHER STDs

Although many empirical studies have implicated other STDs in contributing to the spread of HIV infection in sub-Saharan Africa, due to methodological problems, the exact nature of the relationship between HIV and other STDs still remains unclear (see 2.1). Modelling exercises, in this case, can provide a valuable tool to extend our understanding of possible relationships between HIV and other STDs.

This exercise sought to explicitly model the dynamics of other STDs and their interaction with HIV, not only to facilitate assessment of STD treatment interventions, but also to assess results from epidemiological studies, and to estimate the proportion of infections that may be attributable to other STDs. Since true enhancing effects of STDs on HIV transmission

per sexual contact are unknown, scenarios were developed for different assumed cofactor effects, and the consistency with which these models fit observed characteristics of the study population were examined.

## REASONS FOR EMPLOYING SIMULAIDS

### *Application of stochastic methods*

To address all the objectives, microsimulation, via Monte Carlo methods, seemed the most appropriate technique for model development. Two features were of particular importance: (1) To be able to model individuals in a population, rather than groups of individuals; and (2) Since the exercise was to be based on a relatively small population of about 10000, random variability was an important feature to evaluate. Furthermore, microsimulation models are generally more flexible, allowing for a wider variety of assumptions about the transmission dynamics, and facilitating model extensions when new epidemiological information becomes available. This freedom from the confines of mathematical tractability can prove rather appealing (*Renshaw 1991*).

### *Unique features of SimulAIDS*

SimulAIDS was conceived by Professor Bertran Auvert and colleagues and its development led to an initial publication in *1990 (Auvert et al)*. Since then SimulAIDS has been further extended, by the motivation of this exercise in particular, to enable new issues to be addressed and to complement increased epidemiologic understanding of HIV infection and AIDS.

The main reasons for extending and employing this early model, rather than developing a new one, were five-fold. (1) SimulAIDS already modelled individuals and used per contact probabilities of HIV transmission; (2) The structure of a new simulation model specific to the study population would, in other respects, have been broadly similar to that of SimulAIDS; (3) With specific extensions and modifications, SimulAIDS could address all the

specified objectives of this research project; (4) A larger part of this exercise could be focused on application of the model in addressing specific research issues; and (5) All parties strongly encouraged the collaboration.

## 1.3 OUTLINE OF THESIS

This thesis describes a simulation modelling exercise, investigating the association of HIV-1 infection and other sexually transmitted diseases (STDs), and its relevance to intervention programmes in rural Uganda. A published simulation model for the transmission dynamics of HIV infection, SimulAIDS, has been modified and extended, and employed for this purpose.

The objectives of this project are given in section 1.2, and their motivation and relevance to our understanding of the epidemiology and control of HIV infection in sub-Saharan Africa discussed. A review of the epidemiology of HIV infection in sub-Saharan Africa is presented in 2.1. Previous work in modelling the dynamics of HIV transmission in sub-Saharan Africa is reviewed in section 2.2. Details of SimulAIDS are introduced in chapter 3. These include model assumptions, input parameters used, and modifications required to address the specific objectives of this research project.

Chapters 4-7 address the four primary research objectives in turn. In each case, methods, results and discussion are presented. Chapter 4 outlines the research undertaken by the MRC Programme on AIDS in Uganda and, with application of relevant empirical data collected from the study population, shows how observed characteristics can be replicated by the model for a range of input scenarios, defined by differing per contact STD cofactor effects. The dependence of results on the different scenarios and their consistency with empirical understanding is discussed for each of the subsequent objectives in chapters 5, 6 and 7.

Chapter 8 gives a summary of the main conclusions, and outlines future research which needs to be addressed.

CHAPTER 2

# REVIEW OF PREVIOUS WORK

# 2. REVIEW OF PREVIOUS WORK

## 2.1 THE EPIDEMIOLOGY OF HIV-1 INFECTION IN SUB-SAHARAN AFRICA

It is now well established that HIV infection results in disease and early death, after a variable incubation period. Perhaps the most striking and unequivocal epidemiological evidence comes from initial follow-up of the study population itself in south-west Uganda (*Mulder et al 1994a*). In adults, more than half of all deaths (73 out of 135) during two years of follow-up were in HIV-1 seropositive individuals. In the 13-44 age band, the age-adjusted mortality rate ratio for HIV-positive adults compared with HIV-negatives was 60 (95% CI: 28-129). This evidence clearly refutes other hypotheses that contend that HIV may not be the cause of AIDS, and demonstrates the profound impact that the HIV-1 epidemic is already having on adult mortality in rural Uganda (*Dondero et al 1994*). It has taken a decade to document such strong evidence primarily due to the difficulty in acquiring reliable data in sub-Saharan Africa due to lack of resources and both poor infrastructure and communication. Lack of good empirical data has had important consequences for monitoring HIV and AIDS epidemics and thus also for the accuracy of epidemiological information used in modelling exercises.

### 2.1.1 A BRIEF HISTORY OF HIV INFECTION

In 1981 the first documented cases of a new disease syndrome, which was subsequently to be known as AIDS, were diagnosed in the United States (*CDC 1981*). Case histories from the very earliest reports were generally linked by one common factor, they were all men who had had sex with other men. The number of cases grew rapidly over the next year or two, including cases in women, and research efforts intensified to identify the cause of this new disease syndrome. In 1983 the causative agent, a virus initially known as HTLV-III but now known as the human immunodeficiency virus (HIV), was discovered (*Barré-Sinoussi et al 1983, Popovic et al 1984*), and tests for antibodies to the virus were rapidly developed. It soon became clear that HIV was being transmitted, not only during penetrative anal intercourse between men, but also via penile-vaginal intercourse, from blood transfusions and blood products, and through needles shared by intravenous drug users (*Curran et al*

*1988*).

In the early 1980's the first cases of what was also believed to be a new disease were detected in sub-Saharan Africa on border towns of Lake Victoria in Uganda and Tanzania (*Serwadda et al 1985*), and in neighbouring countries of Rwanda and Zaire (*Piot et al 1984, Van de Perre et al 1984*). These were characterised by a wasting syndrome in both adult males and females. There were no distinct risk factors in these men and women although virtually all had reached sexual maturity. Disease symptoms were strongly associated with HIV infection, and transmission was considered most likely from sexual contact (*Serwadda et al 1985*). Although some early test kits may have been non-specific, showing cross-reactions with other pathogens, leading to false positives, by the mid- to late-1980's it was clear that HIV infection had already spread widely in some populations in sub-Saharan Africa. Today tests are both highly sensitive and specific, and accurately record the current severity of the problem (*Nunn et al 1993*).

### 2.1.2 PREVALENCE OF HIV INFECTION

In the mid- and late-1980's a wealth of epidemiological reports recorded the spread of HIV infection in different regions within countries, and in different population subgroups within these regions (*Nkowane 1991*). Reports characterise the heterogeneity in spread of infection between and within countries. In general, higher prevalence rates are found in urban environments and among the more sexually active.

Although two distinct viruses have been discovered, HIV-1 and HIV-2, the following discussion and the work undertaken here has specifically focused on HIV-1 infection. In Central Africa where HIV infection has been spreading most rapidly, HIV-2 is still rare. In West Africa HIV-2 infection was more prevalent in the mid- to late-1980's, but its importance is now becoming overshadowed by HIV-1 as it spreads rapidly in this region (*De Cock et al 1991*). It is likely that these transmission patterns are attributable to lower infectivity of HIV-2 than HIV-1 (*Donnerty et al 1993, Kanki et al 1994*).

Individual countries have experienced epidemics at different times and to different extents

during the 1980's. In Kinshasa, the capital of Zaire, for example, HIV prevalence in pregnant women has not been observed to increase since 1986 when it was recorded at about 7% (*US Census Bureau (12) 1993*). In Yaounde´, the capital of Cameroon, HIV prevalence in samples of pregnant women have remained at under 2% (*Ndumbe et al 1991, Nkowane 1991, US Census Bureau (11) 1993*). These examples are in striking contrast to the situation in Kampala, the capital of Uganda, and capital cities of other central African countries, including Rwanda, Burundi, Malawi, and Zambia, where HIV infection was seen to spread earliest and which have subsequently experienced the most severe epidemics to date (*US Census Bureau (11) 1993*). In Kampala prevalence rates in antenatal clinic attenders have been recorded at over 20% since 1987, increasing to about 30% by 1991 (*US Census Bureau (12) 1993*). In particular groups of individuals who regularly engage in one-off sexual contacts (eg commercial sex workers (CSWs) and their clients) even higher rates are usually recorded (*US Census Bureau (11) 1993*). In Nairobi, for example, an explosive epidemic of HIV-1 infection occurred among a group of CSWs between 1981 and 1986; HIV-1 seroprevalence rose from 4% in 1981 to over 85% in 1986 (*Cameron et al 1989*).

In rural populations prevalence levels are usually considerably lower than in capital cities or other main urban trading centres. A study undertaken in the Rakai district of south-west Uganda documented a strong dependence of infection levels on location of residence (*Wawer et al 1991*). Prevalence levels among adults recorded from agricultural villages, secondary trading villages and main road centres were 8.6%, 25.4%, and 38.5% respectively. Among 13-34 year old females from the main road trading centres over 50% were seropositive. This shows how documenting results for all adults can often mask even higher rates in males and females in specific age bands. Even though prevalence levels are usually higher in urban areas, it is clear that, since over 70% of the population in sub-Saharan Africa is rural (*World Bank 1990*), a substantial burden of disease will be experienced in rural areas.

### 2.1.3 RISK FACTORS FOR SEXUAL TRANSMISSION OF HIV INFECTION

Penetrative sexual contact between males and females is the most common route for transmission of HIV infection in sub-Saharan Africa (*Piot et al 1987, N'Galy et al 1988*). Even though precise details of sexual behaviour in a population are extremely difficult to

elicit, crude measures of sexual behaviour, such as number of sexual partners over a period of time, consistently implicate sexual transmission as being the predominant route of infection. Strong epidemiological support also comes from observed profiles of HIV prevalence by age and sex. Many studies have consistently shown similar profiles in populations in sub-Saharan Africa, and are characterised by a small number of infections in children under 5, few, if any, in children between the ages 5 and 14, and with peak prevalence levels in young adults, usually 20–29 females and 25-34 year old males. This highlights the very few infections found in non-sexually active children (excluding mother-child infections).

Prior to acknowledgement of HIV as a sexually transmitted disease, little quantitative research on sexual behaviour had been carried out in sub-Saharan Africa (*Larson 1989*). The nature of sexual behaviour has always made it a sensitive issue, and in many environments a taboo subject altogether. Much early research was summarised in a review and annotated bibliography by *Standing and Kisekka (1989)*. As both they and *Larson (1989)* highlight, it is difficult to generalise about sexual behaviour in sub-Saharan Africa since it is largely characterised by its heterogeneity. It has taken dramatic circumstances such as these to focus on the critical need for better understanding of sexual behaviour, not only in sub-Saharan Africa but globally (*Johnson et al 1989, Caraël et al 1991, Wadsworth et al 1993*).

More recent research efforts in this area have been important but further empirical research must still take high priority (*Caraël et al 1991*). Two issues have a central role in our understanding of the dynamics of HIV infection. The first is sexual mixing patterns, which create the conditions for uninfected individuals to engage in sexual contacts with infected partners. The second issue addresses the factors which may enhance the transmission of HIV per sexual contact. These include: sex during episodes of concurrent STDs, lack of use of condoms, use of desiccating substances in the vagina, and sex during menses. These issues are discussed below.

## SEXUAL MIXING PATTERNS AND HIV INFECTION

Modelling exercises have highlighted the critical nature of sexual mixing patterns for the spread of HIV infection in sub-Saharan Africa (*Anderson et al 1989, 1991, Bolly et al 1991a*). The most important features include: (a) Proportion of males and females engaged in different types of sexual partnerships (including long-term, short-term and one-off); (b) Rates of partner change within different types of partnerships; (c) Extent of concurrent sexual partnerships; and (d) Age difference in sexual partnerships. Each of these issues are briefly discussed.

The larger the proportion of males and females engaged in shorter-term relationships and one-off sexual contacts, the greater the likely impact on the spread of HIV infection. It is widely believed that core groups of high frequency transmitters, such as commercial sex workers and their partners, may have a critical influence on the spread of HIV infection (*Plummer et al 1991a*).

Many studies have highlighted the strong association between HIV prevalence and rate of sexual partner change (*Carael et al 1988, Berkley et al 1989, Serwadda et al 1992, Malamba et al 1994*). Populations with higher rates of partner change would be expected to generate higher rates of HIV infection. Reducing numbers of sexual partners clearly marks an important intervention message (*Schopper 1990*).

The role of concurrent partnerships may also be important in generating rapid HIV epidemics. If levels of infectivity are associated with viraemia levels, then infected individuals are likely to be most infectious during early and late stages of infection (*Clark et al 1991, Daar et al 1991, Hudson 1993*). This, coupled with high rates of concurrent partnerships could have contributed to HIV epidemics in sub-Saharan African populations (*Hudson 1993*).

Large age differences in relationships may have important implications for the spread of HIV infection. At one extreme if everyone was to engage in sexual contacts with others of the same age then HIV infection would soon disappear from populations. A large age difference probably serves to increase the spread of infection (*Anderson et al 1991*). In sub-Saharan Africa older men often engage in sexual relationships with much younger women,

exposing them to HIV infection earlier than they might otherwise have been.

## FACTORS ENHANCING EFFICIENCY OF HIV-1 TRANSMISSION

Reports have highlighted the lack of association between number of sexual contacts and transmission of HIV (*May 1988, Peterman et al 1988, Wiley et al 1989, Kaplan 1990, Padian et al 1990*). This is likely to be due to the presence of enhancing factors, such as other STDs and time dependency of infectivity, for some but not all contacts. This would obscure any simple pattern between risk of infection and the number of sex acts that may be expected (*Jewell et al 1990, Shiboski et al 1992*). STDs and other possible enhancing factors are discussed below.

### *Sexual contact in the presence of other STDs*

Sexual behaviour is a risk factor for all STDs. Different STDs would therefore be expected to be associated with each other since sexual behaviour acts as a confounding variable (*Mertens et al 1990*).

Many cross-sectional studies have documented associations between HIV infection and a history of other STDs, such as chancroid, syphilis, gonorrhoea, and chlamydia (*Pepin et al 1989, Mertens et al 1990, Ryder et al 1990, Nzila et al 1991*). For ulcerative STDs, associations measured as odds ratios (ORs) from cross-sectional studies have generally been in the range of 2 to 5. For non-ulcerative STDs, ORs have usually been less than 3. After adjusting for the confounding effect of reported sexual behaviour, associations often remain strongly positive (*Mertens et al 1990*). Since sexual behaviour can rarely be measured accurately enough, this may, at least in part, result from residual confounding effects of sexual behaviour. Results from cross-sectional studies are subject to further problems of recall bias, and misclassification due to asymptomatic episodes of STDs. Associations between HIV and other STDs also give little indication of the time sequence of events. Despite these problems, the consistency of results, strength of associations, and biological plausibility all support the hypothesis that presence of other STDs during sexual contact may have an enhancing effect

on the transmission of HIV infection.

In follow-up surveys more reliable information can usually be obtained on sexual behaviour and current or recent episodes of STDs, and if HIV serostatus is also regularly monitored, STD associations with incident HIV infections can be assessed (*Mertens et al 1990, Laga et al 1991, Wasserheit 1992*). Well designed and closely monitored follow-up studies provide our most rigorous technique to assess enhancing effects of concurrent STDs on HIV transmission. Three follow-up studies, all focusing on high risk population sub-groups (CSWs and their clients), have been carried out (*Cameron et al 1989, Plummer et al 1991b, Laga et al 1993*). The main advantages of using high risk groups rather than the general adult population are that high risk groups are firstly likely to have both higher STD and HIV incidence rates, enabling more powerful studies to be undertaken, and secondly observed associations are less likely to be confounded by heterogeneity in sexual behaviour characteristics since, in this respect, the groups are likely to be more homogeneous.

Results from each of these studies further support the hypothesis that STDs do truly enhance HIV transmission. In a study of HIV-1 uninfected prostitutes in Nairobi, both genital ulcers (adjusted OR 3.3 [95% CI: 1.2-10.1]) and *Chlamydia trachomatis* (adjusted OR 2.7 [0.9-7.8]) were associated with HIV-1 seroconversion, suggesting that the susceptibility of women to HIV infection may be increased in the presence of these STDs (*Plummer et al 1991*). In a prospective study of initially seronegative men who had acquired an STD from a group of prostitutes, seroconversions were associated with acquisition of genital ulcer disease (adjusted OR 4.7 [1.3-17.0]) (*Cameron et al 1989*). It is most likely that, in this case, ulcers serve to raise the infectivity of HIV infected women. A third study followed a cohort of initially HIV-1-negative female prostitutes in Kinshasa prospectively for a mean duration of 2 years, with monthly STD check-ups and 3-monthly HIV-1 serology (*Laga et al 1993*). After controlling for sexual exposure, adjusted ORs for seroconversion were 4.8 (2.4-9.8) for gonorrhoea, 3.6 (1.4-9.1) for chlamydia infection, and 1.9 (0.9-4.1) for trichomoniasis. It is probable that non-ulcerative STDs increased the susceptibility of the women to HIV infection and/or increased the infectivity of the HIV infected male partners. Today it is widely acknowledged that other STDs can enhance the transmission of HIV infection and thus do probably contribute to epidemics of HIV infection. To what extent is, however, unknown.

Assuming STDs do act as cofactors for transmission of HIV, what enhancing effects of STDs on HIV transmission per sexual contact are consistent with observed ORs in the ranges described above? Though the actual magnitude of the per contact enhancing effects remain imprecise, it has been shown that per contact cofactor effects of 100 or more are consistent with empirical results for associations between HIV and ulcerative STDs (*Hayes et al 1994*) (see 5.3.6 for further discussion). The magnitude of the cofactor effect will influence the proportion of HIV infections that may be attributable to other STDs, and also has important implications for assessing the likely impact of STD prevention programmes. As described below, in these respects mathematical modelling exercises can prove very useful.

*Lack of use of condoms*

Condoms protect from transmission of HIV infection (*Mann et al 1987, Van de Perre et al 1987, Ngugi et al 1988, Plummer et al 1991b*). Lack of use of condoms therefore contributes (perhaps substantially) to HIV epidemics (*Lamptey et al 1991*). Use of condoms is most important during one-off sexual contacts where rates of HIV infection are relatively high in both males and females, and efficiency of transmission is likely to be high due to increased prevalence of concurrent STDs (*Mastro et al 1994, Robinson et al 1994*). In a study of female prostitutes working in London *Ward et al (1993)* found that the prevalence of HIV infection was less than 1% and that the reported use of condoms with commercial clients was high (98%). In sub-Saharan Africa lack of regular condom use by CSWs often results in very high rates of infection among CSWs, which consequently has important implications for spread of infection to the general population (*Plummer et al 1991a, Robinson et al 1993c*).

*Other factors*

There is some suggestion that sexual contact during menses may increase both the susceptibility of women to HIV infection, and the infectivity of women with HIV (*Lazzarin et al 1991, Malamba et al 1994*). Use of desiccating substances in the vagina may increase both the susceptibility of uninfected women to HIV infection, and the infectivity of women with HIV (*Hunter 1993, Winsbury et al 1994*). Circumcision also possibly reduces the

susceptibility of uninfected men to HIV infection, and the infectivity of men with HIV (*Bongaarts et al 1989, De Vincenzi et al 1994*). Other possible enhancing factors include genetic factors, and intercurrent infections which may, for example, increase infectivity due to an increase in viral load. It would appear that sexual transmission via penile-anal intercourse either from male-to-female or male-to-male is rare in sub-Saharan Africa (*Quinn et al 1986, Anonymous 1987, Berkley et al 1989*).

### 2.1.4 RISK FACTORS FOR NON-SEXUAL TRANSMISSION OF HIV INFECTION

#### INJECTIONS, TRANSFUSIONS AND SCARIFICATIONS

Profiles of HIV prevalence by age and sex also serve to refute the hypothesis that other routes of infection, such as from injecting needles, blood transfusions and scarifications are critical contributes to AIDS epidemics in sub-Saharan Africa. The proportion of adult infections attributable to these routes in this Ugandan study population is, at about 1%, believed to be very small (*Mulder et al 1991*). In other parts of sub-Saharan Africa transmission of HIV infection via injections and scarifications is also believed to be rare (*Berkley 1991*), but transmission via blood transfusions is more important (*Jager et al 1991*). Furthermore profiles of HIV prevalence also provide convincing evidence that HIV infection is not transmitted via mosquitoes.

#### MOTHER-CHILD INFECTIONS

In sub-Saharan Africa studies suggest that transmission of HIV infection from an infected mother to her child, before, at or after childbirth occurs, on average, about 30% of the time (*Newell et al 1990, Ryder et al 1991*). This rate is higher than that observed in Europe (*European 1992*). The difference may, at least in part, be attributable to transmission through breast-feeding, which is much more common in sub-Saharan Africa (*De Martino et al 1992*).

### 2.1.5 NATURAL HISTORY OF HIV INFECTION

Very few empirical data exist from sub-Saharan Africa on the natural history of HIV infection. Anecdotal evidence has, however, suggested that the AIDS incubation period is somewhat shorter than in America and Europe, where the median incubation period is about 10 years, and annual progression from asymptomatic seropositivity to symptomatic disease is about 5% (*Bacchetti et al 1989, Longini et al 1989, Moss et al 1989*). Recent reports from the Ugandan study population describe an annual mortality rate of 11.6% among seroprevalent adults (*Mulder et al 1994a*). This is consistent with the rate in a study of female prostitutes in Nairobi (*Anzala et al 1991*), and further supports the hypothesis for a shorter incubation period in sub-Saharan African populations.

Survival after onset of disease symptoms is also considered to be rather shorter in sub-Saharan Africa and, in the Ugandan study population, a substantial proportion of patients progressed within six months from asymptomatic infection or mild disease to death (*Mulder et al 1994a*). This compares with a median AIDS survival period of one year or more in Europe and the USA (*Batalla et al 1989, Pederson et al 1990, Piette et al 1991, Tu et al 1993*). Clearly drug therapies play a part in extending survival rates in the developed world (*Tu et al 1993*).

### 2.1.6 UNDERSTANDING HETEROGENEITY IN HIV PREVALENCE

Why should HIV infection spread at very different rates through penile-vaginal intercourse in different parts of sub-Saharan Africa, and why should the spread of infection via penile-vaginal intercourse be so much more rapid in sub-Saharan African populations than in North America and Europe? It is likely that population differences in sexual behaviour and differences in the role of core groups (*Plummer et al 1991a, Robinson et al 1993*) both play an important part. Even if, on their own, particular mixing patterns are not sufficient to cause epidemics, they may be necessary to create conditions in which severe epidemics can take place. It is possible that cofactors, such as other STDs, may also be necessary for rapid and widespread epidemics to occur. To better understand these issues, standardised studies of distributions of risk factors for HIV infection, in populations which have experienced very

different epidemics, need to be undertaken.

### 2.1.7 DISCUSSION

Research in the late 1980's has shown that populations can quickly become highly informed about HIV infection and AIDS. Uganda is a model example (*Forster et al 1989, Konde-Lule et al 1989, Agyei et al 1992*). Unfortunately knowledge itself is not enough to control the spread of infection. It also requires individuals to act on this knowledge. This has proved more difficult (*Agyei et al 1992*), and, in this regard, there is still an immense hurdle to surmount (*Konde-Lule et al 1989*). Clearly achieving modifications in sexual behaviour is the single most important objective, but to complement the very slow process of behaviour change, this needs to be supplemented with other intervention approaches.

## 2.2 REVIEW OF MODELLING EXERCISES FOR HIV INFECTION IN SUB-SAHARAN AFRICA

### 2.2.1 INTRODUCTION TO TRANSMISSION MODELS FOR HIV INFECTION

The development of transmission models for infectious diseases was long established before the discovery of HIV infection in 1983 (*Bartlett 1960, Bailey 1975, Anderson 1982, Hethcote et al 1984*). However, this proved a new focus for research interest in modelling infectious diseases. The first transmission models for HIV infection focused on homosexual communities where data had first become available. Since then an extensive literature has developed, predominantly focusing on populations in developed countries (*Castillo-Chavez 1989, Cox et al 1989, Fusaro et al 1989*). Most is rather experimental and theoretical in nature due to the lack of good empirical data. This review does not attempt to cover all projects undertaken, but rather focuses on modelling exercises relevant to populations in sub-Saharan Africa. The main review (2.4.4) is guided by the motivation of the particular exercises rather than the definition and structure of the different models.

### 2.2.2 PURPOSES OF MODELLING

Exercises in modelling the transmission dynamics of HIV infection prove useful in many respects. Their most widely perceived benefits are that they can be used to make future short- and long-term projections for numbers of HIV infections and AIDS cases (*HMSO 1987, 1988*), and to assess both the impact of the epidemic on, for example, demographic characteristics (*UN/WHO 1991*), and the impact of simulated interventions on the future course of the epidemic (*Auvert et al 1990, Robinson et al 1993b, Rowley et al 1994*).

Without reliable empirical data on epidemiological parameters, future projections will have wide margins of error (*HMSO 1988*). In this case, in the absence of well-validated transmission models, other approaches to short-term predictions are usually more useful. These specifically include direct extrapolation (*Healy et al 1988*) and back-calculation methods (*Brookmeyer et al 1990, Becker et al 1991*). The literature on these is also extensive as they have been widely employed for making short-term forecasts for HIV infections and

AIDS cases in developed countries. The main difference between these two techniques and models of the transmission dynamics is that, unlike transmission models, they make no attempt to describe the dynamics of HIV transmission, and thus require much less input data (*Gail et al 1988, Palloni et al 1991*).

Direct extrapolation involves the fitting of statistical models to past data on AIDS cases, and extrapolation of these models into the future (*Healy et al 1988*). Back-calculation methods use recorded numbers of AIDS cases and an assumed distribution for the AIDS incubation period to estimate past numbers of HIV infections. These estimates are then used to project future numbers of AIDS cases, based on the assumed AIDS incubation period (*Hellinger 1990*). Extrapolation and back-calculation methods are not discussed further in this report.

Models mimicking the transmission dynamics of HIV infection should as far as possible be guided by data. However, even without access to ideal data, modelling exercises can still prove useful and highly illuminating. Models:

(a) Can be used to make future short- and long-term projections for numbers of HIV infections and AIDS cases;

(b) Can be used to assess the impact of the epidemic on, for example, demographic characteristics;

(c) Enable study of the possible effects of intervention policies on the spread of HIV infection, which can be useful in providing guidance for policy making;

(d) Help to organise information and stimulate explicit statements of assumptions;

(e) Provide guidance on data needed from epidemiological and behavioural studies;

(f) Contribute to our understanding of the dynamics of HIV transmission, and to the role that different epidemiological parameters play in the spread of HIV infection;

(g) Assist in studying problems that prove to be methodologically difficult or

prohibitively time-consuming or expensive to study empirically; and

(h) Can be used to estimate values for statistical and epidemiological parameters that prove difficult to measure empirically.

### 2.2.3 STRUCTURE OF TRANSMISSION MODELS

*Last (1988)* gives various definitions of models, mathematical models, and Monte Carlo (computer simulation) studies. These may be summarised as follows: "A mathematical model is a representation of a system, process, or relationship in mathematical form in which equations are used to simulate the behaviour of the system or process under study. A mathematical model is said to be deterministic if the relations between the variables involved take on values not allowing for any play of chance, and stochastic if random variation is allowed to enter the picture. ... Complex relationships that are difficult to solve by mathematical analysis are sometimes studied by computer experiments that simulate and analyze events using random numbers. Such techniques are often referred to as Monte Carlo simulations." This summarises the framework of models that have been developed to study the transmission dynamics of HIV infection and AIDS (*Palloni et al 1991*).

All transmission models typically incorporate three fundamental features: initial conditions; definition of the states into which all individuals in the population are classified at each time point; and the rates of movement (or transition) between the states. A deterministic model gives an approximation to the average behaviour of the underlying stochastic models. In deterministic modelling, it is assumed that the number of persons at risk and infected are sufficiently large so that stochastic variability is negligible. The spread of infection, starting from specified initial values, will always take the same course. Only the very simplest deterministic models can be solved analytically. Computer intensive methods, such as numerical approximation techniques, soon become necessary to generate solutions. Monte-Carlo simulation exercises are always computer intensive.

The structure of models vary considerably. The simplest published models of HIV transmission have incorporated just one homogeneously mixing population (*Anderson et al*

*1986*). Though this is unrealistic since HIV transmission takes place in populations that are heterogeneous in a variety of ways, it provided a useful starting point. Clearly some groups have higher contact rates than others; people may have contacts primarily with others who are similar, or with a wide variety of partners; and behaviour is not uniform geographically or temporally. The most common way in which to incorporate these heterogeneities is to consider models with multiple groups (*Knox 1986, Jacques et al 1988, 1989, Bongaarts 1989*). Even given the same remit to develop a transmission model for a particular purpose two research teams are unlikely to develop identical models. Although both would probably include all the main features which are, at the time, believed to be important in the dynamics of transmission of HIV infection, the way these are represented may vary considerably. The groups would have a choice to develop deterministic or stochastic models, and to represent the epidemiological parameters in a variety of ways. They may choose different distributions for the AIDS incubation period, or choose to represent sexual behaviour mixing patterns in different ways. One group may choose to model per sexual contact transmission probabilities for HIV infection while the other may employ per partnership transmission probabilities.

Deterministic models have been more widely employed for modelling HIV transmission dynamics. The main reasons for this have typically been that: (1) Solutions are more difficult to find for stochastic models (and this is often reflected in considerably greater computing time); (2) Given the large populations involved in the AIDS epidemic and, once the epidemic is established, the large numbers infected, deterministic models should give similar results to the underlying stochastic models; and (3) The considerable uncertainty attached to estimates of the important parameters means that further sophistication may not be warranted. The second point should be tempered with a qualification because, for models involving a stratified population, it would be necessary for all the subpopulations to be 'large'.

In some situations, however, the variation between realisations of the epidemic could be such that knowledge of the behaviour of the average is not the only important feature. This might be true, for example, in modelling small populations (*Barrett 1988*). HIV infections might persist in a few isolated individuals for extended periods. This might give rise to sporadic local epidemics when, for example, the virus is transmitted to an individual with a

particularly high level of sexual mixing. In such situations the virus could spread rapidly and extensively without warning, infecting many people. These sporadic outbursts can only be represented by a stochastic model. In the case of a deterministic model, these local random events would be smoothed over. Stochastic simulation modelling also enables assessment of the extent to which random variation may influence results. Repeated simulations of the same input parameter set will rarely give the same outcome and can therefore be used to assess likely bounds of confidence for the results (*Auvert et al 1990*). This is again much more important when considering small populations. Furthermore, Monte Carlo simulation exercises can increase flexibility and, with the revolution in powerful desktop computing facilities, are now becoming more accessible.

### 2.2.4 MODELLING EXERCISES RELEVANT TO POPULATIONS IN SUB-SAHARAN AFRICA

There have been relatively few applied modelling exercises relevant to populations in sub-Saharan Africa due to lack of good empirical data. In general, exercises have been rather academic in nature. The main foci have been principally to simulate hypothetical populations from urban areas in sub-Saharan Africa to either: (1) Evaluate the role of epidemiological parameters on the spread of HIV infection; (2) Assess the possible demographic impact of HIV infection and AIDS; and (3) Evaluate effects of simulated intervention programmes.

Results from transmission models are highly dependent on model assumptions and values assigned to input parameters. In sub-Saharan Africa lack of reliable data for many epidemiological parameters has hindered attempts to make reliable predictions of numbers of infections and AIDS cases. Forecasts that have been made have generally been presented as examples of how models may be used when data becomes available.

#### MAIN MODELS

The main published modelling exercises applied to situations in sub-Saharan Africa include those by *Anderson et al (1988b, 1991)*, *Bongaarts (1989)*, *Auvert et al (1990)*, *John (1991)*,

*UN/WHO (1991)*. In the following sub-sections the main results of these and other exercises will be discussed, before addressing the main differences between the models.

## ROLE OF EPIDEMIOLOGICAL PARAMETERS

The first modelling exercises focused on assessing the importance of different epidemiological parameters in the dynamics of HIV infection (*May et al 1987, Anderson et al 1988a*), including AIDS incubation period (*Blythe et al 1988a, Hyman et al 1988*), variable infectivity associated with time since infection with HIV (*Blythe et al 1988b, Hyman et al 1988*); and sexual behaviour representations (*Blythe et al 1988c, Jacquez et al 1988, Gupta et al 1989 & 1990*). These exercises mainly considered transmission within homosexual communities in developed countries, and principally served to highlight areas of ignorance, thus helping to guide future data needs. The critical role of assumed sexual mixing patterns for the spread of HIV infection was most striking (*Jacquez et al 1988, Gupta et al 1989*). Modelling heterosexual populations from urban centres in sub-Saharan Africa has also found assumed patterns of sexual mixing to have a major impact on the course of spread of HIV infection (*Anderson et al 1991*), with patterns of strong assortative (like with like) mixing predicted to generate the least spread of infection. Assumed patterns of sexual behaviour seem to dominate the predicted outcome, more than refinements associated with rates of vertical or horizontal transmission or duration of incubation and infectious periods (*Anderson et al 1991*).

There are few published modelling exercises investigating the influence of STDs on HIV transmission. As demonstrated by a number of abstracts presented at recent AIDS conferences, interest in this area has been growing. As illustrated by way of a simple model of the interaction between HIV and a second STD, *Anderson (1989)* presented results showing that HIV did not spread extensively in a heterosexual population if the prevalence of other STDs could be maintained at a very low level. Similarly for a simple model incorporating HIV and another STD *Stigum et al (1993)* also found that there would be no spread of HIV without assuming an STD cofactor effect. These results are consistent with those presented here (see chapter 6) which support the critical role of other STDs in generating HIV epidemics (*Robinson et al 1993d*). *Boily et al (1991b)* developed a stochastic

model facilitating transmission of HIV and a second STD. They applied the model to a hypothetical population to assess sampled associations between HIV and other STDs assuming different enhancing effects for STDs. Preliminary results found sampled associations between HIV and STDs to be highly sensitive to the type of study design. Further issues on sampling associations between HIV and other STDs are introduced in chapter 5 of this report. *Over et al (1991)* developed simple models to simulate the dynamics of HIV infection and concomitant STDs, based on models developed by *Hethcote et al (1984)*. They were primarily used to compare the effect of preventing STD cases both in core and non-core groups, and to investigate the dynamic effect of STDs on HIV epidemics. Results illustrated the substantial gains that could be made by focusing STD interventions in core groups, rather than non-core populations.

## IMPACT ASSESSMENT

### *Impact of HIV on population growth rates*

The likely impact that HIV will have on population growth rates in sub-Saharan Africa has proved a contentious issue. Some researchers believe that, in the absence of successful interventions and change in sexual behaviour, HIV infection could reduce population growth rates by 3% or more (inducing zero or negative population growth) in some of the worst affected areas (*Anderson et al 1988b, 1991, May et al 1988, Bolly et al 1991, Garnett et al 1993*), while others predict a slowing of population growth rates by no more than 1% to 2% (*Bongaarts 1989, John 1991*).

The reasons for these differences seem to lie both with the application of different models and different input parameter sets and also in the interpretation of simulated results. As might be expected decline in population growth rates will depend on endemic HIV prevalence levels. *John (1991)* found that for a simulated scenario where HIV prevalence reached an endemic level of 18% in adults (after about 40 years), the population growth rate declined by about 2% (from 3.4% to 1.3%). An illustrative model presented by *Bongaarts (1989)* found that for a scenario in which seroprevalence in adults reached 21% by year 25, the annual population growth rate was reduced by "only"1.1% at year 25. Similarly an upper

bound estimate of HIV prevalence in Malawi of 18% by the year 2000, resulted in a decline in population growth of up to 1% (*Gresham et al 1992*). Projected population growth rates for various African countries with high rates of HIV infection were also estimated to remain largely positive by *Heuveline et al (1992)*.

These results contrast with those of *Anderson et al (1988b, 1991), Boily et al (1991)* and *Garnett et al (1993)* who consider that observed prevalence of infection is sufficient to reduce population growth rates to close to, or below, zero in the coming decades. The main difference in results probably arises from Anderson and colleagues assuming HIV prevalence rates of 30% or more among adults. This is probably more important than differences in the structure of the models. This is illustrated by results from a modelling workshop which found that 5 out of 6 different models predicted population growth after 25 years to be near zero or negative for HIV prevalence levels ranging from 30% to 58% among adults (the so-called worst case scenario) (*UN/WHO 1991*). HIV prevalence levels of 30% or more amongst adults probably do reflect rates in the worst affected regions of sub-Saharan Africa. Fortunately, not only do rural populations generally have much lower prevalence levels, but so do the majority of urban populations in sub-Saharan Africa. Thus though it does seem feasible that some populations may experience no population growth due to high levels of HIV infection, it is likely that this will represent only a small proportion of the population of sub-Saharan Africa (*Chin et al 1992*).

*Impact of HIV on Dependency ratio*

The dependency ratio is a summary measure of the economic implications of population age structure, defined as the ratio of the number of people in the population less than 15 years old or more than 65 years old, to the number of people between the ages of 15 and 65. The ratio thus captures, in a rough sense, the number of non-workers who must be supported by each worker. Developing countries typically have dependency ratios of about unity. There seems to be, in this case, reasonable agreement that the dependency ratio is unlikely to change markedly after introduction of HIV (*Anderson et al 1988a & 1989, May et al 1988, John 1991*). This implies that there will be little economic impact of AIDS reflected through population structure. However, the dependency ratio obscures much of the age effect of

HIV-1 related deaths. Within the 15 to 65 age group *John (1991)* found that there would be pronounced changes in the age structure of the population with adults between 40 and 65 years old constituting a much smaller share of the adult population than they would in the absence of HIV-1 induced mortality. The potential loss of experienced members of the labour force may be economically crucial.

## SLOWING SPREAD OF HIV INFECTION

*Rowley et al (1990)* used a transmission model described by *Anderson et al (1989)* to investigate the implications of reducing HIV transmission on demographic patterns and national health budgets in sub-Saharan Africa. Their analysis emphasises the benefits to be gained from a concerted effort to reduce the spread of HIV infection as early as possible in the time course of the epidemic. Further work (*Rowley et al 1994*) on modelling the impact and cost-effectiveness of HIV prevention efforts served to highlight the continuing need to collect better data on the impact and costs of prevention programmes. If the spread of infection is to be controlled, it seems that changes in the behaviour of the high risk groups are critical (*Auvert et al 1990, Anderson 1991, Potts et al 1991*). Furthermore it would appear that control programmes combining the major interventions, such as STD control, access to condoms and education, are likely to be most effective (*Potts et al 1991*). Applied modelling exercises simulating the effects of focused interventions are striking by their absence.

## DIFFERENCE BETWEEN MODELS

For the most part the models described here are macro-simulation deterministic models (*Bongaarts 1989, Anderson et al 1991, John 1991*). SimulAIDS developed by *Auvert et al (1990)* is, however, a micro-simulation stochastic model based on monte-carlo methods which can follow individuals in a population. A basic structure of all of these is a two-sex population, age-structured, incorporating heterogeneities in sexual behaviour, and representing the various stages of HIV infection. These might be considered the minimal basic features required to model the dynamics of HIV transmission in sub-Saharan African

populations.

The main focus of the research carried out by Anderson's group has been to use simple models to gain a qualitative understanding of the dynamics of HIV transmission. Models have usually been deliberately oversimplified, assuming a baseline structure of constant infectiousness, a constant rate of movement from HIV infection to AIDS, equal male-to-female and female-to-male transmission rates, and the same average rate of acquiring new heterosexual partners for all individuals (*Anderson et al 1988b*). Such models serve as a point of departure before introducing refinements, such as non-homogenous mixing patterns, asymmetric transmission rates, and age structuring which then facilitate qualitative insights to be made (*Anderson et al 1988b, 1989, 1991, May et al 1988, Bolly et al 1991*). Rather than performing 'experimental' modelling exercises to gain an understanding of the dynamics of infection and the relevance of various epidemiological parameters, other authors developed models including all apparently essential components, such that they could be employed for predictive purposes, or to assess possible intervention policies ... as and when appropriate data became available (*Bongaarts 1989, Auvert et al 1990, John 1991*).

Perhaps the most critical differences between the model formulations are their representations of sexual behaviour groups, which clearly influence the sexual mixing patterns that can be simulated. In an age-structured population *Anderson et al (1989, 1991)* assume all sexually active males and females have the same rates of partner change and investigate sexual contact patterns between age classes, whereas *Bolly et al (1991)* employ high and low sexual activity classes for males and females in a non age-structured population. Anderson and colleagues ignore stable unions and concurrent partnerships in all their exercises (*Anderson et al 1988b, 1989, 1991, May et al 1988, Bolly et al 1991*), and have not yet included different sexual behaviour classes in an age-structured population. By comparison sexually active behavioural groups used in the model by *John (1991)* include sexually active adults with many partners and those in a stable union. *Bongaarts (1989)* also included similar sexual behaviour strata, whereas *Auvert et al (1990)* allowed for combinations of one-off, short-term, and long-term partnerships. For models excluding stable unions the size of simulated HIV epidemics may be increased (*Denning 1987*).

A second important difference between the model formulations is that Anderson and

colleagues employ per partnership probabilities of HIV transmission (*Anderson et al 1988b, 1991*) whereas other modelling exercises have used per contact probabilities (*Bongaarts 1989, Auvert et al 1990, John 1991*). Only crude mechanisms, if any at all, have been employed to account for the role of cofactors and other STDs in the dynamics of HIV transmission (*Bongaarts 1989, Auvert et al 1990*). None of the models included migration.

*Anderson et al (1988b, 1989, 1991), Bongaarts (1989), Auvert et al (1990),* and *John (1991),* and all developed numerical examples for "typical" urban populations in sub-Saharan Africa. As all the authors discuss, the many simplifying assumptions made results hypothetical and illustrative rather than of practical importance. Input parameter values for demographic, and HIV-related parameters were not dissimilar in the different exercises, but as discussed above parameter inputs for sexual behaviour are harder to compare due to different model structures with respect to sexual behaviour representations. With respect to values for HIV-related parameters in the different models, all HIV infected adults were assumed to develop AIDS after a variable incubation period of between 7 and 9 years, and the interval between AIDS onset and death was taken to be about 1 year. Mother-to-child infections were assumed to occur with probability 0.5. The standard transmission risk from male-to-female was assumed to be higher than that for female-to-male and ranged from 0.001 to 0.009 per sexual contact. *Anderson et al (1989)* use probabilities per partnership of the order of 0.1. Injections and/or transfusions were included by *Bongaarts (1989), Auvert et al (1990)* and *John (1991)* but are only likely to have played a minor contribution to the spread of infection. None of the models used a dynamic representation of other STDs (or other cofactors) in the population.

Modelling exercises have generally not replicated the very rapid spread of HIV infection in some urban adult populations in sub-Saharan Africa, ie from a likely handful of individuals in the late 1970's to 20% or 30% by 1990 (*Bongaarts 1989, Anderson et al 1991, John 1991*). As is shown later (see chapter 4) this might be explained by the lack of use of enhancing effects of other STDs on HIV transmission. This results, on average, in higher per contact probabilities of HIV transmission during one-off sexual contacts than for contacts with regular partners, as has been documented (*Mastro et al 1994, Robinson et al 1994*). This may give rise to much more explosive epidemics of HIV infection. In models presented by *Bolly et al (1991)* infection rates per partnership were taken to be the same for both high and low

risk partnerships. However, since high risk partnerships were, on average, shorter, higher transmission rates per contact are attributed to higher risk partnerships. In this case rapid spread of HIV infection was recorded.

This is far from an exhaustive summary of the models that have been developed to simulate the dynamics of HIV transmission in heterosexual populations, which also include, in particular, other models presented at a workshop on modelling the demographic impact of the AIDS epidemic in pattern II countries (*UN/WHO 1991*). Those presented here are, however, the main published modelling exercises that have focused on HIV epidemics in sub-Saharan Africa.

CHAPTER 3

# SIMULAIDS

# 3. SIMULAIDS

This chapter covers four sections. After a brief introduction to SimulAIDS, the underlying model assumptions and parameter inputs for the version employed in this exercise (V5.02) are described in detail. The third section outlines the main extensions to earlier versions of SimulAIDS that were necessary to be able to address the specified objectives of this project. The final section describes how each of the objectives were addressed in practice.

## 3.1 INTRODUCTION TO SIMULAIDS

SimulAIDS is a Monte-Carlo simulation model which has been developed to simulate the dynamics of HIV infection in sub-Saharan Africa. Since its publication (*Auvert et al 1990*), SimulAIDS (V4.0) has been considerably extended, principally resulting from this new collaboration. SimulAIDS (V5.02), employed in this exercise, includes: age-structuring, migration, two dynamic STDs (which have been used to represent ulcerative and non-ulcerative STDs), and HIV parameters. Representations of sexual behaviour are based on three types of sexual relationships: one-off sexual contacts, and short-term (casual) and long-term (regular) partnerships.

At the beginning of a run an initial population is randomly created in computer memory using specified parameter inputs, and the population is then monitored over time. At some future point a few randomly chosen adults are infected with HIV.

At each time step (taken to be five days in this exercise), events occur with given probabilities, defined by input parameter values, and the status of the entire population is updated. For example at each time step:

* Every individual has a probability of dying;

* Individuals in specified age-bands have ascribed probabilities of migrating out of the population; and

* Individuals in relationships have a probability of sexual contact with their partners, and if infected with HIV or an STD there is an associated probability of transmission of one or other or both of these.

Each individual is represented by a set of coded characteristics (see 3.3) which are updated at each time step. These characteristics can be recorded in a data file after each completed year of simulation for every individual in the population. This facilitates internal checks to be carried out and statistical analyses to be performed.

Output variables from simulations, such as STD and HIV prevalence levels, are recorded as a function of time by repeated annual examination of the entire population.

## 3.2 UNDERLYING MODEL ASSUMPTIONS AND PARAMETER INPUTS

Real life is exceptionally complex and any attempt to model the transmission dynamics of HIV infection must make many simplifying assumptions. In developing SimulAIDS assumptions have been made about variations in parameters for an individual as a function of time, and from one person to another.

The models developed for this exercise have not included all features available in SimulAIDS V5.02. The models have been kept as simple as possible, while retaining all the main features believed to be of particular importance in the spread of HIV infection in the study population. Details of the internal structure of the model (V5.02) and input parameter requirements are described below. Unless otherwise stated, all assumptions described in this section are model assumptions (rather than parameter assumptions) and thus were not explicitly specified by the user and can not be modified. A full account of input parameter values used in the different scenarios is given in chapter 4. Features of SimulAIDS not employed in this exercise have not been discussed.

### 3.2.1 DEMOGRAPHY

Demographic inputs employed for this exercise comprise three main sections: fertility, background mortality & net out-migration.

#### FERTILITY

SimulAIDS assumes that every female of specified child-bearing age has a given probability each time step of having a single birth. This probability is specified for females under 25, 25 to 34, and over 34. Birth is assumed independent of sexual behaviour of the female, previous birth history, and HIV status. A newborn is equally likely to be male or female. Multiple births (twins, triplets etc) are not explicitly considered.

### BACKGROUND MORTALITY

SimulAIDS requires inputs for background age-specific mortality rates. It is assumed that, at each time step, each individual has a given probability of dying, dependent on age. Mortality rates for males and females are assumed identical. In the absence of reliable data, sex specific mortality rates were not considered an important extension to the model.

### NET OUT-MIGRATION

One year follow-up revealed more mobility out of than into the study population. This is not uncommon for rural populations in sub-Saharan Africa, with young adults often seeking employment in the bigger towns and cities. Since age-specific HIV prevalence rates for in- and out-migrants were roughly the same, and since numbers joining the study population were, in all age bands, either less than or roughly equal to the numbers leaving, out-migration parameters were used to represent the net out-migration in the population.

Minimum and maximum ages for out-migrants are required together with the ratio of female-to-male out-migrants and the total proportion of the population out-migrating annually.

## 3.2.2 SEXUAL BEHAVIOUR

All sexual contacts are assumed heterosexual. SimulAIDS categorises men's sexual relationships into three types: long-term (regular) partnerships, short-term (casual) partnerships, and one-off sexual contacts. In this exercise these have respectively been chosen to represent marriages, casual partnerships and one-off sexual contacts with, for example, commercial sex workers (CSWs) or bar girls. The terms marriage and regular partnerships are used interchangeably.

A man can have all possible combinations of these types of relationships, ie $2^3$ behaviour groups, and can move easily between the groups. Females either have only one-off sexual

contacts or can have a combination of regular and casual partnerships (see figure 3.1). Sexual behaviour does not change with STD and HIV status.

## MARRIAGE

Males may have a maximum of two regular partners at any one time. A specified proportion of males above a given age are sampled to have a regular partner. Of these a proportion are sampled to have a second regular relationship. Both proportions are maintained at roughly constant levels throughout by monitoring the level at each time step and introducing new partnerships when necessary. Note that the specified proportion of males in a regular relationship represents the proportion of males from the specified age range, that is the proportion from the "at-risk" population. Thus, for example, if 70% of males are specified as married, this refers to 70% of males within a specified age band, say 25 to 74. Similarly proportions of males in casual partnerships and one-off sexual contacts represent proportions from "at-risk" populations.

Female regular partners supply the demand from the males and are chosen at random from a subset of the "at-risk" population containing females of the same age as the male or less than 10 years younger, and not involved in one-off sexual contacts. They may, however, be involved in a casual relationship. Females may have no more than one regular partner.

The duration of a regular relationship is randomly sampled from a uniform distribution bound by specified upper and lower limits.

A specified average number of sexual contacts per week between regular partners is converted to a probability of sexual contact at each time step.

## CASUAL RELATIONSHIPS

In casual relationships males and females can have up to one casual partner as well as any regular partners (and in the case of males can also have one-off sexual contacts). Sexual

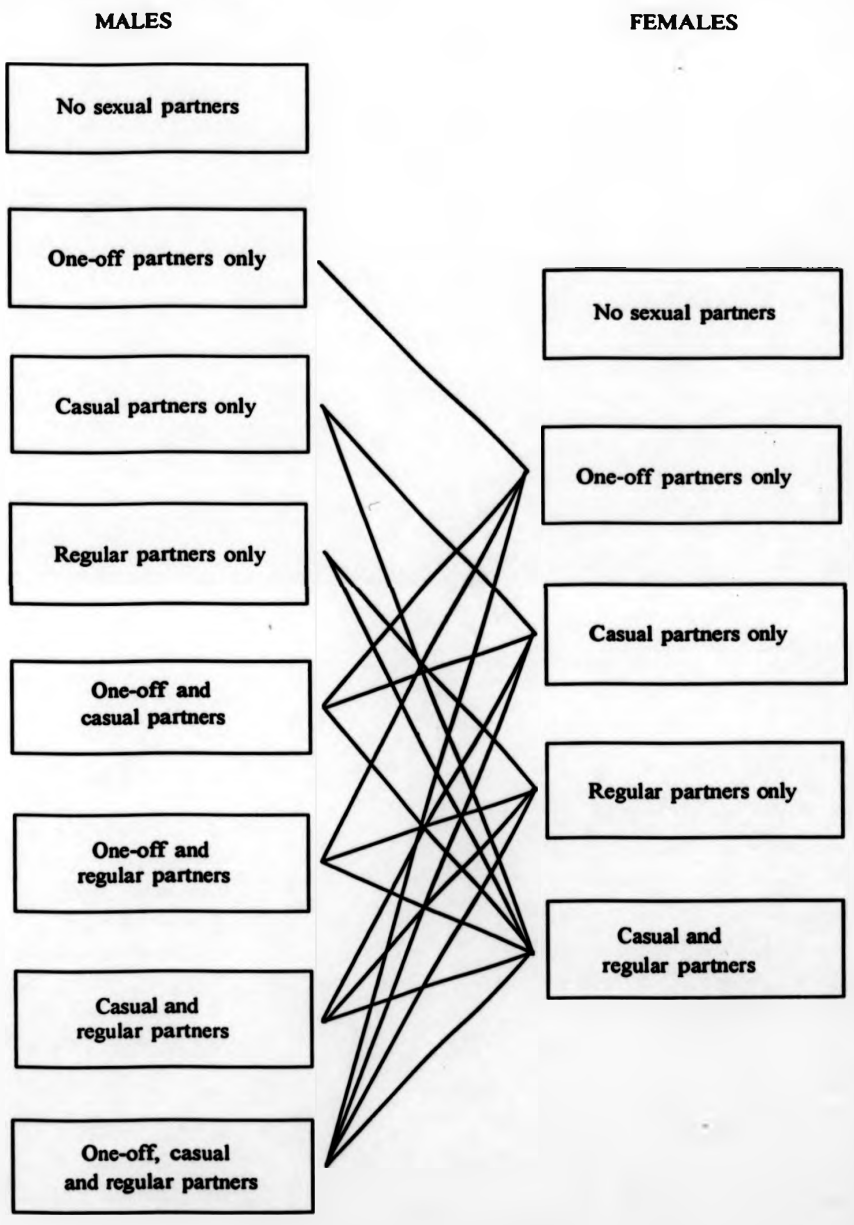



**Figure 3.1 Sexual behaviour groups in SimulAIDS**

behaviour can also be modified according to marital status of the male.

Thus a proportion of both married and unmarried males in a specified age range are defined to have casual partners. The demand is supplied by females in a specified age range. Married males with casual relationships are chosen at random firstly from the subset of married males with previous casual relationships, and then from all other married males in the specified age band. Similarly unmarried males are sampled for casual relationships firstly from those with previous casual relationships. The proportion of both married and unmarried males in casual relationships is kept roughly constant by introducing new partnerships when necessary at each time step. The female partner in a casual relationship is chosen at random from a subset of the population containing females younger than the male and initially from those with previous casual relationships.

The duration is again sampled from a uniform distribution with specified upper and lower bounds, and an average number of sexual contacts per week is specified for both married and unmarried males.

## ONE-OFF SEXUAL CONTACTS

For unmarried males above the specified minimum age at which they can have one-off sexual contacts, each has a given probability of being ascribed the characteristic to have regular one-off sexual contacts while they remain unmarried. Unmarried males not ascribed this characteristic have no one-off sexual contacts while unmarried. When males become married, each again has a specified probability to have one-off sexual contacts as a personal characteristic for the rest of their married lives, constrained by the maximum age for males in one-off sexual contacts. This probability, however, depends on past history of one-off sexual contacts, and the specified proportions of married and unmarried males in one-off sexual contacts. If the specified proportions are the same then, at marriage, all males retain the same characteristic as they had while they were unmarried. If the proportion of married males exceeds that for unmarried males then in addition to all unmarried males with the characteristic retaining it when they marry, all those without the characteristic are sampled with an associated probability to be attributed the characteristic when they marry. If the

proportion of married males is less than that for unmarried males, then every unmarried male with this characteristic has an associated probability of losing it when he becomes married.

This differs from regular and casual partnerships in that, although the proportion of males sampled to join those already in one-off sexual contacts at any time step is known and remains fixed, the proportions of the "at-risk" male populations in one-off sexual contacts at any time are not kept constant by monitoring and updating. Thus, for example, a higher mortality rate among men who have one-off contacts would be reflected in a smaller proportion of men in the at-risk population actually engaging in one-off sexual contacts. Men choose partners for one-off sexual contacts at random from the pool of women engaging in one-off sexual contacts.

Females are recruited to satisfy the demand generated by the males. Having been recruited they continue to have one-off sexual contacts regularly until they reach a specified maximum age, after which they are considered to cease all sexual activity. When there is a short-fall further females are sampled from those without a regular partner in the at-risk age band.

Both married and unmarried males have a specified average number of one-off sexual contacts per month, and females are specified to have an average number of contacts per week. In practice males have a probability of sexual contact with a one-off partner each time step, consistent with their average number of contacts per month.

### 3.2.3 SEXUALLY TRANSMITTED DISEASES

SimulAIDS (V5.02) has the facility to concurrently model two dynamic STDs. For this exercise these represent ulcerative and non-ulcerative STDs. The set of input parameters for each is identical (though the parameter values ascribed clearly differ). The simplest representation of STDs has been employed in this exercise. That is, an STD episode is considered to have one symptomatic period of fixed duration during which the probability of transmission of the STD at each time step is fixed, and the enhancing effect of the STD on HIV transmission is also fixed. If an STD episode is treated the duration of the episode

is truncated by a specified amount. Features that have not been employed include asymptomatic periods before and after this symptomatic period during which the STD is still considered infectious but there is no enhancing effect of the STD on HIV transmission.

Inputs are required on the probability of STD transmission per sexual contact from male-to-female and female-to-male. These are assumed constant for the duration of STD episodes, which can be specified separately for: all males; females in one-off sexual contacts; and all other females.

Enhancing effects of HIV transmission in the presence of an STD are specified for males and females per sexual contact. The cofactor effect for the susceptibility to HIV infection for an individual with an STD has been assumed equal to the cofactor effect for the infectivity of an individual with both HIV and an STD. At the outset, in the absence of reliable data, inclusion of separate input parameters for the cofactor effects for susceptibility and infectivity was considered an unnecessary complicating factor. It is assumed that transmission of HIV is enhanced at all times during an STD episode.

The introduction of STD treatments in the model is carried out by specifying the proportion of males, females in one-off contacts, and other females who are treated, and the respective durations of the treated STD episodes.

### 3.2.4 HIV INFECTION AND AIDS

#### PROGNOSIS FOR HIV INFECTED INDIVIDUALS

The model assumes that the sole cause of death through HIV infection results from the development of AIDS, which is always fatal. An individual's actual AIDS incubation period is sampled from a uniform distribution with specified upper and lower bounds. The incubation period has three defined phases: early, standard and late. Different probabilities of HIV transmission may be specified for the different phases. The early phase starts immediately an individual becomes infected. The late phase of infection ends with the onset of AIDS. The standard phase represents that period not defined by the early and late phases

of infection (see figure 3.2). Thus, for example, if the early phase is specified to have a fixed duration of 1 month and the final phase a fixed duration of 6 months, and the incubation period for a particular infected individual is randomly sampled to be 6.0 years, then the standard phase will have a duration of 5 years and 5 months beginning 1 month after initial infection.

A fixed period with AIDS immediately follows the incubation period, after which an individual is removed from the population. In this exercise all HIV infected individuals were assumed to develop AIDS.

Mother-to-child infections are specified to have a different incubation period, and different survival with AIDS. Again all infected children were assumed to develop AIDS.

## HIV INFECTION THROUGH SEXUAL CONTACT

All uninfected individuals are assumed equally susceptible to HIV infection and all infected individuals are assumed equally infectious to others. It is assumed that HIV is a single virus, which does not change during the development of the infection. All infected individuals are seropositive, and remain infected and infectious for their lifetime. People with HIV or AIDS do not modify sexual behaviour. The probability of transmitting HIV infection for people with AIDS is assumed to be at the same level as in the final phase of the incubation period. All seronegative individuals engaged in sexual contacts with seropositive individuals are at risk of infection.

### *In the absence of symptomatic STDs or condom use*

In the absence of STDs, sexual transmission of HIV is assumed to depend on the direction, ie male-to-female or female-to-male, and time since infection, ie whether the index case is in the early, standard or late phase of infection. In this modelling exercise the probability of HIV transmission is assumed higher for a brief period after primary infection and during the symptomatic terminal phase of illness. This corresponds to six distinct parameter inputs.

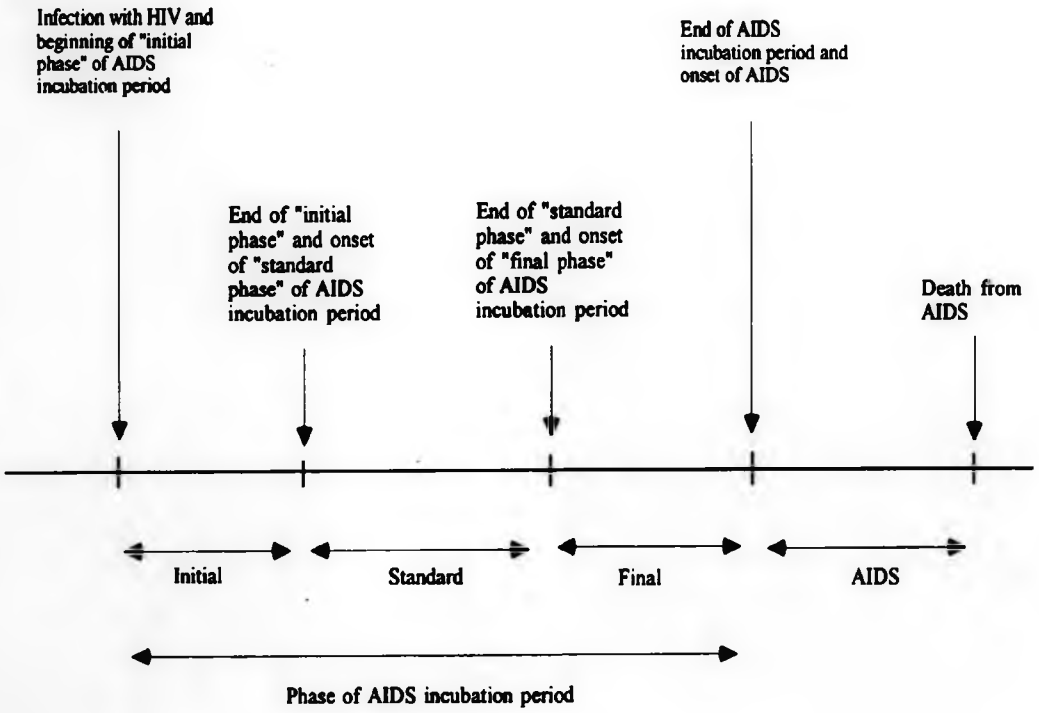



Figure 3.2 Prognosis for HIV infected individuals

Let the probability of HIV transmission during a single sexual contact from an infected male index case to an uninfected female partner be $p_{mf}(t)$. Similarly let the probability of infection from an infected female index case to an uninfected male partner be $p_{fm}(t)$. The time since infection is represented by t. There is the facility to incorporate three different values for each of $p_{mf}$ and $p_{fm}$, corresponding to the three distinct periods of infection in the index case: early, standard and late. For clarity dependency on time since infection is not explicitly stated in the following discussion.

*In the presence of symptomatic STDs*

If the female partner has a symptomatic ulcerative STD then the probability of HIV transmission to either the female or to the male is enhanced (ie multiplied) by a factor $g_{1f}$. Similarly if the male partner has a symptomatic ulcerative STD then the probability of HIV transmission is enhanced by a factor $g_{1m}$. If both male and female partners have a symptomatic ulcerative STD, the enhancing effect can be specified to be either the maximum of $g_{1f}$ and $g_{1m}$ or their product. In this exercise the maximum value has been used. The second (non-ulcerative) STD is based on an identical set of assumptions and employs cofactor effects $g_{2f}$ and $g_{2m}$. Again the maximum value of the cofactor effects has been used when both male and female partners have an STD episode.

There are many further combinations of STDs that may be experienced. For example, the male may have both an ulcerative and non-ulcerative STD and the female just an ulcerative STD, or the male may have just an ulcerative STD and the female just a non-ulcerative STD. In all cases other than the simple cases initially described, the enhancing effect of HIV transmission in the presence of combinations of symptomatic STDs always takes the value of the maximum of the individual cofactor effects.

*In the presence of condom use*

Males may choose to use condoms in regular, casual or one-off sexual contacts, and females may demand the use of condoms in one-off sexual contacts. Condom use may be specified

to be a characteristic of an individual. So, for example, when males choose to use condoms for a proportion of casual contacts, the model can be specified to interpret this in one of two ways. If, say, 20% of all male casual contacts are specified to be protected by condoms, then either a condom is used with probability 0.2 for every casual contact at each time step, or 20% of all males engaging in casual contacts always use condoms in all their casual contacts. In this latter case condom use is specified to be a characteristic of the male. Since males using condoms regularly in casual contacts are less likely to become infected with HIV and are therefore likely to live longer, the actual level of condom use may differ from that specified.

In the case of one-off sexual contacts condom use may be specified to be a characteristic of the male, and/or demand for condom use may be specified to be a characteristic of the female. This results in 8 ways to specify condom use in one-off sexual contacts, representing all combinations of characteristic, non-characteristic, or no condom use in males with characteristic, non-characteristic, or no demand for condom use in females (excluding the case of no condom use at all).

Incorrectly used condoms are considered ineffective. If $p_{cu}$ is the probability that a condom is used correctly and $e_c$ represents the efficiency of a correctly used condom in preventing the transmission of all STDs (including HIV), then during a condom protected sexual contact the probability of transmission of all STDs is multiplied by $(1-p_{cu}e_c)$. However, for this exercise, when condoms were used for simulating interventions, all condoms were assumed to be correctly used with 100% efficiency, ie in the presence of condoms HIV (and other STDs) could not be transmitted.

*Overall probability of HIV transmission via sexual contact*

Seronegative individuals who have a sexual contact with seropositive individuals, have a probability $P_s$ of becoming infected, where

$$P_s = p_{mf}(t)xyz$$

and $x=1$ or $(p_{fm}(t) / p_{mf}(t))$, depending on whether the male or the female is infected;

$y=1$ or $g_{1f}, g_{1m}, g_{2f}$, or $g_{2m}$, depending on the presence of STDs in either partner; and

$z=0$ or 1, depending on the use of condoms.

## MOTHER-TO-CHILD HIV TRANSMISSION

All women of reproductive age are assumed to be fertile. An infected mother has a probability $p_b$ of giving birth to an infected child, independent of the mother's stage of infection.

### 3.2.5 INITIAL CONDITIONS

To generate an initial population, initial conditions need to be specified. These include: an initial age structure of the simulated population; proportions of males and females specified to have ulcerative and non-ulcerative STDs; and an initial proportion of adults with HIV infection.

## 3.3 EXTENDING SIMULAIDS FROM VERSION 4.0

Four critical and fairly extensive features needed to be incorporated into SimulAIDS to enable the specific objectives of this project to be addressed. The programming for this was carried out by Professor Bertran Auvert and Gianluca Buonamico in Paris. Further modifications and extensions were also made during the development of SimulAIDS V5.02, but are not specifically discussed here. The motivation for these generally came from NJR while evaluating earlier versions of SimulAIDS.

The four main extensions to SimulAIDS V4.0 are outlined below.

(1) To replicate age structuring of the study population at baseline it was necessary to introduce the facility for out-migration. Extensive simulations were initially carried out on earlier versions to model the demographic structure of the Ugandan study population. Simulated results, however, always gave an over-representation of young adults and an under-representation of young children. The deficiency in young adults in the study population most likely reflected high levels of net out-migration in the years prior to 1990, resulting in over 53% of the study population below the age of 15 at baseline. This feature was particularly important since an over-representation of young adults would lead to a rather more extensive spread of HIV infection in the population.

(2) Since the initial representation of sexual behaviour was rather crude, it needed to be refined in order to facilitate reasonable replication of HIV prevalence by age and sex in the study population. For example, a male's sexual behaviour characteristics could not be modified during his lifetime, ie at different ages or during different phases. All males "at-risk" of having casual partners or one-off sexual contacts were equally likely to be sampled for these partnerships, and once chosen would all, on average, have the same number of sexual contacts per unit time. For all plausible scenarios this resulted in much more homogeneity in levels of HIV prevalence across age bands for males and females than was observed. In the Ugandan study population, HIV prevalence levels were much higher in the young adults, and especially 15-29 year old females and 20-34 year old males.

At the other extreme sexual behaviour would be allowed to be specified in, say, one-year age bands. This is, however, undoubtedly too refined since the data can not justify such precision. The dependency of sexual behaviour on marital status seemed a sensible compromise and facilitated a much better representation of HIV prevalence by age and sex. An alternative approach might have been to allow sexual behaviour to vary with age, but using broad age-bands.

To investigate associations between HIV and other STDs, to estimate the proportion of HIV infections attributable to ulcerative and non-ulcerative STDs, and to investigate the effects of simulated STD interventions two further extensions were necessary.

(3) Since SimulAIDS V4.0 only modelled one STD (which was assumed independent of sexual behaviour), it was important both to include a second STD, so that ulcerative and non-ulcerative STDs could be modelled simultaneously, and also to introduce a dependency of STDs on sexual behaviour.

(4) In SimulAIDS, every individual is represented by a set of coded characteristics. These are updated every time step. In order to be able to assess associations between HIV and other STDs, a facility was introduced to record the characteristics of individuals in the simulated population to a data file at the end of each completed year. In this way standard statistical analyses were carried out on the simulated population, just as if the data had arisen from observational studies. This feature also proved invaluable as a method for validating the model.

Recorded dates refer both to events that have already occurred (eg date of birth, and, for a person already infected with HIV, the date of infection) and to events that will occur in the future, assuming a person lives until then. Thus every individual has a date of removal from the population which is defined at birth to be on their 75th birthday. At the time an individual is sampled to have a relationship, the duration of that relationship is sampled from a specified distribution, and thus the end date is known and recorded. Individuals who are transmitted an STD have it for a fixed duration depending on gender, and so the end date is known at initial transmission. Date of onset of AIDS is also defined when an individual becomes infected with

HIV, since the AIDS incubation period is sampled from a specified distribution when an individual first becomes infected with HIV.

The set of recorded characteristics for every individual, that were used in this exercise, included:

1) Identification number
2) Date of birth
3) Date of removal from population (75 years after birth)
4) Gender
5) Identification numbers of different sexual partners
6) Dates of end of current relationships
7) Use of condoms as an individual characteristic
8) Dates of end of current STDs without treatment
9) Dates of end of current STDs with treatment
10) Lifetime number of episodes of ulcerative STDs
11) Lifetime number of episodes of non-ulcerative STDs
12) Date of HIV infection
13) Route of HIV infection, including via type of partnership
14) Date of onset of AIDS.

## 3.4 ADDRESSING OBJECTIVES: SUMMARY

In order to address the objectives, simulations were carried out in three consecutive stages: (1) an initial 50 years without HIV infection; (2) the introduction of HIV in a few individuals and the subsequent spread of infection over 10 years to mirror the study population at baseline in 1990; & (3) prospective simulations from the baseline population in 1990 (see figure 3.3). This strategy was carried out for three different scenarios (defined in 4.1).

1) An initial 50 year simulation was run in order to give relatively stable levels with respect to: (a) demographic features; (b) sexual behaviour; & (c) dynamic ulcerative & non-ulcerative STDs. This was important since the initial population is generated in a rather random fashion with, for example, STDs unrelated to age or sexual behaviour. At the end of the 50 year simulation characteristics for each individual in the population were recorded in a data file. One run was carried out for each of three different scenarios.

2) From the population recorded in (1), HIV was introduced in a few of the more sexually active individuals and the spread of infection simulated over 10 years, after which the population was again recorded in a data file. This was carried out for 10 consecutive runs for each of the three different scenarios.

3a) From each of the populations recorded in (2), simulations were continued for one year and the population again recorded. The population data files from baseline and a year later were then combined and analysed using standard statistical software. This enabled investigation of associations between HIV and other STDs for scenarios assuming different STD cofactor effects.

3b) From one population for each scenario recorded in (2), simulations were continued for up to 10 years both with and without STD cofactor effects operative. These were replicated 10 times. The comparison of incident HIV infections from these simulations enabled assessment of the proportion of HIV infections attributable to other STDs. Simulations were also re-run from introduction of HIV, without STD

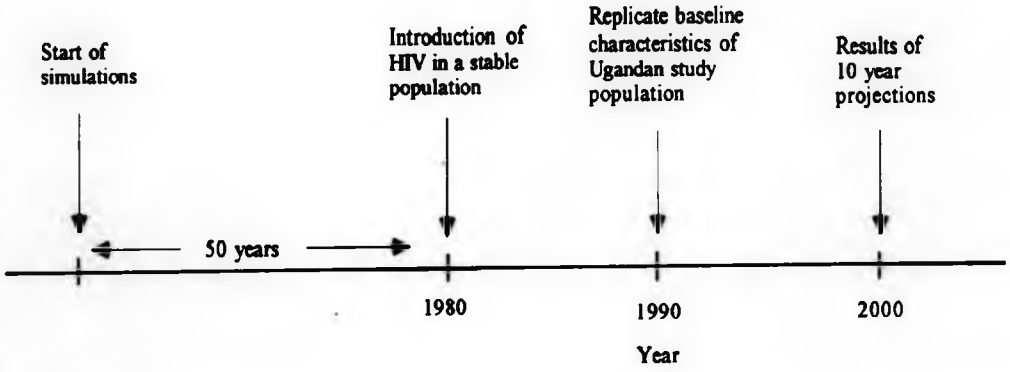



Figure 3.3 Time scale for simulations

cofactor effects operative, to assess the proportion of HIV infections attributable to other STDs in the years immediately following introduction of HIV.

3c) From one population for each scenario recorded in (2), simulations were continued for 10 years to investigate the effect on HIV incidence of introducing possible intervention measures. Again runs were replicated 10 times for each simulated intervention for each of the cofactor scenarios.

CHAPTER 4

# MODELLING THE DEVELOPMENT OF THE HIV EPIDEMIC TO 1990

# 4. MODELLING THE DEVELOPMENT OF THE HIV EPIDEMIC TO 1990

The first objective was to mirror the development of the HIV epidemic in a rural population cohort of 10000 in Masaka District, south west Uganda, drawing on data collected by the MRC Programme on AIDS in Uganda at baseline in 1990.

## 4.1 METHODS

### 4.1.1 INTRODUCTION

### UGANDAN STUDY POPULATION

Collaboration with the MRC/ODA Programme on AIDS in Uganda has provided a unique opportunity to begin development of transmission models, drawing on perhaps the most complete and extensive data available from Africa on the demographic, biological, behavioural and HIV-related characteristics of a general population cohort.

The MRC/ODA Programme is a multidisciplinary programme with the primary aim of investigating the population dynamics of infection with HIV-1, the natural history of HIV-associated disease and strategies for AIDS control in a rural setting in south-west Uganda.

The study population includes the total population (approximately 10000) of a cluster of 15 villages in Masaka district in south-west Uganda. Population surveys have been carried out annually. The first (baseline) survey was completed in August 1990. The fourth survey was completed in August 1993.

The main research strategy has been to combine a broad ethnodemographic and epidemiological follow-up of the whole population cohort with a detailed biomedical and social follow-up of a clinical sub-cohort. Other supplementary anthropological and clinical studies have also been carried out.

Surveys of the general cohort were based on questionnaires to household heads and

individual family members aged 13 or over. Individuals of all ages, for whom consent was obtained, had a blood specimen taken. From this study the demographic structure of the entire population was documented, together with age- and sex-specific seroprevalence rates for HIV infection from the bled population.

To determine the rate of progression from HIV infection to disease, and risk factors for such progression, a random sample of prevalent HIV positive cases at baseline and matched seronegative controls were enroled in the clinical sub-cohort. Incident cases and matched controls identified during follow-up surveys of the population cohort were also included in the sub-cohort, together with seronegative individuals at high risk of acquiring HIV infection. By monitoring this sub-cohort 3-monthly, transmission of HIV infection and the natural history of HIV disease are being closely observed. Details of sexual behaviour including frequencies of partner change and sexual contact have been collected. A detailed medical examination is also carried out at each visit.

A case-control study to investigate possible risk factors for HIV infection was also carried out by enroling all HIV-positive cases identified at baseline together with matched controls.

All data presented in this section from the study population were collected for one or other of the studies outlined above; ie the general population cohort, the clinical sub-cohort or the case-control study. The data presented here have specifically focused on the input parameter requirements of SimulAIDS (V5.02).

Approximately 75% of the total population had confirmed HIV serostatus at baseline. The documented profile of HIV prevalence by age and sex was assumed representative of the total population (see 4.1.2). Details of age structure and characteristics of the population other than HIV serostatus were estimated from the total population, rather than the bled population.

For the purpose of this modelling exercise those aged 15 and over were defined as "adults".

## EMPLOYING SIMULAIDS

SimulAIDS was used to simulate the spread of HIV infection in the Ugandan cohort, from its assumed introduction via a few individuals in 1980, up until the first survey of the cohort in 1990. Though the actual date of introduction of HIV in the study population is unknown this is consistent with reports of initial rapid spread of HIV infection in these regions in the early to mid 1980's. Since HIV seroprevalence levels have been accurately recorded by age and sex in 1990, this has been regarded as a real time reference for simulations.

Values for parameter inputs were chosen on the basis of data from the cohort and, where necessary, from other published sources. They were adjusted, within feasible bounds, so that simulations achieved a reasonable fit to certain well-documented characteristics of the study population in 1990, including: age structure; profile of HIV prevalence by age and sex; HIV prevalence among adults of about 9.5%; and a male-to-female HIV prevalence ratio of about 0.9.

For this exercise input parameters used for modelling the baseline population in 1990 were categorised as either fixed or variable, or parameters specifying initial conditions. Other parameter inputs were additionally employed for running simulated interventions (see chapter 7).

Three different scenarios were used to model the study population. They were defined by assuming different STD cofactor effects. The first assumed no true enhancing effects of STDs on HIV transmission. The second assumed that transmission of HIV per sexual contact was enhanced 10-fold during all episodes of ulcerative STDs and 2-fold during episodes of non-ulcerative STDs in females. This has been referred to as the low cofactor scenario. The third scenario employed STD cofactor effects of 100 and 5 for ulcerative STDs, and for non-ulcerative STDs in females, respectively. This has been referred to as the high cofactor scenario. For all scenarios episodes of non-ulcerative STDs in males were assumed not to enhance the transmission of HIV. The particular values used for per contact cofactor effects in the low and high scenarios were chosen to reflect a plausible range of values, consistent with estimates of associations between HIV and other STDs derived from published studies (see 5.3.6).

A fixed parameter was defined to take the same value for the different scenarios. For example, the proportion of males over 24.0 years with one regular partner was assumed to be fixed at 0.66.

A variable parameter was not constrained to take the same value for all scenarios. STD cofactor effects, for example, took different defined values for the various scenarios. Transmission probabilities for HIV infection also took different values for the different scenarios, but these were adjusted within feasible bounds so that simulated populations achieved certain characteristics reflecting those of the study population at baseline.

To simulate a population of between 9000 and 10000 at baseline in 1990, an initial population of 5000 was generated (60 years earlier). Simulations incorporating demographic features, sexual behaviour characteristics, and other STDs were then run for 50 years to achieve relatively stable levels of: ulcerative and non-ulcerative STDs in various groups in the simulated populations, behavioral mixing patterns, and demographic features, prior to the introduction of HIV infection (ie by 1980). This initial 50 year period should not, however, be considered a true representation of the growth of the study population over this period.

At the end of the initial 50 years (equivalent to 1980), characteristics of each individual in the entire population were recorded in a data file. Simulations from 1980, introducing HIV infection, were then run from this recorded population. A five day time step was used for all simulations.

Fitting of input parameter values was carried out in iterative steps. Initial simulations were run in order to find a set of demographic inputs which gave a reasonable representation of documented demographic characteristics of the study population in 1990. HIV-associated mortality prior to 1990 was assumed, for this purpose, not to have had a strong influence on the structure of the study population by 1990. Subsequent modelling scenarios then introduced sexual behaviour and STD dynamics, before finally introducing HIV infection 50 years later. As new parameter inputs were introduced into models so some of the previous ones required modifications.

For sexual behaviour representations, values employed for proportions in different partnerships, duration of partnerships, and frequency of contacts within partnerships were consistent with the limited data on sexual behaviour from the study population. Though attempts were made to elicit reliable data on sexual behaviour, this proved extremely difficult. The three different scenarios employed one basic representation of sexual behaviour with slight modifications for each. Frequency of contacts and age bounds for partnerships needed to be adjusted in the different scenarios in order to achieve good representations of profiles of HIV seroprevalence by age and sex in 1990.

Input values for the dynamics of other STDs were constrained within plausible bounds. Their particular values were chosen to give STD prevalence levels at baseline consistent with study results. Since STD input parameter values were considered fixed and since slightly different sexual behaviour representations have been used for the different scenarios, levels of STD prevalence prior to the introduction of HIV vary with the different scenarios. For higher STD cofactor scenarios, lower levels of sexual activity were assumed, resulting in lower prevalence levels of other STDs.

HIV parameters were finally considered for each of the scenarios. Input values used were consistent with estimates from published sources. Some parameters were considered fixed. Others were adjusted to give HIV prevalence profiles consistent with those observed in the study population in 1990.

### 4.1.2 FIXED INPUT PARAMETER SPECIFICATIONS

Some input parameter values were considered fixed for <u>all</u> scenarios. The following sub-sections in 4.1.2 give justification for the choice of particular parameter values, followed by a list of fixed parameter inputs used for modelling the baseline population.

## DEMOGRAPHY

### *Fertility*

Among all women having given birth, both the mean and median reported ages at the birth of their first child were 17. About 20% were reportedly under 16 years at the birth of their first child and about 20% were 20 years or over. By including young women who had given birth, and excluding those of the same age who had not yet had children, estimates are biased downwards. There was no apparent cohort effect of older women tending to have their first child at a younger age.

Among women over 49, the mean and median ages at which they reported giving birth to their last child were 37 and 38 respectively. About 15% reported being under 30, and 10% reported being 45 or over.

As well as the age band women can give birth, SimulAIDS also requires fertility rates in three broad age bands. For a much larger sample, these could be estimated from the number of births recorded during the first year of follow-up. This would give current birth rates, rather than underlying rates in the absence of HIV infection, but the difference is likely to be small. Instead of employing direct estimates of fertility rates from the study population, published rates (see below) were scaled according to estimates of the total fertility rate (TFR) in the study population. In total there were 1536 women in the reproductive ages 15-44 followed-up for one year from baseline. During this follow-up period 361 births were recorded. Assuming a reproductive period of 30 years, this would give a very crude estimate of the TFR of 7.1 (361*30/1536).

A TFR was also estimated from the reported number of lifetime births among older women. From data collected on the number of children born alive to all women over 39 at baseline, the mean TFR was 7.3 with standard error (se) 0.13 (n=610). This however may underestimate the actual TFR since early child deaths are often selectively removed from the mother's memory. Furthermore, this estimate may not necessarily reflect the current TFR. For women in the age bands 40-49 and 50+, mean (se) TFRs were 8.3 (0.21) and 6.6 (0.20) respectively. One possible explanation for the rather striking increase in the TFR in

the younger age band is that sexual behaviour may have changed during the lactation period (personal communication, Dr Uli Wagner). It would now seem less common for women to abstain from sexual activity during this period, possibly resulting in increased fertility rates.

In the modelling scenarios, the specified minimum age for women to give birth (17.0 years) is clearly higher than that observed in the study population. This age was chosen because within the age band 17-24 actual fertility rates are likely to be more homogeneous than in a wider age band, eg 15-24. With a maximum age specified for women to give birth of 43.0, the reproductive period has been assumed to have a duration of 26 years.

The fertility pattern described in table 4.1 was derived by Dr Ian Timeaus from *Booth (1984)* for a "standard" central African population. It was further adapted in this exercise to give fertility rates in three broad age bands, and then scaled according to an estimated total fertility rate in the study population.

From age specific rates in table 4.1 the TFR for this particular fertility profile can be calculated as simply the sum of the age specific rates multiplied by 5, ie (0.185 + 0.308 + 0.304 + 0.261 + 0.201 + 0.104 + 0.016) * 5 = 6.9.

The age specific fertility rates in table 4.1 were adapted to the specified age bands 17-24, 25-34, and 35-42, while maintaining the total fertility rate. Thus the fertility rate in the 17-24 age band was calculated as [(0.185*5) + (0.308*5)] / 8 = 0.31, since the age band was only 8 years. Similarly the fertility rates in the age bands 25-34 and 35-42 were calculated as [(0.304*5) + (0.261*5)] / 10 = 0.28 and [(0.201*5) + (0.104*5) + (0.016*5)] / 8 = 0.20.

Simulations were initially run using these fertility rates, but the result was a pronounced under-representation of under 5s. Higher rates were then employed by scaling the TFR. The observed age distribution of the study population was best replicated for a TFR of about 8.6. Although this is high, it is not untenable for a region with renowned high fertility rates (personal communication, Dr Ian Timeaus). The chosen set of rates were therefore derived by scaling the fertility rates 0.31, 0.28 and 0.20 by 1.25 (ie 8.6/6.9), giving 0.39, 0.35 and 0.25 respectively. The result was a set of high fertility rates, and especially for the youngest age group. This, however, merely reflects a smaller age band for the youngest age group (8 years

Table 4.1 Fertility rates for "standard" Central African population*

| Age group | Fertility rate |
|---|---|
| 15-19 | 0.185 |
| 20-24 | 0.308 |
| 25-29 | 0.304 |
| 30-34 | 0.261 |
| 35-39 | 0.201 |
| 40-44 | 0.104 |
| 45-49 | 0.016 |

* Derived by Dr Ian Timeaus, LSHTM from *Booth (1984)*, employing a relational Gompertz function with fertility distribution parameters: alpha = -0.052, beta = 0.933.

rather than 10).

| | |
|---|---|
| 17.0 | Minimum age women give birth |
| 43.0 | Maximum age women give birth |
| | |
| 0.39 | Average annual number of children born to each woman under 25 |
| 0.35 | Average annual number of children born to each woman 25-34 |
| 0.25 | Average annual number of children born to each woman 35 or over |

*Mortality*

Mortality rates can, in principal, be calculated from recorded deaths during follow-up. However, these would be likely to overestimate the underlying mortality in the absence of HIV infection. In practice, number of deaths in the first year of follow-up were too few to derive age-specific mortality rates by 5-year bands. Published mortality indices for this region were therefore employed to choose an appropriate mortality life table to give background estimates of mortality in the absence of HIV infection.

Model life tables describe feasible representations of population mortality structures which have been derived from a large number of empirical studies. "North" is often used for child mortality and "West" for adult mortality. "South" is perhaps most appropriate when considering mortality patterns in the all-age population (personal communication, Dr Ian Timeaus). Model life tables are available for varying levels of female life expectancy at birth.

For this exercise age-specific mortality rates were taken from the "South" model life table with mortality level 16 for females (*Coale and Demeny 1988*). This table is based on a life expectancy from birth of 57.5 years for females and 54.1 years for males. Estimates of the q(5) statistic for this table, ie the probability that a live born child will die before its 5th birthday, are 0.172 for males and 0.158 for females. These are consistent with estimates from Uganda (*Feachem et al 1992*, Table A-1d) and neighbouring countries (*Hill 1991*).

Estimates of the q(5) statistic from the 1980 Ugandan census for Masaka district would have provided an ideal guide for the choice of level of life table, since mortality rates at this time would have been little affected by the HIV epidemic. Unfortunately results from the 1980 census for Masaka district were stolen before they were ever published. Estimates of the

q(5) statistic from the 1969 Uganda census for Masaka district were 0.210 and 0.195 using the Brass and Sullivan "West" techniques respectively (*Report ...*). These represented combined estimates for males and females. It is likely, however, that these values would overestimate the q(5) statistic for 1980. Comparative results from the 1969 and 1980 Ugandan population censuses for the South Kampala region showed just this trend, with the Brass and Sullivan q(5) statistics falling from 0.15 and 0.14 in 1969 to 0.13 and 0.12 in 1980 (*Agyeyi et al 1988*).

The difference between male and female mortality patterns is probably small. It was not deemed important to extend the model to include mortality patterns by sex as well as age.

| | |
|---|---|
| 0.11095 | Under 1 mortality rate |
| 0.01399 | Annual 1-4 mortality rate |
| 0.00258 | Annual 5-9 mortality rate |
| 0.00161 | Annual 10-14 mortality rate |
| 0.00235 | Annual 15-19 mortality rate |
| 0.00308 | Annual 20-24 mortality rate |
| 0.00348 | Annual 25-29 mortality rate |
| 0.00374 | Annual 30-34 mortality rate |
| 0.00422 | Annual 35-39 mortality rate |
| 0.00496 | Annual 40-44 mortality rate |
| 0.00596 | Annual 45-49 mortality rate |
| 0.00836 | Annual 50-54 mortality rate |
| 0.01188 | Annual 55-59 mortality rate |
| 0.01950 | Annual 60-64 mortality rate |
| 0.03228 | Annual 65-69 mortality rate |
| 0.05663 | Annual 70-74 mortality rate |

*In- and Out-migration*

For initial modelling scenarios assuming no migration, the observed age structure of the study population could not be replicated since less than 45% of the simulated population were under 15, compared with over 53% of the study population. This also resulted in an over-representation of young adults, which is clearly important when considering the dynamics of HIV infection since highest infection rates are found in young adults.

One year follow-up of the study population provided crude estimates of trends among in- and out-migrants. These were used to guide the choice of input values for migration parameters.

The overall size of the study population changed little between baseline (round 1) (n=10246)

and round 2 (n=10262), even though there were nearly three times as many births (361) as deaths (132). This is because more people left the study population (1011) than those who joined (798). If people leaving and joining the study population truly reflected migrants (ie those migrating in and out of the study area) then the net out-migration rate could be estimated at approximately 2% per annum (ie 213/10246). Subsequent data collected from round 3, however, latterly suggested that perhaps some people were incorrectly reported as leaving the study population at round two, while others, recorded as joining the population, should in fact have originally been included in the baseline population. The result is that net out-migration rates may have been less than 2% during the first year of follow-up.

The numbers leaving and joining the study population were roughly similar in all age groups apart from the 10-24 year age band, in which there was a considerable excess leaving the study population. The mean ages among those leaving and joining were 15 and 14 respectively. Profiles of HIV seroprevalence by age were similar for the two groups, and with 19.6% and 17.3% infection among the adults joining and leaving respectively, prevalence levels were approximately double that in the overall population. Thus, since in- and out-migrants had a similar profile in all age bands apart from those between 10 and 24, in modelling scenarios presented here out-migration parameters were used to represent net out-migration from the study population. The values were adjusted so as to achieve an age structure for the simulated populations similar to that observed in the study population. This necessitated employing an annual net out-migration rate of about 2%.

The choice of the input parameter value for the proportion of out-migrants under 15 was guided by the data. By assuming a slightly higher rate of out-migration in males, on average this resulted in a slightly higher proportion of females in the general population, as observed at baseline (see 4.1.4).

| | |
|---|---|
| 10.0 | Minimum age for out-migrants |
| 25.0 | Maximum age for out-migrants |
| 0.02 | Annual rate of out-migration in the general population |
| 0.25 | Proportion of out-migrants under 15 |
| 0.75 | Proportion of out-migrants in age-range 15-34 |
| 0.975 | Female-to-male ratio of out-migrants |

## SEXUAL BEHAVIOUR

SimulAIDS characterises sexual relationships as either regular or casual partnerships, or one-off sexual contacts. The parameter values specified (especially for proportions of males engaging in casual and one-off sexual contacts) were based on rather sparse (if any) empirical data from the study population. The inputs were adjusted so as to mirror features of the study population at baseline.

Regular relationships in SimulAIDS represented marriages in the study population. As far as possible casual relationships represent partnerships outside marriage, excluding one-off sexual contacts. CSW contacts and other types of contacts with infrequent partners were classified as one-off sexual contacts. In practise these one-off sexual contacts may be with female beer sellers from the actual study population, or bar girls or CSWs from nearby towns who, for the purpose of this exercise, may be considered honorary members of the study population.

Since questions on sexual behaviour were not addressed in the general population cohort until the round 4 survey, only very limited data from the case-control study and anecdotal reports were available on short-term partnerships. The most relevant data reported that 18 (of 147) men had more than one sexual partner in the last 4 weeks, compared with none of 146 women. This and other anecdotal reports suggest that men may be having more concurrent partners than women. Of those reporting one sexual partner in the last 4 weeks (94 men and 90 women), the mean number of sexual contacts in the last week were 2.2 and 1.6 respectively. Clearly inferences from such limited data need to be made cautiously.

No direct questions were asked about condom use in the first two years in any of the main studies. Anecdotal evidence and data from focus group discussions, however, support very little use of condoms in this community in any sexual contacts. It is therefore unlikely that condom use contributed to control of HIV infection prior to 1990, and was not explicitly treated in modelling scenarios to baseline in 1990.

*Regular partnerships*

From baseline data on the proportion of young males and females married by age, it is clear that males tend to marry older. Just 4% of 18 year old men were married compared with 30% of 18 year old women, and by 20 about 10% of men were married compared with 60% of women of the same age. By 24 over 50% of men were married.

In total 1078 men were recorded as married. This represented about 22% of all males, 50% of all adult males (15+), and 75% of males aged 24 or over. Clearly in modelling scenarios the proportion of males specified to be married will depend on the specified input value for "minimum age for males in regular partnerships".

The number of married women was 1220. It was assumed that these were unbiased estimates, and represented an excess of 142 married women. Assuming no man had more than two marriages, it was estimated that about 13% (142/1078) of married men had a second wife. This is equivalent to about 10% of all 24+ men having a second wife (0.13*0.752). Thus inputs for the proportion of males with one and two regular partners were specified as 0.65 and 0.10 respectively.

Values for the input parameters for minimum ages for males and females in regular relationships were specified to be high since the model assumes all individuals are equally likely to be sampled for regular relationships. Using younger ages led to an over-representation of younger adults in marriage. The distribution of duration of regular partnerships is assumed to be uniform in SimulAIDS and was specified to have minimum and maximum durations of 5 and 45 years respectively. These inputs were only based on anecdotal reports, but results were insensitive to these particular parameter values. In practise the duration of each regular relationship is randomly sampled from this distribution.

For modelling purposes (and corresponding to the empirical data) it was specified that 75% of males aged 24 or over were married. It was not necessary to specify the proportion of married females since this is determined by the demand made by the males.

The average number of weekly sexual contacts with a regular partner was left variable and

adjusted for the different scenarios to enable the main criteria at baseline to be satisfied for each of the scenarios (see 4.1.3).

| | |
|---|---|
| 18.0 | Minimum age for females in regular partnerships |
| 24.0 | Minimum age for males in regular partnerships |
| 5.0 | Minimum duration (years) of a regular relationship |
| 45.0 | Maximum duration (years) of a regular relationship |
| 0.65 | Proportion of males with 1 regular partner |
| 0.10 | Proportion of males with 2 regular partners |

*Casual partnerships*

Very few data were available from the study population on short-term or casual partnerships, and so these input parameter values should not be thought of as truly reflecting the sexual behaviour characteristics of the study population. However these input parameter values were consistent with anecdotal reports and adjusted so that the profile of HIV prevalence by age and sex could be reasonably replicated, and the main criteria at baseline satisfied. In order to generate the high level of HIV infection observed in 15-19 females (7%), casual relationships were assumed to start early in females (from 13 years). For these modelling scenarios these were the only sexual partnerships of females under 18. Since the specified minimum age for males to have casual partnerships was several years less than the specified minimum age for regular partnerships or contacts with CSWs, in general, males also experienced their first sexual partnerships (from the age of 16) with casual partners, younger than themselves.

Men were assumed to cease all casual relationships at 50, whereas females were assumed to cease all casual relationships at a variable but much younger age (see 4.1.3).

SimulAIDS assumes the distribution of the duration of casual relationships is uniform. In this exercise minimum and maximum durations were specified to be 40 and 160 days respectively. The actual duration of all casual relationships was sampled from this distribution. For much shorter mean durations of casual partnerships, rates of partner change were rather high and less consistent with data. For much longer mean durations, rates of partner change decrease, making it difficult to replicate high HIV prevalence in 20-

24 females.

The proportion of unmarried males in casual relationships (in the specified age range) was fixed at a roughly constant level of about 60%. The average number of weekly contacts with casual partners for unmarried males varied with the cofactor scenario (see 4.1.3). For married males 30% were assumed to have casual partnerships, with an average of one sexual contact every two weeks with their casual partner. These proportions were chosen as roughly lower bound values that enabled profiles of HIV prevalence by age and sex to be replicated for all the scenarios, using plausible inputs for frequency of sexual contact. Similar profiles of HIV prevalence could be generated for smaller assumed proportions of males in casual partnerships, but employing a higher number of weekly contacts with casual partners. This, however, seemed less consistent with empirical data from the case-control study on frequency of sexual contacts.

| | |
|---|---|
| 13.0 | Minimum age for females in casual relationships |
| 16.0 | Minimum age for males in casual relationships |
| 50.0 | Maximum age for males in casual relationships |
| 40 | Minimum duration (days) of a casual relationship |
| 160 | Maximum duration (days) of a casual relationship |
| 0.3 | Proportion of married males in a casual relationship |
| 0.6 | Proportion of unmarried males in a casual relationship |
| 0.5 | Average weekly contacts with casual partners for married males |

*One-off sexual contacts*

No documented data were available from the study population on one-off sexual contacts (or their equivalent). It is believed that there is very little, if any, "professional" commercial sex work in the study population itself. However, anecdotal reports suggest that some men may have one-off sexual contacts with partners from outside the study population, and especially in nearby towns and trading centres. These sexual contacts may be with bar girls or "professional" commercial sex workers. Preliminary results from a study in a nearby trading centre, which is used as a truck stop for long distance lorry drivers, have shown much higher levels of HIV prevalence than in the study population, with about 40% of all adults found to be infected with HIV. As would be expected if travel outside the study population was accompanied by more frequent one-off sexual contacts with partners with a high

prevalence of HIV infection, higher mobility among men was found to be a risk factor for HIV infection in the study population (as discussed above).

For this exercise the inclusion of women who have one-off sexual contacts is an attempt to represent these high risk sexual contacts. A relatively small group of high risk women only engaging in regular one-off sexual contacts were considered "honorary members" of the study population. On the basis of data from the study population and the nearby trading centre, females in one-off sexual contacts were assumed to have, on average, two sexual contacts per week; the maximum number of partners recorded for females in the last week. Increasing the average number of weekly contacts reduces the pool of females who engage in one-off contacts. This consequently leads to higher prevalence levels in this group of women which serves to make them more important in the dynamics of the spread of HIV infection.

The assumed minimum and maximum ages for females to have one-off sexual contacts were 18 and 35 respectively. It was necessary to vary the minimum age men had one-off sexual contacts to replicate the profile of HIV prevalence in males (see 4.1.3). Data from the study population suggest that some men have sex outside their regular partnerships even at relatively old ages. Figure 4.6 demonstrates a rather striking peak prevalence of 10% in 70-74 year old males. For this exercise males were therefore allowed to continue one-off sexual contacts up to 69, but the average number of monthly contacts for married males was assumed to be low. Rates of sexual contact for married and unmarried males are described in 4.1.3.

The proportions of married and unmarried men specified to have one-off sexual contacts (30% and 40% respectively) actually represent the proportions of males initially ascribed this characteristic. Again these represent approximate lower bound values that allow profiles of HIV prevalence to be replicated. If men engaging in one-off sexual contacts are removed more rapidly than others, then the proportions actually engaged in one-off sexual contacts will, in general, be less than those specified. This is exactly what happens after the introduction of HIV, and so the proportions of married and unmarried men actually having one-off sexual contacts at baseline were generally less than the proportions specified (see 4.2).

| | |
|---|---|
| 18.0 | Minimum age for females to have one-off sexual contacts |
| 35.0 | Maximum age for females to have one-off sexual contacts |
| 69.0 | Maximum age for males to have one-off sexual contacts |
| 0.3 | Proportion of married males who have one-off sexual contacts |
| 0.4 | Proportion of unmarried males who have one-off sexual contacts |
| 2.0 | Average number of weekly contacts for females who have one-off sexual contacts |

## ULCERATIVE AND NON-ULCERATIVE STDS

The baseline medical survey of the whole population found that 3.4% (144/4271) of adults reported a history of genital ulcers in the previous 6 month period, 3.9% (88/2238) of females and 2.8% (56/2033) of males. The main aetiological agents for genital ulcerations in this population appear to be the herpes simplex virus type 2 (HSV-2) and *haemophilus ducreyi*, though results are only based on the sample in the cohort study. Just under 50% of episodes were reported to have lasted 2 weeks or more in both males and females. This would suggest prevalence levels for symptomatic ulcerative STDs considerably less than 3% at any one time. This is in accord with recent results published for a study in a rural area in the Mwanza region in Tanzania, on the other (southern) side of Lake Victoria (*Mosha et al 1993*).

Due to the more asymptomatic nature of non-ulcerative STDs, it is harder to estimate prevalence levels in the population. However, they are likely to be considerably higher than for ulcerative STDs (*Wagner et al 1993*).

Approximately one third (28/83) of females and one half (24/51) of males sought treatment from qualified medical personnel. Those seeking such treatment did not seem to spend less time with ulcerations. One interpretation is that the duration of an ulcer may influence treatment seeking behaviour, with medically qualified assistance sought for the more persistent ulcerations.

Estimated STD prevalence levels were used to fix the dynamics of STDs in SimulAIDS. So, for example, duration of ulcerative STD episodes and the probability of transmission of ulcerative STDs were adjusted to give a prevalence level for ulcerative STDs of roughly 1% at baseline. Further guidance on values for these input parameters came from *Over and Piot*

*(1991)* and Schulz (personal communication).

For modelling scenarios, when no restriction is placed on the minimum prevalence of STDs, they were sometimes removed from the population altogether. In reality, however, STDs would also occasionally be re-introduced into the population. This might occur, for example, when males in the study population have one-off sexual contacts with females from elsewhere. In this exercise the minimum level for both ulcerative and non-ulcerative STDs among women having one-off sexual contacts was set at 10%. In this way STDs were never totally removed from the population.

*Ulcerative STDs*

The specification of the dynamics of ulcerative STDs was set in order to achieve a prevalence of roughly 1% at baseline. Prevalence levels were assumed similar in males and females. Application of data from *Over and Piot (1991, page 26)* on durations and probabilities of transmission of different STDs initially resulted in very high STD prevalence levels at baseline (about an order of magnitude higher than those observed). Clearly prevalence of STDs depends not only on the dynamics of STDs but also on the sexual behaviour patterns in the population. However, modifying sexual behaviour patterns to reduce STD prevalence levels at baseline resulted in virtually no epidemic of HIV infection in the population. The STD dynamics finally employed therefore used shorter durations for episodes of STDs. This might, in part, also reflect some treatment of STDs.

The resulting inputs for the dynamics of STDs were used for all scenarios. The durations of ulcerative STDs in males and females were assumed to be 12 and 30 days respectively, and the probabilities of transmission of ulcerative STDs from male-to-female and female-to-male were taken as 0.30 and 0.25 respectively. The enhancing effects on HIV transmission of ulcerative STDs were defined to vary with the cofactor scenario (see 4.1.3).

| | |
|---|---|
| 12 | Duration (days) of ulcerative STD in males |
| 30 | Duration (days) of ulcerative STD in females |
| 0.30 | Probability of transmission of ulcerative STD from male to female |
| 0.25 | Probability of transmission of ulcerative STD from female to male |
| 0.1 | Among females having one-off sexual contacts, minimum proportion with ulcerative STDs |

*Non-ulcerative STDs*

The specification of the dynamics of non-ulcerative STDs was set in order to achieve prevalence levels approximately two to three times those for ulcerative STDs. The resulting inputs for the duration of episodes of non-ulcerative STDs in males and females were 20 and 50 days respectively, and the probabilities of transmission of non-ulcerative STDs from male-to-female and female-to-male were taken as 0.35 and 0.20 respectively.

There was assumed to be no enhancing effect on HIV transmission of non-ulcerative STDs in males for any of the cofactor scenarios. That is, for males with non-ulcerative STDs, neither their susceptibility to HIV infection nor their infectiousness to others was increased. For females the enhancing effect on HIV transmission of non-ulcerative STDs was defined to vary with the cofactor scenario (see 4.1.3).

| | |
|---|---|
| 20 | Duration of non-ulcerative STDs in males |
| 50 | Duration of non-ulcerative STDs in females |
| 0.35 | Probability of transmission of non-ulcerative STD from male to female |
| 0.20 | Probability of transmission of non-ulcerative STD from female to male |
| 1 | Enhancing effect on HIV transmission of non-ulcerative STDs in males |
| 0.1 | Among females having one-off sexual contacts, minimum proportion with non-ulcerative STDs |

## HIV INFECTION AND AIDS

Seroprevalence levels in the study population increased when individuals aged 75 and over were excluded from analyses. HIV prevalence among adults increased from 9.2% to 9.5% and in the general population from 4.9% to 5.0%. As has been recorded in other areas of Uganda, HIV prevalence was higher in females than males (*Berkley et al 1990*). The ratio of male-to-female HIV prevalence in adults was 0.88. This did not change with the removal of adults aged 75 and over.

The histograms in figures 4.5 and 4.6 document the profile of HIV prevalence by age and sex in the study population. In females prevalence peaked in the 20-24 year age band. In males peak prevalence was some years later in the 25-34 year age group. Very few infections

were observed in 5-14 year old females and 5-19 year old males.

For the modelling scenarios, input parameter values for sexual behaviour characteristics and HIV related parameters (for which little empirical data were available) were adjusted (within plausible ranges), so that simulations reasonably replicated these profiles of HIV prevalence by age.

The age structure of the bled population had proportionately fewer under 5s than for the total population. This resulted from a larger proportion of untested children than untested adults, and a larger proportion of these with unconfirmed HIV tests.

If the total population is assumed to have the same age-seroprevalence profile as that in the bled population, then the expected prevalence estimates for the total population can be estimated by multiplying age-specific prevalence rates by the number in each age band from the total population. Making this adjustment for age had negligible effect on prevalence rates, which remained at 5.0% and 9.5% in the general population and among adults respectively.

For children infected from mothers, the majority seem to progress to AIDS within two or three years. In the study almost 50% of seropositive children under two at baseline had died by round 2. The December 1991 report from Uganda's AIDS Control Programme (ACP) supports a short incubation period in children, with the majority of infected children progressing to AIDS before their second birthday.

The AIDS incubation period in children is, however, not important for the dynamics of infection since it is unlikely that many (if any) children infected from their mother around the time of birth would live long enough to reach adulthood.

Follow-up data from the clinical sub-cohort should eventually provide some of the best estimates from sub-Saharan Africa for the incubation period of AIDS in adults. Data from the study population does, however, support high rates of progression. A mortality rate of 11.6% among seroprevalent adults is much higher than those in industrialised countries where annual progression from asymptomatic seropositivity to symptomatic disease is in the

range of 5% to 6% (*Mulder et al 1994a*).

In modelling scenarios all individuals infected with HIV were assumed to develop AIDS after a variable incubation period. The incubation period for children, who acquire infection from their mothers, was assumed to follow a uniform distribution bounded by 0 & 2.5 years. In adults the incubation period was bounded by 1 and 7 years, with a mean of 4 years (*Robinson et al 1993a*). However, this was not predefined, since no data were initially available. The mean was forced to be this short, since this enabled data from the study population on seroprevalence by age and sex to be reasonably replicated. Although simulations employing longer mean incubation periods were generated, prevalence of HIV infection always tended to peak at older ages than those observed. This seems reasonable considering most incident infections occur in females in their late teens and early twenties and males in their mid- to late-twenties. It is difficult to find other plausible explanations for the observed prevalence profile.

Based on early anecdotal reports, the average survival with AIDS for all individuals was taken as 0.5 years. Empirical results from subsequent follow-up of the study population are consistent with this relatively short period of survival with AIDS (*Mulder et al 1994a*). The duration of the early and late phases of HIV infection, where transmission of HIV was assumed to be 10-fold higher, were 30 and 100 days respectively.

Mother-to-child HIV transmission could not be estimated with any accuracy from data collected at baseline and round 2. Data were not only limited by absolute numbers but also since many tests in children were either not carried out or were unconfirmed. Further complications arise from the presence of maternal antibodies in the children in the first 12-18 months and early deaths which cannot necessarily be attributed to HIV infection (refs). Consistent with other published reports from sub-Saharan Africa, mother-to-child transmission was assumed to occur with probability 0.3 (*Ryder et al 1991*).

HIV transmission attributable to injections and transfusions has been estimated to play only a very minor role in the spread of infection amongst adults in the study population, and probably not more than 1% (*Kengeya-Kayondo et al 1991*). Neither injections nor transfusions have been modelled in this exercise.

| | |
|---|---|
| 0.3 | Probability of HIV transmission from mother to child |
| 0 | Minimum incubation period (years) for mother-child infections |
| 2.5 | Maximum incubation period (years) for mother-child infections |
| 1 | Minimum incubation period for sexually transmitted infections |
| 7 | Maximum incubation period for sexually transmitted infections |
| 30 | Duration (days) of early phase of infection |
| 100 | Duration (days) of final phase of infection |
| 1.0 | Proportion of mother-child infections developing AIDS |
| 1.0 | Proportion of sexually transmitted infections developing AIDS |
| 0.5 | AIDS survival (years) for mother-child infections |
| 0.5 | AIDS survival (years) for sexually transmitted infections |

## 4.1.3 VARIABLE INPUT PARAMETER SPECIFICATIONS

The following input parameters did not take the same values for the different scenarios. The three values given for each input parameter represent the values taken in the no, low and high STD cofactor scenarios respectively.

### SEXUAL BEHAVIOUR

In general, higher frequencies of sexual activity needed to be specified for the lower STD cofactor scenarios. For the same sexual behaviour representations and standard probabilities of HIV transmission, more infections occur in the higher cofactor scenarios, attributable to the cofactor effect of other STDs. So compared to the high cofactor scenario, the no cofactor scenario compensates for no infections attributable to other STDs by increasing the average number of sexual contacts and the standard probability of HIV transmission. In this way the same level of HIV prevalence at baseline is achieved.

#### *Regular partnerships*

The average number of weekly contacts with a regular partner was taken as two for the no cofactor scenario and 1.5 for both the low and high cofactor scenarios.

| | | | |
|---|---|---|---|
| 2.0 | 1.5 | 1.5 | Average number of weekly sexual contacts with a regular partner |

*Casual partnerships*

Average weekly contacts with casual partners for unmarried males were again assumed higher for the no cofactor scenario. The maximum age for females in casual relationships needed to be kept low to give a peak HIV prevalence in 20-24 females. Since females were therefore assumed to cease casual contacts at 24 or 25, all incident infections after this age (apart from a few among females with one-off sexual contacts) are attributed to infections from regular partners.

| | | | |
|---|---|---|---|
| 1.5 | 1.25 | 1.0 | Average weekly contacts with casual partners for unmarried males |
| 25 | 25 | 24 | Maximum age for females in casual relationships |

*One-off sexual contacts*

For the high cofactor scenario, males were assumed, on average, to be older when they first experienced one-off sexual contacts. It was necessary to make this assumption since incident infections in males having one-off sexual contacts are more frequent for the high cofactor scenario. This results from the high proportion of contacts in the presence of STDs, which leads to proportionately more HIV infections. Thus when males are assumed to start one-off sexual contacts under 20, this results in an overestimate of HIV prevalence in 15-19 males.

For married males the average number of monthly one-off contacts was considered much lower than in unmarried males. However, males were assumed to continue one-off sexual contacts until age 69. Again for both married and unmarried males the average number of monthly one-off sexual contacts was assumed to be higher for the no cofactor scenario.

| | | | |
|---|---|---|---|
| 18 | 18 | 20 | Minimum age for males to have one-off sexual contacts |
| 0.75 | 0.25 | 0.25 | For married males, average number of monthly one-off sexual contacts |
| 1.5 | 1.0 | 1.0 | For unmarried males, average number of monthly one-off sexual contacts |

## ULCERATIVE AND NON-ULCERATIVE STDS

The enhancing effects on HIV transmission of ulcerative STDs defined the three cofactor scenarios.

*Ulcerative STDs*

The enhancing effects on HIV transmission of ulcerative STDs were defined to be 10-fold and 100-fold for the low and high cofactor scenarios respectively. For the no cofactor scenario there was no assumed enhancing effect of ulcerative STDs on HIV transmission.

| | | | |
|---|---|---|---|
| 1 | 10 | 100 | Enhancing effect on HIV transmission of ulcerative STDs in males |
| 1 | 10 | 100 | Enhancing effect on HIV transmission of ulcerative STDs in females |

*Non-ulcerative STDs*

The enhancing effects on HIV transmission of non-ulcerative STDs were defined to be 2-fold and 5-fold in females for the low and high cofactor scenarios respectively. For the no cofactor scenario there was no assumed enhancing effect of non-ulcerative STDs on HIV transmission.

| | | | |
|---|---|---|---|
| 1 | 2 | 5 | Enhancing effect on HIV transmission of non-ulcerative STDs in females |

## HIV INFECTION AND AIDS

The age distribution & HIV prevalence rates by age and sex were among the most reliable data collected at baseline in the study population. Simulations have therefore been constrained to fit well-documented baseline data on HIV prevalence levels. In order to achieve good representations HIV transmission probabilities had to be adjusted for the different scenarios.

The probability of HIV transmission was assumed to be 10-fold higher during early and late phases of infection compared with the standard phase, for both male-to-female and female-to-male transmission. This was consistent with observed high levels of viraemia during early and late phases of infection (*Clark et al 1991, Daar et al 1991*). People with AIDS were <u>not</u> assumed to modify sexual behaviour, and HIV transmission probabilities during the period with AIDS were also considered to be at the higher level.

Perhaps best estimates of the standard probability of HIV transmission can be made from results of partner studies. In the absence of cofactors, standard transmission probabilities per contact are probably of the order of magnitude of 1 in 1000 (*Robinson et al 1994*). Male-to-female transmission was assumed to be more efficient than female-to-male transmission (*Padian et al 1992*).

The values for inputs for transmission probabilities were adjusted to fit the specified baseline criteria. The ratio of male-to-female to female-to-male transmission probabilities were adjusted to give a ratio of male-to-female HIV prevalence in adults at baseline of about 0.9. Transmission probabilities are larger the smaller the cofactor scenario, and the ratio of transmission probabilities from male-to-female to female-to-male increases with the cofactor scenario. This results from proportionately more transmission of HIV from females in one-off sexual contacts to their male partners, due to high levels of other STDs during one-off sexual contacts. Thus, to reduce the number of infections in males, in order to fit observed baseline criteria, the probability of female-to-male transmission of HIV had to be reduced.

| | | | |
|---|---|---|---|
| 0.0043 | 0.004 | 0.0015 | Standard HIV transmission probability from male to female |
| 0.0022 | 0.00105 | 0.00029 | Standard HIV transmission probability from female to male |

## 4.1.4 INITIAL CONDITIONS

To generate an initial population, initial conditions needed to be specified. These are summarised below.

### INITIAL POPULATION

In the modelling exercise an initial population of 5000 was specified to have the same age structure as the study population at baseline (histogram in figure 4.1). This was similar to that recorded for the population of the entire sub-county (n=28400, approximately three times the size) in the 1991 population and housing census for Masaka district, Uganda. The age structure is typical of rural populations in sub-Saharan Africa, with over 50% under the age of 15.

At baseline 50.4% of the study population were female, giving a ratio of the number of males to females in the total and adult populations of 0.98 and 0.96. The age structure for males and females were similar, but for an slight excess of females in the 25-44 age range. From the 1991 Uganda census data for the entire sub-county, all 5-year age bands between 20 and 54 demonstrated this under-representation of adult males. This probably reflects higher rates of net out-migration among adult males than females.

For compatibility with SimulAIDS, which removes all adults 75 years and over, the same upper age band was applied to the study population. Thus people in the study population who were reportedly 75 and over were excluded from analysis. This represented just 1.5% of the total population.

By excluding those 75 and over (n=157) the proportion under 15 increases (from 53.1% to 53.9%) and the average age of the population decreases (from 20.4 to 19.5). The ratio of the number of males to females in the total and adult populations remain the same. The life expectancy from birth decreases.

| | |
|---|---|
| 0.041 | Initial proportion of the population under 1 |
| 0.163 | Initial proportion of the population 1-4 |
| 0.172 | Initial proportion of the population 5-9 |
| 0.163 | Initial proportion of the population 10-14 |
| 0.110 | Initial proportion of the population 15-19 |
| 0.073 | Initial proportion of the population 20-24 |
| 0.058 | Initial proportion of the population 25-29 |
| 0.038 | Initial proportion of the population 30-34 |
| 0.032 | Initial proportion of the population 35-39 |
| 0.031 | Initial proportion of the population 40-44 |
| 0.027 | Initial proportion of the population 45-49 |
| 0.027 | Initial proportion of the population 50-54 |
| 0.018 | Initial proportion of the population 55-59 |
| 0.022 | Initial proportion of the population 60-64 |
| 0.013 | Initial proportion of the population 65-69 |
| 0.012 | Initial proportion of the population 70-74 |

## ULCERATIVE STDs

The initial proportions of males and females specified to have ulcerative STDs were 1%.

| | |
|---|---|
| 0.01 | Initial proportion of males with ulcerative STDs |
| 0.01 | Initial proportion of females with ulcerative STDs |

## NON-ULCERATIVE STDs

An initial proportion of 1% of males was specified to have non-ulcerative STDs. It was not necessary to also introduce non-ulcerative STDs in females since many soon became infected via sexual contact with male partners.

| | |
|---|---|
| 0.01 | Initial proportion of males with non-ulcerative STDs |
| 0 | Initial proportion of females with non-ulcerative STDs |

## HIV INFECTION AND AIDS

The initial spread of HIV infection depends on the number of individuals initially assumed infected with HIV, their sexual behaviour, and the size of STD cofactor effects. When just one or two randomly selected adults were initially infected with HIV there was often no resulting epidemic for a particular input scenario. However, when an equivalent number of females in one-off sexual contacts were initially infected with HIV, then for the same input scenario an HIV epidemic was much more likely to occur. In general when the epidemic did take off then the resulting levels of HIV prevalence were similar. The time taken to reach these levels varied with the time taken for HIV to become established in the population. For the initially infected individuals, time since infection will have been sampled from the specified incubation period. Thus "initial infection" in 1980 does not necessarily represent the time these individuals became infected, which, on average, would have been a few years earlier.

For the no cofactor scenario approximately 30% of women having one-off sexual contacts were initially assumed infected with HIV, representing about 10 women. Without assuming such a high initial level the epidemic rarely took off. For scenarios with STD cofactor effects this high initial level was not necessary.

| | | | |
|---|---|---|---|
| 0.3 | 0.1 | 0.1 | Among females in one-off sexual contacts, initial proportion with HIV infection |

## 4.2 RESULTS

Results of ten year simulations to baseline (1990) are presented for the three scenarios. Results are given as arithmetic and, for skewed data, geometric means (and 95% confidence intervals) based on ten consecutive simulations for each scenario. Confidence intervals give a range of uncertainty associated with the specified input parameter sets. Results focus on demography, sexual behaviour, ulcerative and non-ulcerative STDs, and HIV infection.

### 4.2.1 DEMOGRAPHY

The simulated baseline (1990) populations have many demographic features consistent with recorded characteristics from the study population. Figure 4.1 shows the actual age-structure of the study population as a histogram. The three lines represent the age-structure derived from the means of ten runs for each of the simulated scenarios. Variability between individual runs was negligible. The different scenarios all replicate the age structure of the study population reasonably well.

Table 4.2 shows how simulated demographic characteristics from the different scenarios mirror observed results from the study population at baseline. All results have been given as arithmetic means. The mean age for all scenarios was a little higher than observed and the proportion under 15 years a little lower. These result from an under-representation of children in the age range 0-4, for all scenarios (figure 4.1).

Table 4.3 shows simulated mean values (and 95% CIs) both prior to the introduction of HIV and at baseline for demographic characteristics not available at baseline from the study population. Mortality rates in the age ranges 10-14 and 30-34 are given as geometric means since distributions were skewed, while the other estimates are given as arithmetic means. Zero values for mortality rates from individual runs were ascribed values of 0.001. Mean values "prior to HIV" were calculated from the last ten years of the initial 50 year simulation for each scenario, ie immediately prior to the introduction of HIV.

At baseline (1990) the crude birth rate had declined by about 5% for all scenarios, due to

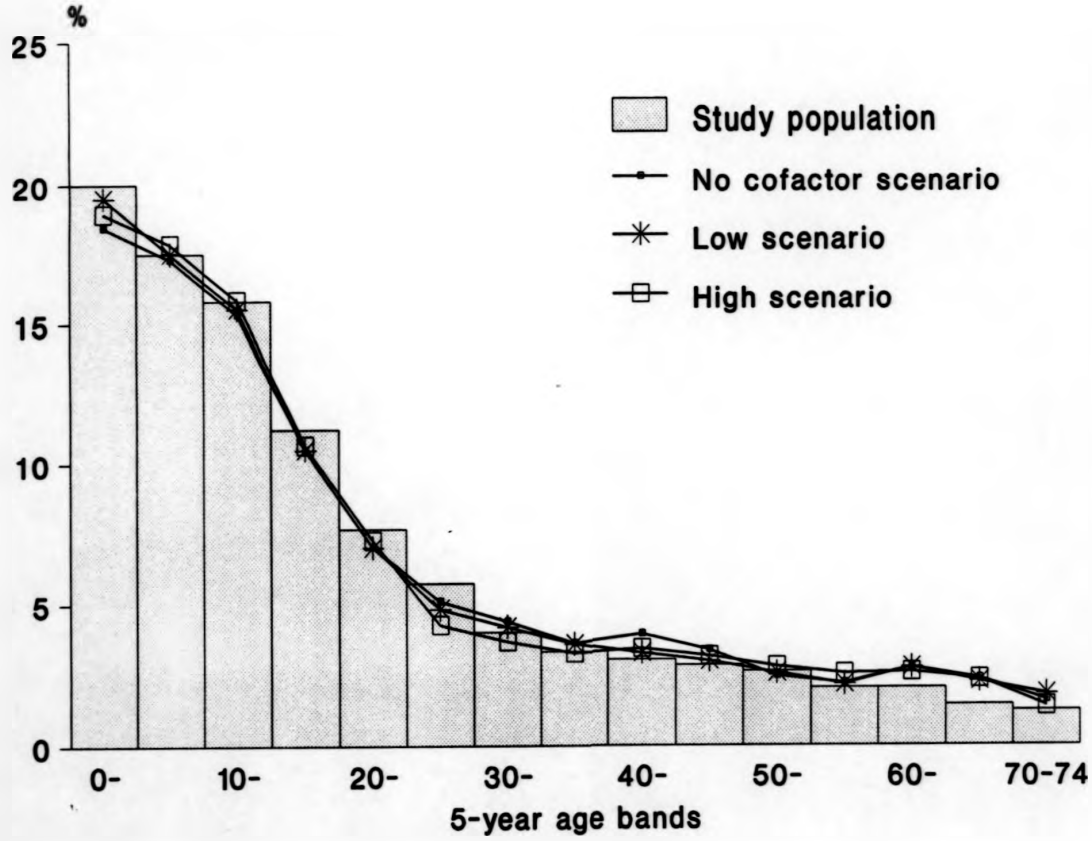



Figure 4.1 Age structure of population (mean of 10 runs for each scenario)

Table 4.2 Mean values (95% CI) for simulated demographic characteristics at baseline

| | Study population | No scenario | Low scenario | High scenario |
|---|---|---|---|---|
| Population size | 10089 | 9710 (9570-9860) | 9930 (9690-10170) | 9090 (8840-9340) |
| Mean age | 19.5 | 21.3 (21.1-21.5) | 20.8 (20.7-21.0) | 20.8 (20.5-21.1) |
| Proportion under 15 | 53.9 | 51.1 (50.5-51.7) | 52.5 (52.1-52.8) | 52.6 (51.8-53.4) |
| Male : Female ratio in general population | 0.98 | 0.99 (0.96-1.01) | 0.95 (0.92-0.98) | 0.95 (0.92-0.98) |
| Male : female ratio in adult population | 0.96 | 0.97 (0.91-1.02) | 0.89 (0.84-0.93) | 0.91 (0.86-0.96) |

**Table 4.3** Mean values (95% CI) for other simulated demographic characteristics both prior to introduction of HIV and at baseline

| | No scenario | Low scenario | High scenario |
|---|---|---|---|
| **Crude birth rate (/1000)** | | | |
| Prior to HIV | 47.1 (46.1-48.0) | 49.3 (48.2-50.3) | 47.1 (45.9-48.4) |
| At baseline | 44.2 (42.6-45.8) | 47.1 (45.2-48.9) | 44.7 (43.2-46.2) |
| **Crude mortality rate (/1000)** | | | |
| Prior to HIV | 15.9 (13.4-18.3) | 16.5 (13.4-19.6) | 16.2 (13.1-19.3) |
| At baseline | 24.9 (22.3-27.5) | 25.4 (22.8-28.1) | 27.7 (25.8-29.7) |
| **Mortality rate in 10-14 age band (/1000)** | | | |
| Prior to HIV | 1.73 (0.58-5.19) | 2.12 (0.67-6.73) | 1.58 (0.58-4.30) |
| At baseline | 2.41 (0.67-8.62) | 1.13 (0.48-2.67) | 1.69 (0.56-3.97) |
| **Mortality rate in 30-34 age band (/1000)** | | | |
| Prior to HIV | 2.77 (0.79-9.72) | 3.32 (0.49-22.67) | 2.43 (0.58-10.18) |
| At baseline | 21.76 (11.85-39.95) | 23.34 (10.87-50.12) | 34.47 (19.91-59.67) |
| **Life expectancy** | | | |
| Prior to HIV | 51.1 (47.7-54.5) | 50.3 (46.4-54.2) | 50.9 (45.9-56.0) |
| At baseline | 36.9 (34.1-39.6) | 35.9 (32.2-39.7) | 32.1 (29.1-35.1) |

higher mortality in young adult females resulting in proportionately fewer births. Crude mortality rates increased substantially. This, however, masks changes in mortality rates in the different age bands. There was no evidence of a change in the mortality rate in the 10-14 year age band, but there was a dramatic increase in the 30-34 year age band, for all scenarios. An overall higher mortality rate at baseline results in a striking decrease in life expectancy from about 50 to 35 years in the 10 years to baseline.

### 4.2.2 SEXUAL BEHAVIOUR

Table 4.4 gives the mean proportions of married and unmarried males having one-off sexual contacts both prior to the introduction of HIV (1980) and at baseline (1990), for each of the cofactor scenarios. The results show declining proportions of males in one-off sexual contacts after the introduction of HIV. On average, at any one time, between 30 and 40 women have one-off sexual contacts.

For married men the proportions having one-off sexual contacts at baseline were similar for the different scenarios. The proportion of unmarried men having one-off sexual contacts was reduced by about 25% for the high cofactor scenario, but by less than 10% for the no cofactor scenario.

In the model, proportions of males in regular and casual partnerships have been maintained while proportions in one-off sexual contacts entering the at-risk age band remain unchanged. The proportion of males in one-off sexual contacts would only be expected to be maintained if there were no differential mortality patterns between males with and without one-off sexual contacts. However, males engaging in one-off sexual contacts are more likely to become infected with HIV, and therefore have a higher mortality than those not engaging in one-off sexual contacts. This results in the observed decrease in the proportion of males in the population engaging in one-off sexual contacts. For the high cofactor scenario unmarried males engaging in one-off sexual contacts become infected with HIV more quickly and are therefore more rapidly removed from the population. Married males have fewer one-off sexual contacts and so are removed rather more slowly. The net result is that the study population is less sexually active at baseline than it would have been prior to the

Table 4.4 Means (95% CIs) for proportions (%) of married and unmarried males having one-off sexual contacts both prior to introduction of HIV (1980) and at baseline (1990)

| | STD cofactor scenario | | |
|---|---|---|---|
| | No | Low | High |
| **Married** | | | |
| 1980 | 29.66 (28.56-30.76) | 30.03 (29.07-30.99) | 31.45 (30.57-32.33) |
| 1990 | 27.78 (24.84-30.72) | 27.47 (24.71-30.23) | 27.74 (24.96-30.52) |
| **Unmarried** | | | |
| 1980 | 41.01 (38.95-43.07) | 42.00 (39.73-44.27) | 41.80 (40.04-43.56) |
| 1990 | 37.91 (35.89-39.93) | 36.37 (34.74-38.00) | 30.75 (28.01-33.49) |

introduction of HIV, even in the absence of any behaviour change.

### 4.2.3 ULCERATIVE AND NON-ULCERATIVE STDS

Table 4.5 gives geometric means for prevalence of ulcerative and non-ulcerative STDs, both prior to introduction of HIV and at baseline, for the three scenarios. Results are presented for all adult males and females, and for those having one-off sexual contacts. There are four main points to note.

(1) Prevalence levels for non-ulcerative STDs were generally 2 to 4 times higher than those for ulcerative STDs. This merely reflected that inputs for the dynamics of STDs were specified in order to give such differences.

(2) Prevalence levels of STDs were substantially higher among those engaging in one-off sexual contacts. Females engaging in one-off sexual contacts were constrained to have minimum prevalence levels for both ulcerative and non-ulcerative STDs of about 10%. Males engaging in one-off sexual contacts were therefore exposed to high levels of STDs in one-off partners.

(3) STD prevalence levels generally decreased with increasing STD cofactor scenarios. In order to replicate profiles of HIV prevalence by age and sex for each of the scenarios, sexual behaviour patterns were modified slightly for the different scenarios. Since STD dynamics were assumed fixed, STD prevalence levels, which clearly depend on sexual behaviour patterns, varied for the different scenarios.

(4) STD prevalence levels tended to decline in the general population after the introduction of HIV, even in the absence of change in sexual behaviour, or change in treatment practises for STDs. This results from the rapid removal from the population of males in one-off sexual contacts, leaving a smaller proportion engaging in one-off sexual contacts (see 4.2.2). Thus although STD prevalence levels in males and females engaging in one-off sexual contacts do not necessarily decline, there is a reduction in the proportion of males having one-off sexual contacts, resulting in a

Table 4.5 Mean values (95% CI) for prevalence (%) of ulcerative and non-ulcerative STDs both prior to introduction of HIV (1980) and at baseline (1990)

| | Ulcerative STDs STD cofactor scenario | | | Non-ulcerative STDs STD cofactor scenario | | |
|---|---|---|---|---|---|---|
| | No | Low | High | No | Low | High |
| **Female All** | | | | | | |
| 1980 | 2.27 (1.50-3.43) | 0.79 (0.49-1.26) | 0.57 (0.32-1.01) | 8.50 (7.71-9.37) | 3.60 (2.63-4.92) | 2.12 (1.30-3.46) |
| 1990 | 2.23 (1.53-3.23) | 0.54 (0.32-0.89) | 0.40 (0.17-0.97) | 8.17 (6.71-9.93) | 2.59 (1.71-3.90) | 1.60 (0.89-2.88) |
| **Female HR*** | | | | | | |
| 1980 | 9.03 (5.53-14.73) | 9.21 (6.35-13.36) | 9.30 (5.81-14.89) | 22.42 (17.38-28.93) | 14.01 (7.34-26.76) | 12.81 (6.45-25.43) |
| 1990 | 9.87 (5.70-17.09) | 8.85 (5.42-14.44) | 8.09 (5.05-12.94) | 24.29 (18.83-31.34) | 12.68 (7.18-22.39) | 12.55 (6.08-25.93) |
| **Male All** | | | | | | |
| 1980 | 2.39 (1.35-4.21) | 1.11 (0.68-1.80) | 0.54 (0.15-1.94) | 6.36 (5.23-7.74) | 2.77 (2.03-3.79) | 1.43 (0.88-2.34) |
| 1990 | 2.18 (1.26-3.78) | 0.54 (0.13-2.32) | 0.40 (0.11-1.47) | 5.37 (4.24-6.79) | 2.18 (1.39-3.42) | 1.23 (0.70-2.18) |
| **Male HR*** | | | | | | |
| 1980 | 7.03 (4.14-11.93) | 3.46 (1.96-6.10) | 1.97 (0.54-7.20) | 15.64 (13.11-18.66) | 6.36 (4.74-8.53) | 3.82 (1.89-7.73) |
| 1990 | 6.69 (3.71-12.04) | 1.88 (0.42-8.33) | 1.63 (0.50-5.29) | 14.01 (10.86-18.08) | 6.49 (4.22-9.99) | 3.82 (1.61-9.05) |

* HR (high risk), in this context, represents males and females engaged in one-off sexual contacts.

reduction in STD prevalence levels in the general population.

### 4.2.4 HIV INFECTION AND AIDS

Results of the simulated spread of HIV infection over ten years from five runs for the low cofactor scenario are shown in figure 4.2.The repetitions for the same scenario demonstrate the random nature associated with monte-carlo simulations.

Figure 4.3 shows the mean simulated spread of HIV over 10 years for the three scenarios. The spread of HIV infection was much more rapid for the high cofactor scenario. This results from more rapid initial spread of infection among males and females engaged in one-off sexual contacts (figure 4.4). After 1990 HIV prevalence levels increased for the no and low cofactor scenarios but levelled off for the high cofactor scenario (see chapter 7). This is explained by HIV prevalence reaching saturation levels earlier in the higher risk groups for the high cofactor scenario (figure 4.4). In this regard the high cofactor scenario best replicates subsequent results from initial follow-up of the study population, where there has been no increase in HIV prevalence since 1990.

Figure 4.5 illustrates the changing ratio of male-to-female HIV prevalence during the first ten years of the epidemic. Clearly there is a strong dependency on the phase of the epidemic with many more infections in males than females during the first few years of the epidemic. These results did not depend on the cofactor scenario.

Figures 4.6 and 4.7 show simulated results at baseline (1990) for replicated profiles of HIV prevalence in females and males respectively, from five simulations for the low cofactor scenario. Data from the study population are presented as a bar chart. Variability between the simulations increases with age, as numbers decrease, but in general simulations reproduce the HIV prevalence profiles reasonably well.

Figures 4.8 and 4.9 also show HIV prevalence by 5-year age band in females and males respectively. The three lines, however, represent mean results from ten simulations for each of the scenarios. The scenarios all replicated HIV prevalence profiles reasonably well,


Figure 4.2 HIV prevalence in adults (5 runs for low cofactor scenario)


1990

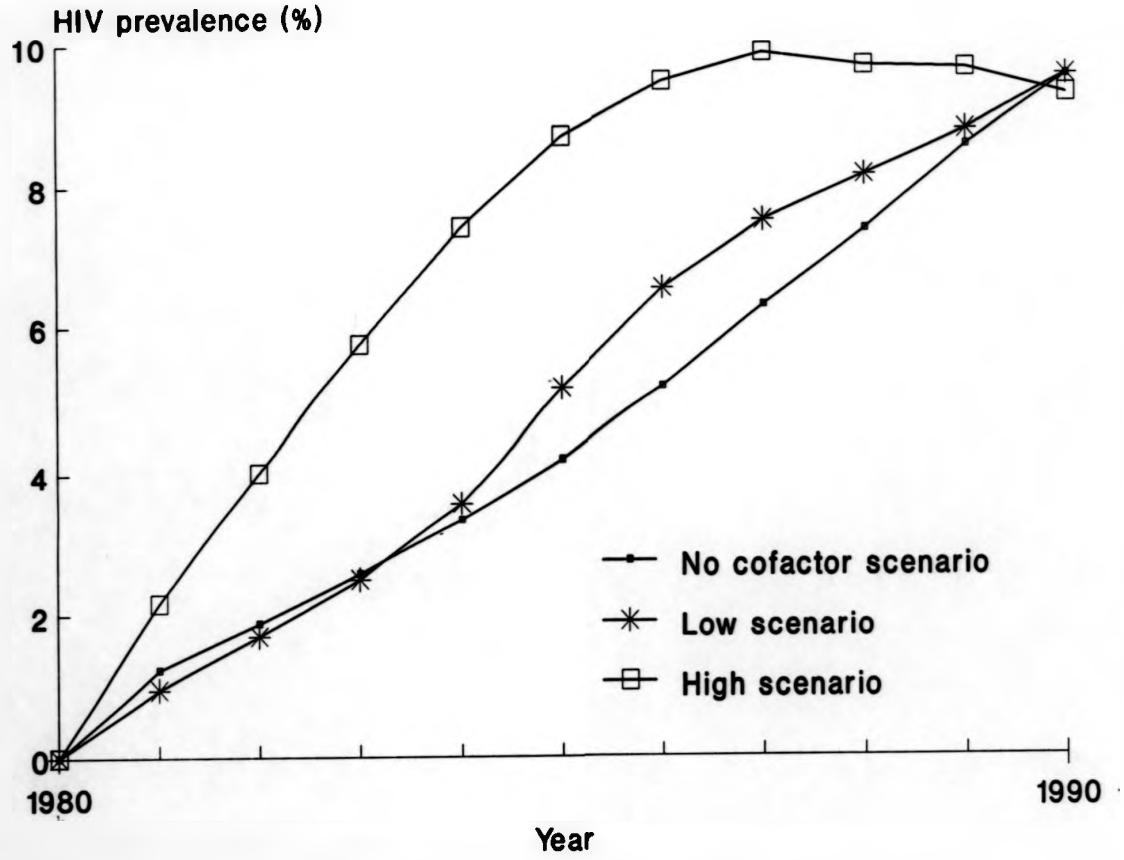



Figure 4.3 HIV prevalence in adults (Mean of 10 runs for each scenario)

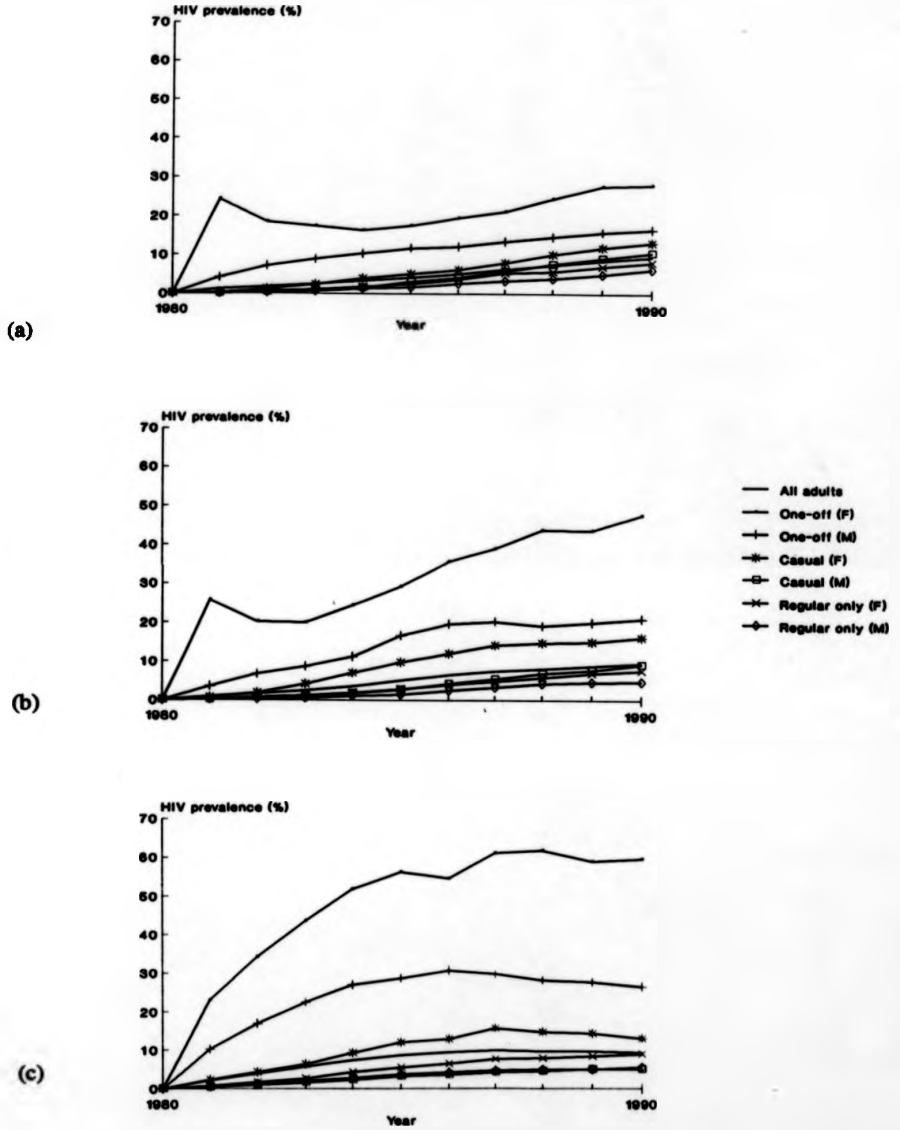



Figure 4.4 HIV prevalence in different risk groups for the (a) no, (b) low, and (c) high cofactor scenarios (Mean of 10 runs for each scenario)

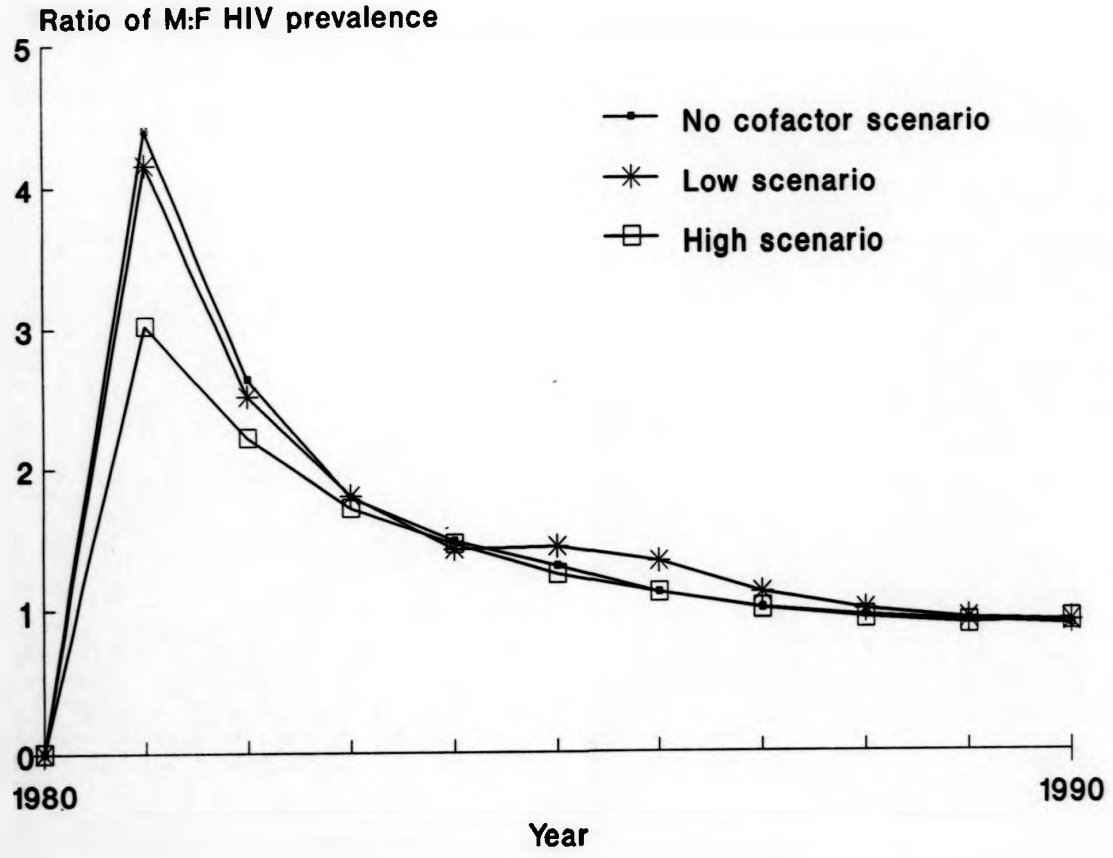



Figure 4.5 Ratio of male to female HIV prevalence in adults (Mean of 10 runs for each scenario)

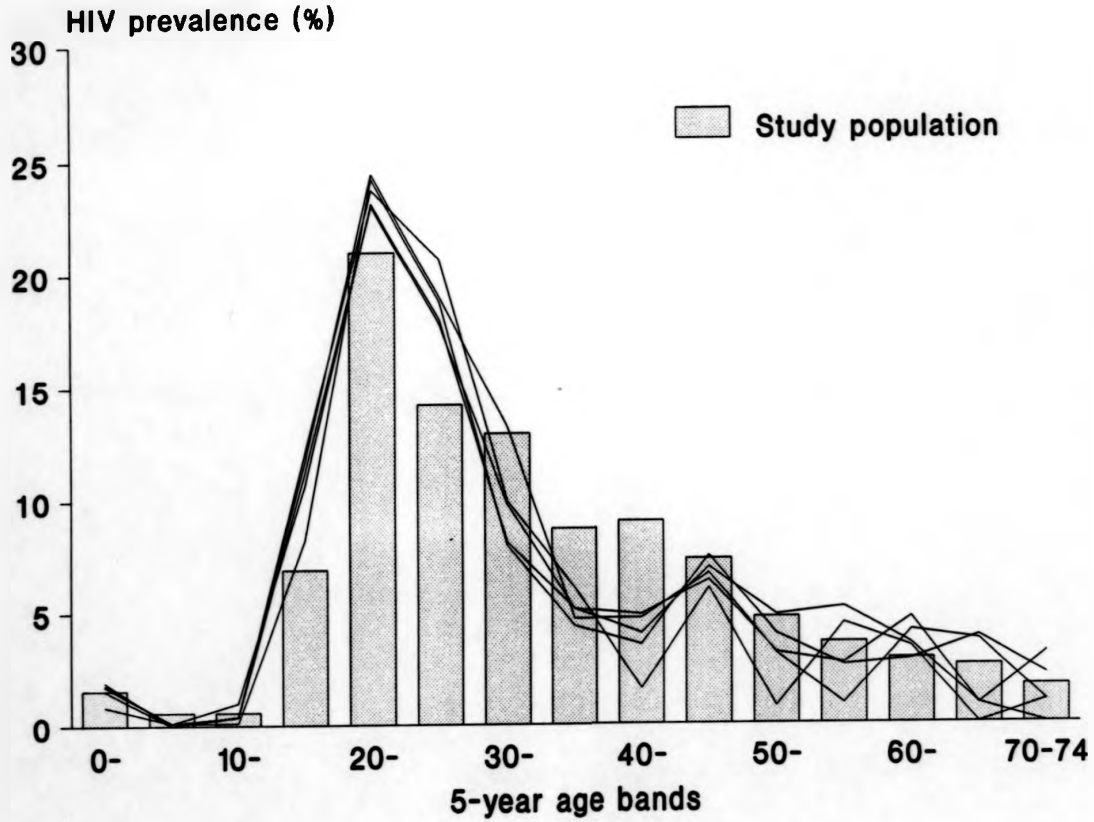



Figure 4.6 HIV prevalence in females (5 runs for low cofactor scenario)

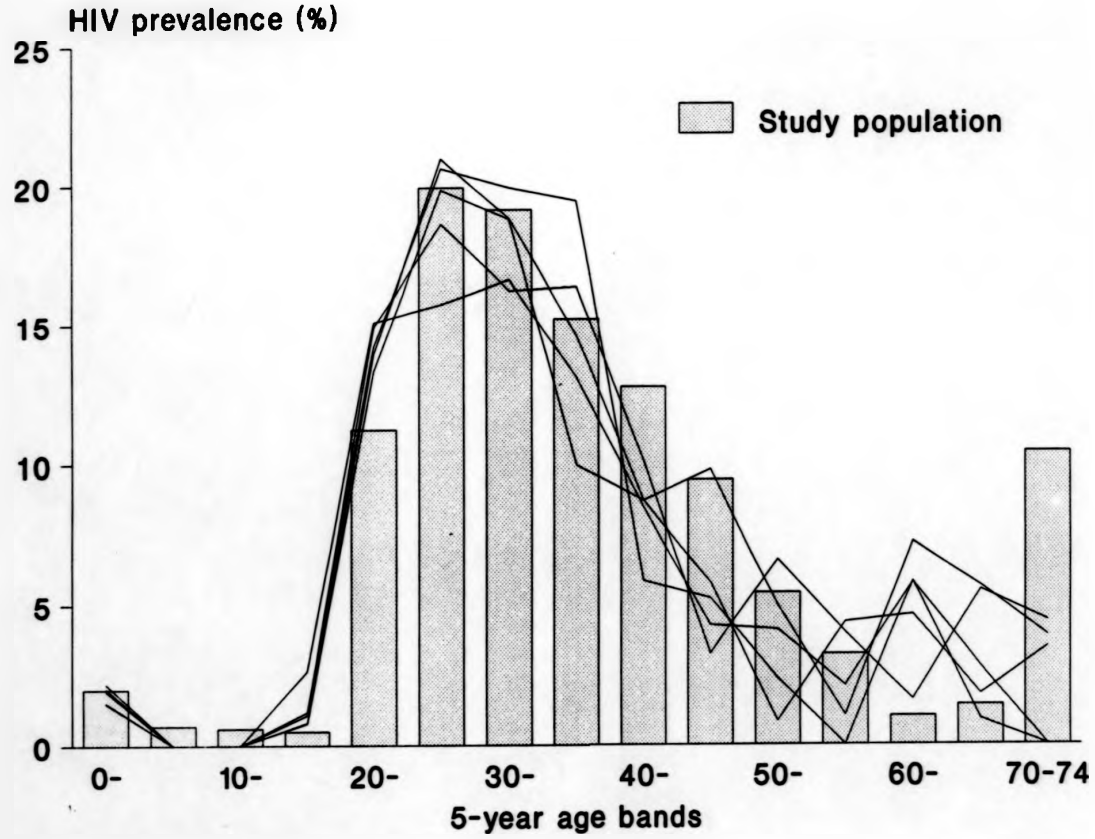



Figure 4.7 HIV prevalence in males (5 runs for low cofactor scenario)

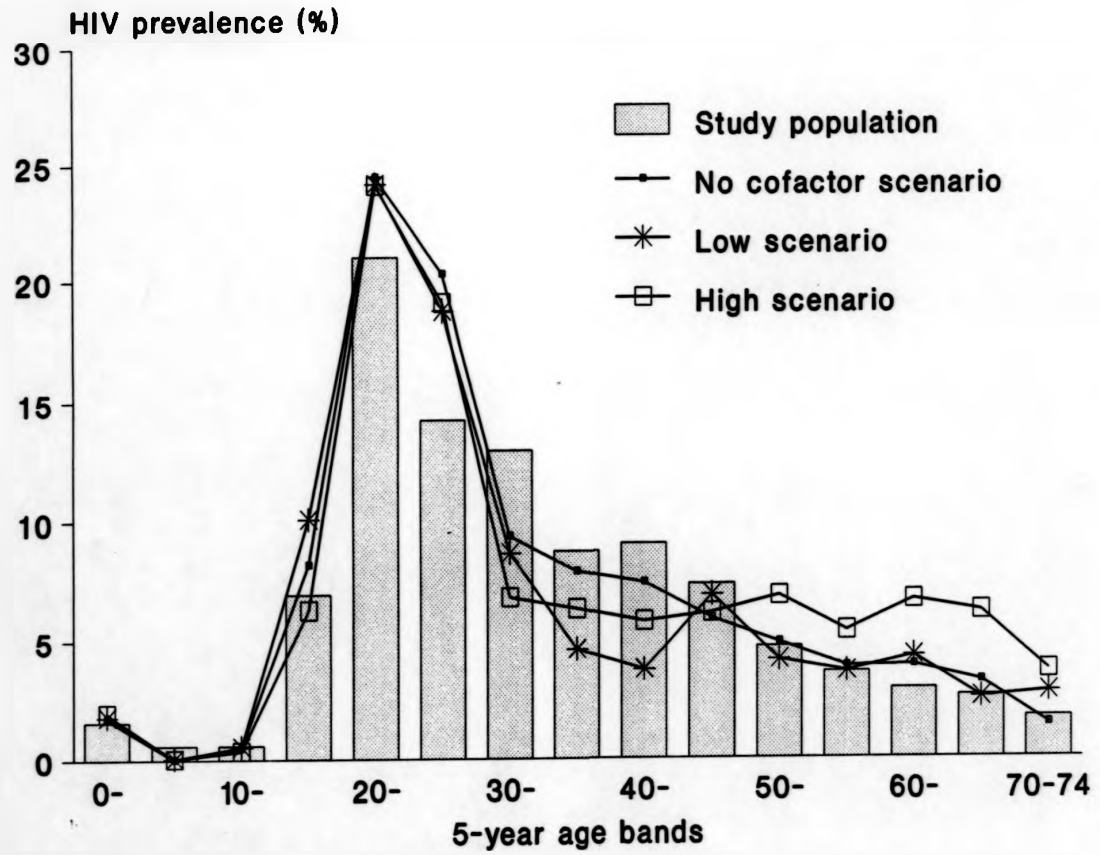



Figure 4.8 HIV prevalence in females (Mean of 10 runs for each scenario)

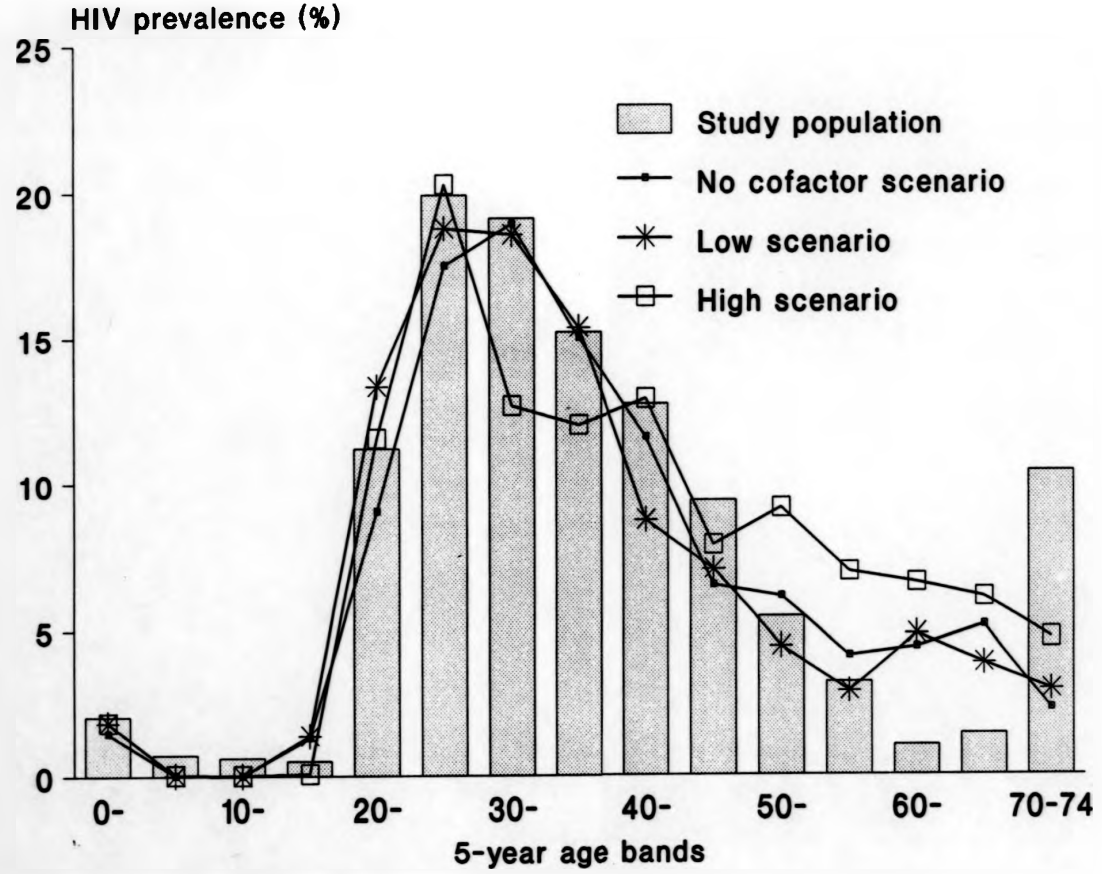



Figure 4.9 HIV prevalence in males (Mean of 10 runs for each scenario)

although simulations tended to overestimate prevalence in the older age bands. Allowing males to continue one-off sexual contacts until age 69 resulted in overestimates of numbers of HIV infections in older age groups, and especially for the high cofactor scenario. However, by allowing men to continue one-off sexual contacts until 69, individual simulations do occasionally replicate the characteristic peak prevalence observed in 70-74 males. Although this only represents a small absolute number of infections, this would not be possible if men were considered to cease all one-off sexual contacts at much younger ages.

## 4.3 DISCUSSION

The age structure of the study population and profiles of HIV prevalence by age and sex can be reasonably replicated for each of the STD cofactor scenarios. The representations do not necessarily give the best representations for each of the scenarios of the dynamics of HIV infection in this population. The true picture is never likely to be attainable, especially since details on sexual behaviour mixing patterns will almost certainly remain elusive.

For each scenario the study population has been described by one representation of the demography, sexual behaviour, ulcerative and non-ulcerative STDs, and HIV parameters. Some inputs for sexual behaviour representations and HIV parameters vary slightly between the different scenarios, whereas those for demography and STDs remain constant. In this exercise sexual behaviour characteristics were chosen to be similar so that the different scenarios mainly reflected differences in the STD cofactor effect. It may be that other reasonable representations of the study population could be achieved; eg for the high cofactor scenario, by employing higher probabilities of HIV transmission per sexual contact and reducing the proportion of males engaging in one-off sexual contacts.

The following discussion focuses firstly on the results and then on the sensitivity of results to certain model and parameter assumptions.

### 4.3.1 DISCUSSION OF RESULTS

#### DEMOGRAPHY

All three scenarios mirrored demographic characteristics of the study population reasonably well, although there was a slight under-representation of children in the age range 0-4. This resulted in a slight under-representation of the proportion under 15, and an over-estimation of the mean age (table 4.2).

For the high cofactor scenario, the more rapid spread of HIV infection resulted in a higher crude mortality rate at baseline (1990), and a shorter life expectancy. The dramatic increase

in mortality rates following the introduction of HIV infection mirrors recent findings in the study population (*Mulder et al 1994a*).

The crude birth rate was about three times the crude mortality rate prior to the introduction of HIV infection. The difference between the crude birth and mortality rates gives an estimate of the rate of natural increase of the population (excluding migration patterns). Prior to introduction of HIV, this was a little over 3%. By baseline the crude fertility rate was less than twice the crude mortality rate and the rate of natural increase was reduced to about 2%. Since net out-migration was assumed to be 2%, the net population growth rate in this rural population was reduced from approximately 1% to 0% by 1990.

## SEXUAL BEHAVIOUR

Results show a decline in the proportion of males engaging in one-off sexual contacts. This is particularly pronounced for unmarried males and for the high cofactor scenario, and results from the relatively rapid removal from the population of men engaged in one-off sexual contacts.

SimulAIDS characterises sexual relationships of females as either having only one-off sexual contacts, or having a combination of one regular partner and/or one casual partner. By specifying that females can have casual partners from the age of 13 up to 24 (for the high cofactor scenario) or 25, and can begin regular relationships at 18, the model assumes that, for females not engaged in one-off sexual contacts, sexual activity generally begins in casual relationships. At the age of 18 females can then have casual and/or regular partnerships, before being constrained to have only regular relationships after the age of 24 or 25. Though this can not be expected to truly reflect reality, this representation does enable the main features observed at baseline in the study population to be mirrored. This particularly relates to the HIV prevalence profile in females, and especially high rates of HIV infection in 20-24 year old females. For this representation most incident infections in 15-24 females would have resulted from casual relationships, whereas almost all incident infections in older ages are attributed to regular partnerships.

Males have been specified to start casual partnerships from 16, one-off sexual contacts from 18 (or 20 for the high cofactor scenario), and regular partnerships from 24. Men have been assumed to cease all casual partnerships by 50 and one-off sexual contacts by 69. Whereas young females have casual partnerships with older men, young males are assumed to have casual partnerships with younger females and are therefore less exposed to the risk of HIV infection. Males then begin one-off sexual contacts from the age of 18 (or 20). For this representation few men become infected with HIV in the age range 15-19, replicating results from the study population. Up until the age of 24 men are unmarried and compared with married males are assumed to have higher frequencies of sexual contacts with their casual and one-off partners. Until they form regular partnerships they are therefore likely to be regularly exposed to HIV infection from their various partners. This results in high incidence of HIV infection in 20-29 males as observed in the study population. The majority of men over 24 are assumed to form regular relationships, and then reduce their frequency of sexual contacts with casual and one-off partners. Thus although marriage serves to protect men from HIV infection, they do still acquire infections from casual partners up to the age of 50, and from one-off sexual contacts up to age 69.

## ULCERATIVE AND NON-ULCERATIVE STDS

For the no cofactor scenario, STD prevalence levels do not influence the spread of HIV infection since STDs are not assumed to enhance the transmission of HIV. For the low and high cofactor scenarios, STD prevalence levels are critical to the spread of HIV infection. For these scenarios prevalence levels for ulcerative and non-ulcerative STDs of about 0.5%, and 1% to 3% respectively at baseline in the general population were consistent with the size of HIV epidemics observed in the study population.

## HIV INFECTION AND AIDS

The simulated population has lower levels of sexual mixing and lower STD prevalence levels at baseline in 1990 as a direct result of the removal of the most sexually active males, without immediate replacement. The extent of this is dependent on the cofactor scenario.

For high cofactor effects infection and removal of males in one-off sexual contacts is more rapid.

The ratio of male to female HIV prevalence is strongly related to the phase of the epidemic. It generally peaks in the early epidemic phase during the first few years of simulations. At this time a comparatively small pool of females with one-off sexual contacts spreads the virus to their numerous male partners, who subsequently begin to infect their casual and regular partners.

To achieve an average male-to-female HIV prevalence ratio slightly less than unity at baseline in 1990, male-to-female and female-to-male HIV transmission probabilities were adjusted. Scenarios with higher STD cofactor effects have a higher ratio of male-to-female to female-to-male HIV transmission probabilities. This ratio increases from approximately 2 to 4 to 6 for the no, low and high cofactor scenarios respectively. Since a higher proportion of female-to-male infections, compared with male-to-female infections, arise from one-off sexual contacts, proportionately more female-to-male infections take place in the presence of STDs. Thus as STD cofactor effects increase for fixed HIV transmission probabilities, the ratio of male to female HIV prevalence in adults also increases. In order to maintain this ratio at about 0.9, female-to-male HIV transmission probabilities need to be reduced. This results in higher ratios of male-to-female to female-to-male HIV transmission probabilities for higher cofactor scenarios.

Assumed standard per contact probabilities of HIV transmission for the no cofactor scenario are least consistent with empirical data. At 0.4% and 0.2% for male-to-female and female-to-male transmission respectively, per contact probabilities are higher than have been estimated from partner studies (at roughly 0.1%) (*Robinson et al 1994*). That the no cofactor scenario assumes that the probability of transmission of HIV from an infected regular partner is, on average, the same as the probability of transmission from an infected one-off partner is also inconsistent with published reports, which support higher transmission rates during one-off contacts (*Mastro et al 1994, Robinson et al 1994*).

Assumed standard transmission probabilities for the high cofactor scenario were 0.15% and 0.03% for male-to-female and female-to-male transmission respectively. These are consistent

with initial results from a study of HIV discordant partners in the Ugandan study population. During one year follow-up, reported infection rates in female and male partners were 16% and 5% respectively (*Kengeya-Kayondo et al 1993*). These transmission probabilities are also consistent with, on average, much higher levels of female-to-male HIV transmission in one-off sexual contacts than regular partnerships, due to much higher prevalence levels of STDs in one-off partnerships.

### 4.3.2 SENSITIVITY OF RESULTS TO MODEL ASSUMPTIONS

The effects of model assumptions (as distinct from parameter assumptions) are very difficult to assess. This theoretically and often practically requires reformulation of the model, which is usually prohibitively time-consuming. In this section, some of the more important assumptions underlying the model are discussed in relation to the limitations they may introduce.

#### DEMOGRAPHY

SimulAIDS removes all adults 75 and over. This should not, however, have much influence on the dynamics of HIV transmission since this represented just 1.5% of the study population and three HIV infections.

Mortality rates in the model were assumed identical for males and females. Although rates are likely to vary between males and females, as illustrated in model life tables, the differences are small, and are unlikely to be important in this exercise.

Migration parameters seem adequate to facilitate replication of the age structure of the study population. Specification of fertility rates, however, would benefit from finer groupings. The model chooses out-migrants randomly from the study population and thus does not allow for out-migrants to have a higher prevalence of HIV infection than in the general population. Therefore, if assumed migration patterns are reasonable and they do not change dramatically with time, model representations may overestimate future HIV prevalence and

incidence in the study population.

## SEXUAL BEHAVIOUR

In the study population a small proportion of men (about 1%) do have more than two regular partners. These were mainly Muslim men. That SimulAIDS assumes men have no more than two regular partners is unlikely to have a large influence on the spread of HIV infection in the population.

The model assumes that the proportions of married and unmarried males in casual relationships remain constant. As with one-off sexual contacts, however, it may be that those with more casual partners are actually likely to be at increased risk of HIV infection and so may also be more rapidly removed from the population, resulting in a decline in the proportion of males in casual relationships. This might serve to further reduce STD prevalence levels and HIV incidence, even in the absence of behavioural change, though any further reduction is likely to be small.

The model assumes that females who have one-off sexual contacts have no other sexual partnerships. In practise, however, some of these women may also have casual and/or regular partnerships. Their partners will be at high risk of becoming infected with HIV. If these men are also highly sexually mobile, they may contribute substantially to the spread of HIV infection in the population. If they have few partners then they will contribute little to the spread of HIV infection. Assuming that some women do have longer term partnerships as well as one-off sexual contacts, and their partners also have other partners, then in the model they may be considered to be represented by unmarried males having one-off sexual contacts. They will become infected relatively rapidly, though perhaps not as rapidly as regular partners of females with one-off contacts, and possibly contribute substantially to the spread of HIV in the population.

Females having one-off sexual contacts cease all sexual activity at age 35. It is likely that the majority, however, will die from HIV-related causes even before age 35.

## ULCERATIVE AND NON-ULCERATIVE STDS

The representation of all STDs that enhance transmission of HIV as just two generic STDs (ulcerative and non-ulcerative) is clearly an oversimplification of reality. However, in the absence of a better understanding of the role of the various STDs in enhancing transmission of HIV, this does not seem unreasonable.

The simplest representation of the dynamics of STDs was chosen for this exercise since data on STDs were limited. With an increased understanding of the role of various STDs and their dynamics in the population, the representations of STDs in SimulAIDS can be further refined.

## HIV INFECTION AND AIDS

The model employs a uniform distribution to represent the AIDS incubation period. Though this is unlikely to reflect reality it is probably adequate for this exercise, especially since the assumed incubation period is relatively short. *Blythe et al (1988a)* investigated the effect of different forms of the distribution of incubation period on the spread of HIV. Since results based on uniform, exponential, gamma and weibull distributions were not dissimilar, they concluded that for a fixed mean duration, almost any distribution of approximately the right shape would suffice.

The model assumes that people with AIDS do not modify their sexual behaviour. It also assumes that during this period the probability of HIV transmission is represented by the probability assumed during the final phase of the incubation period, which in this exercise was taken to be 10-fold higher than standard transmission rates. In reality people with AIDS may modify sexual behaviour. The final phase of the incubation period and the period with AIDS have been kept short to adjust for continued sexual activity at high rates of transmission among people with AIDS.

### 4.3.3 SENSITIVITY OF RESULTS TO PARAMETER ASSUMPTIONS

The sensitivity of model results are usually investigated in one of several ways. One way is to consider the effect on particular results of adjusting parameter inputs separately. However, in general, with such a large number of inputs this is very cumbersome, and often prohibitively time consuming. Another approach is to consider the sensitivity of results to different combinations of parameter inputs. This approach has been employed here.

In order to achieve good representations of characteristics of the study population for the different scenarios, combinations of parameter values were carefully chosen. Rather than fitting models to just one or two reference values, representations were fit to a range of documented baseline characteristics. This narrowed the choice of parameter input values. For the purpose of this exercise it is not individual parameter values that are important (since most are unknown) but combinations of plausible parameter inputs that give rise to reasonable representations of the characteristics of the study population. This has been evaluated for three scenarios defined by their different assumed STD cofactor effects. They all mirror certain documented characteristics of the study population at baseline reasonably well. It is important to assess how sensitive other results are to the particular scenarios, and how consistent they are with what is known from the study population. The following discussion reflects on certain parameter inputs.

#### DEMOGRAPHY

Observed underlying mortality rates in the study population from the initial two years of follow-up were lower than expected, and lower than assumed in this exercise (*Mulder et al 1994a*). If these underlying mortality levels from the study population are accurate, it would suggest that the choice of model life table may not have been the most appropriate. Although assuming lower mortality rates would be less consistent with other published sources, fertility rates would not need to be so high. This may facilitate a better representation of the age structure of the study population, and particularly in the 0-4 year age band. The effect on HIV incidence and prevalence would, however, be negligible.

By changing the youngest age band for fertility rates to 15-24 and decreasing the fertility rate in this age band, the TFR can be maintained. This again has little relevance for the dynamics of HIV infection.

## SEXUAL BEHAVIOUR

Specification of age bounds for relationships have proved important for replicating the profile of HIV prevalence at baseline in both males and females. The inputs were guided by limited data, and adjusted to fit observed age- and sex-specific HIV prevalence levels. Frequency of sexual contacts in casual relationships and with one-off partners have been specified separately for married and unmarried males.

Results were sensitive to the age at which males were assumed to begin regular partnerships. This is important since frequency of sexual contacts with casual and one-off partners changes when men become married. For example, by choosing 24 years rather than 22 years for the age men can begin regular relationships, this allows for higher frequency of sexual activity during these two years, facilitating more transmission of HIV infection in young adults. Starting regular relationships slightly older perhaps compensates (in terms of HIV transmission dynamics) for the lack of facility for young males to have more than one casual partner. The specified age females could begin regular relationships was not critical for the dynamics of infection since the frequency of sexual contacts in casual partnerships depends on the marital status of the male.

The specific age that males and females begin casual partnerships was not found to be critical. Similarly for the age at which males had to cease casual partnerships. However, the specified age females were assumed to cease all casual partnerships was important. This was adjusted so as to achieve a peak prevalence in young adult females in the age range 20-24. Increasing the maximum age to 26 or 27 has a marked influence on the prevalence profile with peak prevalence shifting to the 25-29 age band.

The age that males begin one-off sexual contacts is also important. This exposes young men to contacts with high prevalence females, and subsequently is important in generating HIV

prevalence levels in 15-19 and 20-24 males. The age at which males cease one-off sexual contacts was not critical to the dynamics of infection. However, in this exercise sexual contacts were maintained to an old age since there was evidence from the study population that older men were exposed to HIV infected partners.

Input parameters specifying the proportion of males in casual partnerships and one-off sexual contacts were fixed for all scenarios. They were chosen as roughly minimum proportions needed for all scenarios to generate the observed HIV epidemic, given assumed levels of standard HIV transmission probabilities and frequency of sexual contacts.

Inputs for frequency of sexual contacts with different partners were adjusted within plausible ranges to assist in replicating profiles of HIV prevalence by age and sex.

## ULCERATIVE AND NON-ULCERATIVE STDS

It was assumed that the enhancing effect of HIV transmission in the presence of any combination of STDs in either partner always took the maximum value of the individual cofactor effects. By specifying that the enhancing effect of HIV transmission was the multiplicative effect of the separate cofactor effects, this had little influence on the spread of HIV infection (and other results) since such events are rare. If, for example, the prevalence of ulcerative STDs is about 1% in both males and females in the general population, then the prevalence of ulcerative STDs in both partners during a sexual contact would be considerably less, even with clustering of STDs.

The durations of STD episodes were assumed to be relatively short (*Over and Piot 1991*). For the low and high cofactor scenarios prevalence levels of STDs at baseline were kept relatively low so that estimates of proportions of HIV infections attributable to other STDs would be on the conservative side.

## HIV INFECTION AND AIDS

Values for the AIDS incubation period were chosen to facilitate replication of the profiles of HIV prevalence by age and sex. This modelling exercise has employed a much shorter AIDS incubation period than previous modelling exercises. Initial follow-up data now supports use of a mean incubation period of about four years.

Per contact probabilities of transmission of HIV were taken to be of the order of 0.001. They were adjusted for the different scenarios to give prevalence levels of about 9% at baseline and a ratio of male-to-female HIV prevalence in adults of about 0.9.

CHAPTER 5

# ASSESSING ASSOCIATIONS BETWEEN HIV AND OTHER STDs

# 5. ASSESSING ASSOCIATIONS BETWEEN HIV AND OTHER STDs

The objective was to investigate the magnitude of associations between HIV and other STDs that might be recorded in an observational epidemiological study for scenarios assuming different STD cofactor effects.

In sub-Saharan Africa reported odds ratios (ORs) for associations between HIV and other STDs typically range between about 2 and 5 for ulcerative STDs, and are usually not more than 2 or 3 for non-ulcerative STDs (*Wasserheit 1992, Mertens et al 1990*). This, however, needs qualification, since the most rigorous cohort study to date found adjusted ORs of between 3 and 5 for associations between HIV and non-ulcerative STDs (*Laga et al 1993*). The variation in observed associations is likely to depend on a number of factors. The most important probably include sampling error, differences in study samples and methods, statistical analyses employed (and in particular whether adjustment is made for sexual behaviour), and type of study design, ie cross-sectional or cohort.

Other factors are also important in understanding the relationship between observed HIV/STD associations and STD cofactor effects per sexual contact. The single most important factor is likely to be the duration over which a history of STDs is recorded (see 5.3.6, *Hayes et al 1994*). Other factors include the confounding effect of STDs on one another, and misclassification of (especially non-ulcerative) STDs.

Heterogeneity in sexual behaviour in a study sample is likely to confound associations, since sexual behaviour is associated with other STDs and is also a risk factor for HIV infection (see chapter 2). But by how much? And what effect do other factors have on the magnitude and direction of associations? How large might we expect observed ORs to be in the absence of any true enhancing effects of STDs on HIV transmission? And what enhancing effects of STDs on HIV transmission per sexual contact are consistent with observed ORs?

## 5.1 METHODS

By setting up different scenarios for a range of STD cofactor effects, ORs sampled from simulated populations can be compared with those found from empirical studies. In this way a range of cofactor effects can be explored for their consistency with observed results for ORs. This exercise should not only aid our understanding of factors influencing observed ORs, but it should also assist in the choice of appropriate models for prediction and intervention purposes.

Four specific questions have been addressed. Firstly, how large are associations likely to be in the absence of any true STD cofactor effects? Secondly, how large are associations likely to be in the presence of plausible cofactor effects? Thirdly, if confounding variables are adjusted for in the analysis, how much of the associations are explained? And finally, which factors are likely to be most important in explaining observed variations in ORs?

To address these issues, the following methods were used. For each of the three STD cofactor scenarios, simulations were run for one year from each of the ten recorded baseline (1990) populations. A set of characteristics for every individual in the population was recorded in one data file at baseline and another a year later. These files were then combined. This feature to record characteristics of every individual in the simulated population at the end of each complete year was one of the extensions made to SimulAIDS for this exercise. One year was the shortest period over which a history of STDs could be recorded.

The main recorded characteristics used for analyses included: age at one year follow-up, sex, HIV status in 1990 and 1991, and a 1-year history of ulcerative and non-ulcerative STDs. Since one year was the shortest period over which a history of STDs could be recorded, the influence of duration of history was examined via an example based on a simple probability model (see 5.3.6). Sexual behaviour characteristics were also employed in analyses. These recorded whether men and women had regular and/or casual and/or one-off sexual contacts.

The WHO software EPI-INFO was used to derive unadjusted ORs for associations between HIV and other STDs. The epidemiological software EGRET was used for logistic regression

analyses to adjust for the confounding effects of sexual behaviour and of other STDs.

### 5.1.1 ESTIMATING UNADJUSTED ODDS RATIOS

Univariate analyses were initially carried out to assess unadjusted STD associations with HIV infections. In total 16 sets of analyses for each of the three scenarios have been carried out, representing all combinations of four 2-way characteristics. That is, associations with ulcerative and non-ulcerative STDs, for cross-sectional and cohort study designs, and by sex and behaviour group (all or high risk, as defined below). For each of the 48 sets of analyses ten OR estimates were obtained from the ten different runs, and using a logarithmic transformation, geometric means and 95% CIs were calculated.

The dependency of odds ratios on different assumed STD cofactor effects was of particular interest. ORs are presented for a 1-year history of ulcerative and non-ulcerative STDs, in 15-49 females and 20-49 males. The sensitivity of results to the choice of age band is discussed in 5.3.

To investigate the extent to which heterogeneity of sexual behaviour in the general adult population confounds HIV/STD associations, and to replicate empirical studies, odds ratio estimates were also assessed in high risk (HR) males and females. Males engaging in one-off sexual contacts, and females with current casual partners were chosen as high risk groups. Females engaging in one-off sexual contacts were too few to generate meaningful results. Associations in low risk groups were also difficult to evaluate. Males engaging in only regular partnerships had very low levels of history of other STDs and a low HIV incidence, and associations between HIV and other STDs for females engaging in only regular partnerships were strongly confounded by the sexual behaviour of regular male partners.

A cross-sectional survey was simulated by taking all individuals in the population in 1991, and comparing STD histories between those infected with HIV (prevalent cases) and those uninfected. A one-year cohort study was generated by sampling only individuals uninfected with HIV in 1990, and comparing STD histories in the one-year follow-up period between those who became infected with HIV by 1991 (incident cases) and those who remained

uninfected.

To compare associations between: (1) All and high risk populations; (2) Cross-sectional and cohort study designs; and (3) History of ulcerative and non-ulcerative STDs (for the no cofactor scenario only), analyses on paired data was performed. This was carried out by calculating the ratio of pairs of OR estimates for each of the ten runs for each scenario, and then deriving geometric means and 95% CIs for the ratio of the ORs, using a logarithmic transformation.

### 5.1.2 LOGISTIC REGRESSION ANALYSES

Logistic regression analyses were carried out separately for cross-sectional and cohort study designs, in males and females. ORs were adjusted for sexual behaviour characteristics by including in the logistic model two binary variables representing current involvement in casual partnerships and having a characteristic for one-off sexual contacts. ORs were also adjusted for either a history of ulcerative or non-ulcerative STDs, depending on whether associations with HIV were for non-ulcerative or ulcerative STDs respectively.

For each scenario regression analyses have been carried out for each of the ten runs, and geometric means and 95% CIs were again obtained by logarithmic transformation.

## 5.2 RESULTS

### 5.2.1 UNIVARIATE ANALYSES

Table 5.1 documents the complete set of 48 mean OR estimates (and 95% CIs) in a 5-way table, ie for the three scenarios and all combinations of four 2-way characteristics. Figures 5.1 to 5.5 illustrate the main findings in table 5.1, by considering the relationship between STD cofactor effects and observed HIV/STD associations, and the influence on ORs of each of the four characteristics. The results presented are geometric means of ten OR estimates obtained from ten runs for each of the three scenarios. The error bars in the figures represent 95% CIs for ORs based on repeated simulations. Note that the logarithmic scale for the y-axis varies between the figures. All results are based on associations between HIV and a one-year history of other STDs, for 15-49 year old females and 20-49 year old males.

Figure 5.1 shows ORs for history of ulcerative STDs in all females sampled from a cross-sectional design, for the three different scenarios. The most striking features are:

(1) Increasing ORs with cofactor effects, from a mean of 2.2 with the no cofactor scenario to means of 4.3 and 6.8 with the low, and high cofactor scenarios respectively. For the low and high cofactor scenarios these were considerably less than the per contact cofactor effects of 10 and 100 respectively.

(2) A substantial mean OR of 2.2, even in the absence of any true STD cofactor effects, with a lower confidence limit excluding unity. This is the likely effect of confounding by sexual behaviour. This would suggest that, for this size of population, even in the absence of true STD cofactor effects, one might expect to observe a significant association between HIV and a history of ulcerative STDs. For samples drawn from this population, CIs for estimates of ORs would, in general, be larger, and so the lower confidence bound would be more likely to include unity.

(3) Wide CIs, even with sample sizes over 1000. This principally reflects the relatively low incidence of STDs and HIV infection in the general population. For the low cofactor scenario the 95% confidence interval ranges from 2.2 to 8.2. The upper

Table 5.1 Odds ratio estimates (and 95% CIs) from univariate analyses

| | History of ulcerative STDs | | | History of non-ulcerative STDs | | |
|---|---|---|---|---|---|---|
| | STD cofactor scenario | | | STD cofactor scenario | | |
| | No | Low | High | No | Low | High |
| **Female X-sect** | | | | | | |
| All | 2.20 (1.48-3.29) | 4.27 (2.22-8.23) | 6.82 (3.82-12.18) | 2.51 (2.05-3.06) | 3.56 (2.50-5.09) | 4.22 (2.56-6.96) |
| HR* | 1.32 (0.71-2.46) | 2.01 (0.80-5.05) | 4.06 (2.01-9.58) | 1.42 (1.05-1.92) | 1.54 (0.99-2.39) | 2.16 (1.09-4.26) |
| **Female Cohort** | | | | | | |
| All | 2.69 (1.45-5.00) | 6.75 (2.62-17.41) | 21.76 (11.02-42.95) | 3.19 (2.18-4.66) | 4.97 (2.85-8.65) | 7.92 (3.63-17.29) |
| HR* | 1.45 (0.61-3.42) | 3.32 (1.02-10.80) | 11.82 (5.21-26.84) | 1.45 (0.78-2.69) | 1.63 (0.76-3.49) | 3.71 (1.42-9.68) |
| **Male X-sect** | | | | | | |
| All | 2.10 (1.46-3.00) | 3.03 (2.00-4.59) | 5.31 (3.03-9.30) | 2.64 (2.03-3.43) | 3.10 (2.08-4.62) | 4.31 (2.77-6.69) |
| HR* | 1.12 (0.49-2.53) | 1.43 (0.87-2.36) | 1.84 (1.19-2.86) | 1.21 (0.66-2.20) | 1.52 (0.94-2.46) | 1.51 (0.91-2.48) |
| **Male Cohort** | | | | | | |
| All | 2.39 (1.21-4.71) | 2.99 (1.43-6.21) | 11.59 (5.42-24.78) | 2.80 (1.73-4.53) | 3.42 (1.57-7.46) | 5.47 (2.77-10.80) |
| HR* | 1.11 (0.51-2.41) | 1.72 (0.53-5.58) | 3.32 (1.65-6.69) | 1.16 (0.31-4.35) | 1.97 (0.84-4.66) | 1.58 (0.57-4.39) |

* HR (high risk), in this context, represents males engaged in one-off sexual contacts and females with current casual partners.

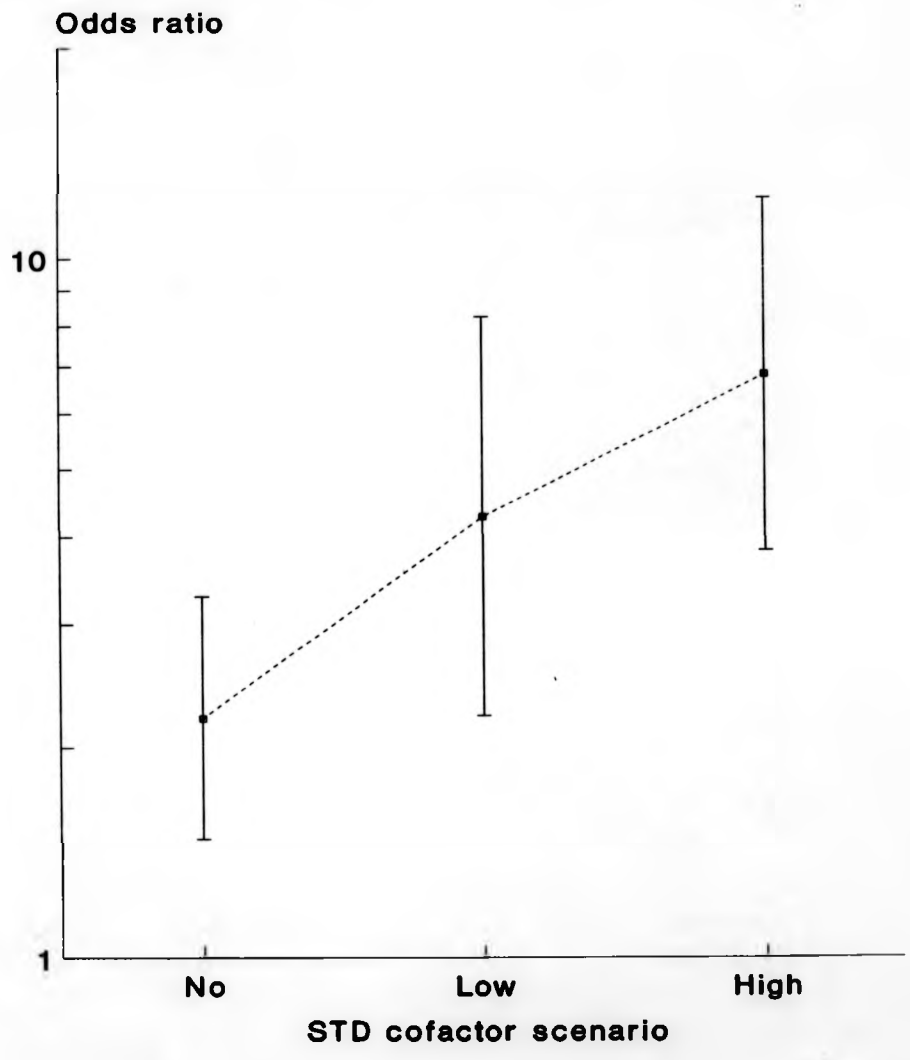



Figure 5.1 Odds ratios for history of ulcerative STDs in females (X-sectional study)

confidence bound for the high cofactor scenario extends to over 12. The range of ORs generated for the low and high cofactor scenarios are rather larger than usually observed in cross-sectional studies. This is mainly due to the distorting effect of substantial heterogeneity in sexual behaviour among females in the general population (including women who only engage in one-off sexual contacts and women who only have regular partners). Published reports almost always refer to studies of high risk groups, which are less heterogeneous with respect to sexual behaviour patterns.

Figure 5.2 shows ORs for history of non-ulcerative STDs, in all females sampled from a cross-sectional design, for the three different scenarios. Most prominent features include:

(1) Increasing ORs with cofactor effects, from 2.5 to 3.6 to 4.2 for the no, low and high cofactor scenarios respectively. For the no and low cofactor scenarios the mean OR is greater than the assumed cofactor effects of 1 and 2 respectively. These are distorted by the confounding effects of both sexual behaviour and history of ulcerative STDs on the association between HIV and history of non-ulcerative STDs. The result is that even in the absence of true cofactor effects for non-ulcerative STDs, and assuming no misclassification of non-ulcerative STDs, one might expect to observe substantial associations between HIV and a history of non-ulcerative STDs.

(2) The range of OR estimates (as represented by CIs) are generally larger than observed for cross-sectional studies. For all three scenarios lower confidence bounds are greater than two. The most plausible explanation for, in general, not actually observing such strong associations with non-ulcerative STDs from cross-sectional surveys is due to the misclassification of non-ulcerative STDs.

Figure 5.3 shows ORs for the different scenarios, for history of ulcerative STDs in all males, sampled from a cross-sectional design. OR estimates show a similar pattern to those in females (figure 5.1), with increasing ORs with cofactor effects. In general, the strength of association is less in males than females. The main reason for this is that sexual behaviour in SimulAIDS is more heterogeneous among females. This is discussed further in 5.3.4.

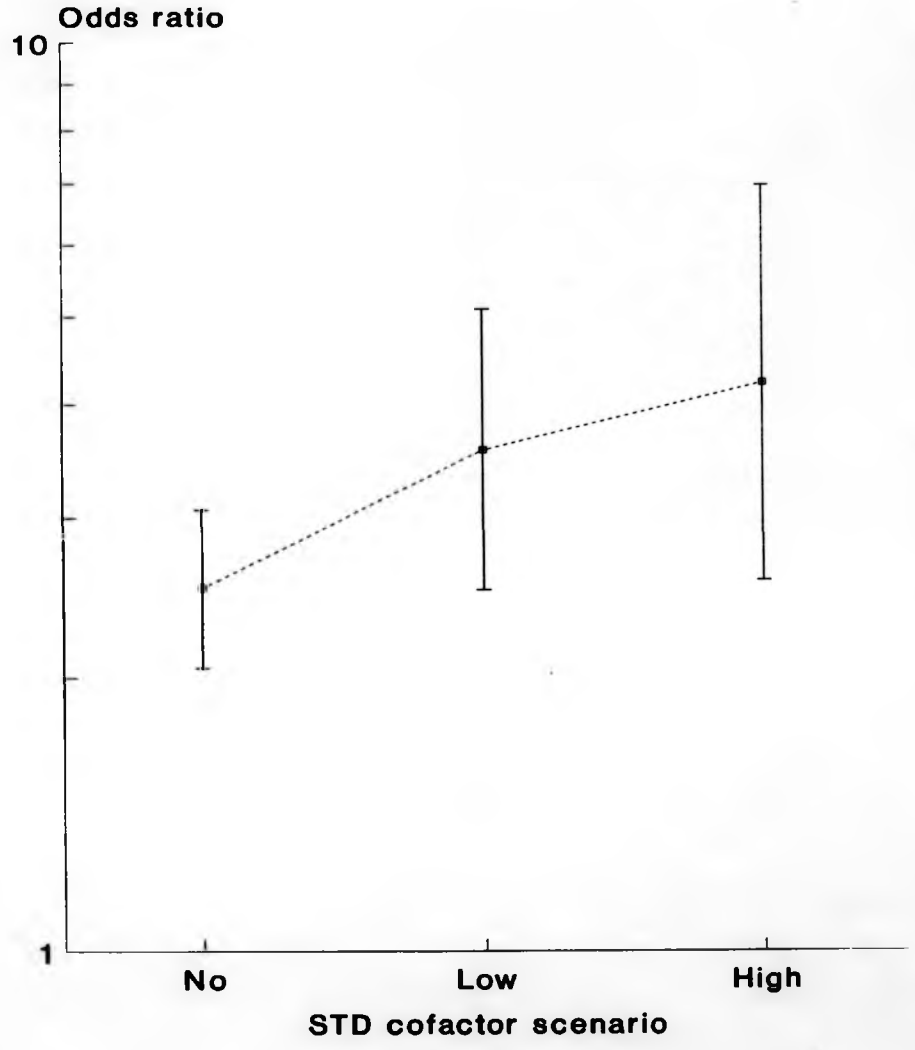



Figure 5.2 Odds ratios for history of non-ulcerative STDs in females (X-sectional study)

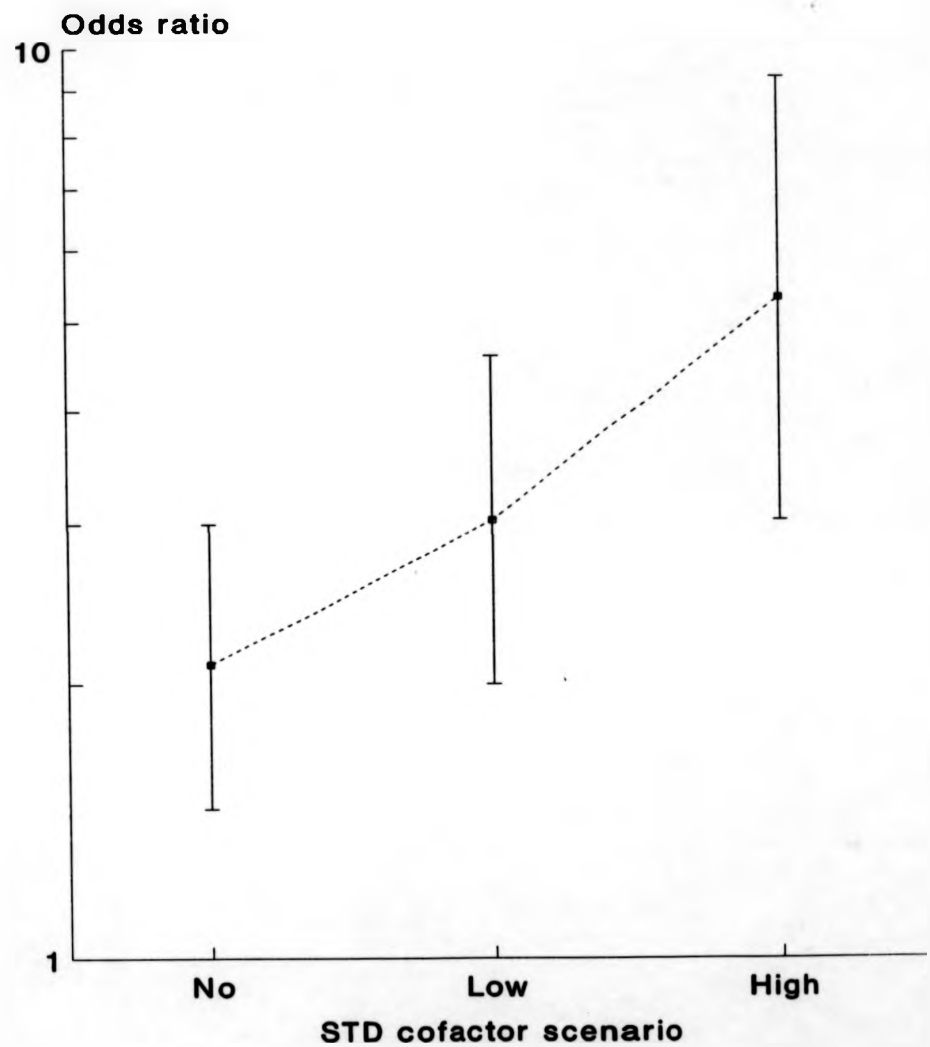



Figure 5.3 Odds ratios for history of ulcerative STDs in males (X-sectional study)

Figure 5.4 shows ORs for history of ulcerative STDs in high risk females sampled from a cross-sectional design. Associations were weaker than for all adult females, with mean ORs of 1.3, 2.0 and 4.1 for the no, low and high cofactor scenarios respectively. This is as expected since this group of females is rather less heterogeneous with respect to sexual behaviour than all adult females. Even so, some confounding effect of both sexual behaviour of females and of their partners is still likely to remain. Note that smaller sample sizes give rise to larger CIs, which include unity for both the no and low cofactor scenarios.

Figure 5.5 displays ORs from cohort designs, for history of ulcerative STDs in all females. As expected, ORs from follow-up studies were generally larger than those sampled from cross-sectional surveys. For the high cofactor scenario the mean OR was 21.8 with CI from 11.0 to 42.9. Even in the high risk group the mean OR was 11.8 for the high cofactor scenario. These results are rather higher than actually observed, principally resulting from confounding by sexual behaviour of both females and their sexual partners.

Of the different simulated populations in table 5.1 (ie all and high risk males and females), high risk males is the only one that can be considered to reasonably replicate samples drawn for empirical studies in sub-Saharan Africa. Studies from the general population (including both high and low risk groups) have rarely been carried out, and those in females have principally been focused on CSWs, where issues of the confounding effect of sexual behaviour of their partners is less important. For high risk males, the high cofactor scenario is most consistent with empirical results, with, for example, a mean OR of 3.32 (95% CI 1.65-6.69) for the association between HIV and history of ulcerative STDs generated from simulated cohort studies. Associations between HIV and ulcerative STDs from high risk males for the no cofactor scenario are inconsistent with empirical results, since mean ORs for cross-sectional and cohort studies are low (at approximately 1.1) and upper bounds of confidence intervals are less than 3.0. This may, in part, reflect the lack of heterogeneity in the frequency of sexual contacts that males have with one-off partners.

Similar trends to those described in figures 5.1 - 5.5 can be seen across the different groups in table 5.1, with associations tending to increase with cofactor effects, and tending to be lower in the high risk groups, in males and in cross-sectional surveys. However, one result that did not follow these trends was that for high risk males, mean ORs for non-ulcerative

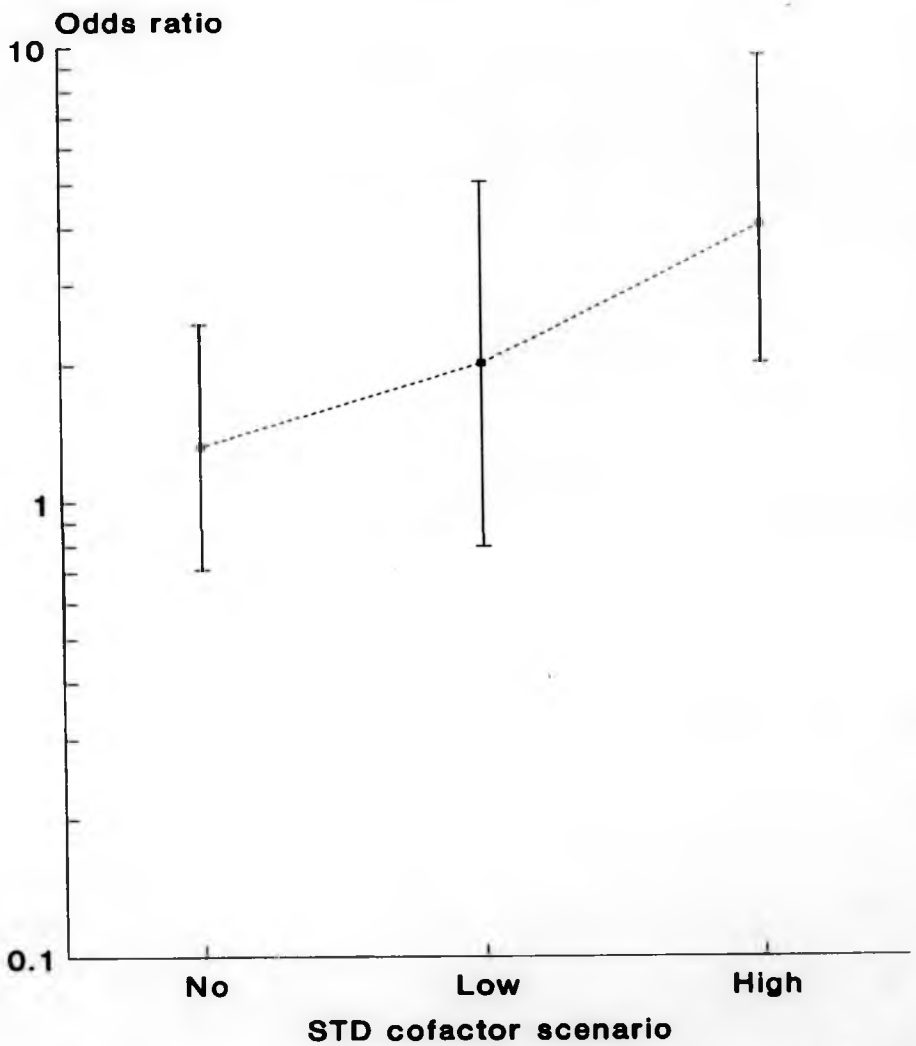



Figure 5.4 Odds ratios for history of ulcerative STDs in females with casual partners (X-sectional study)

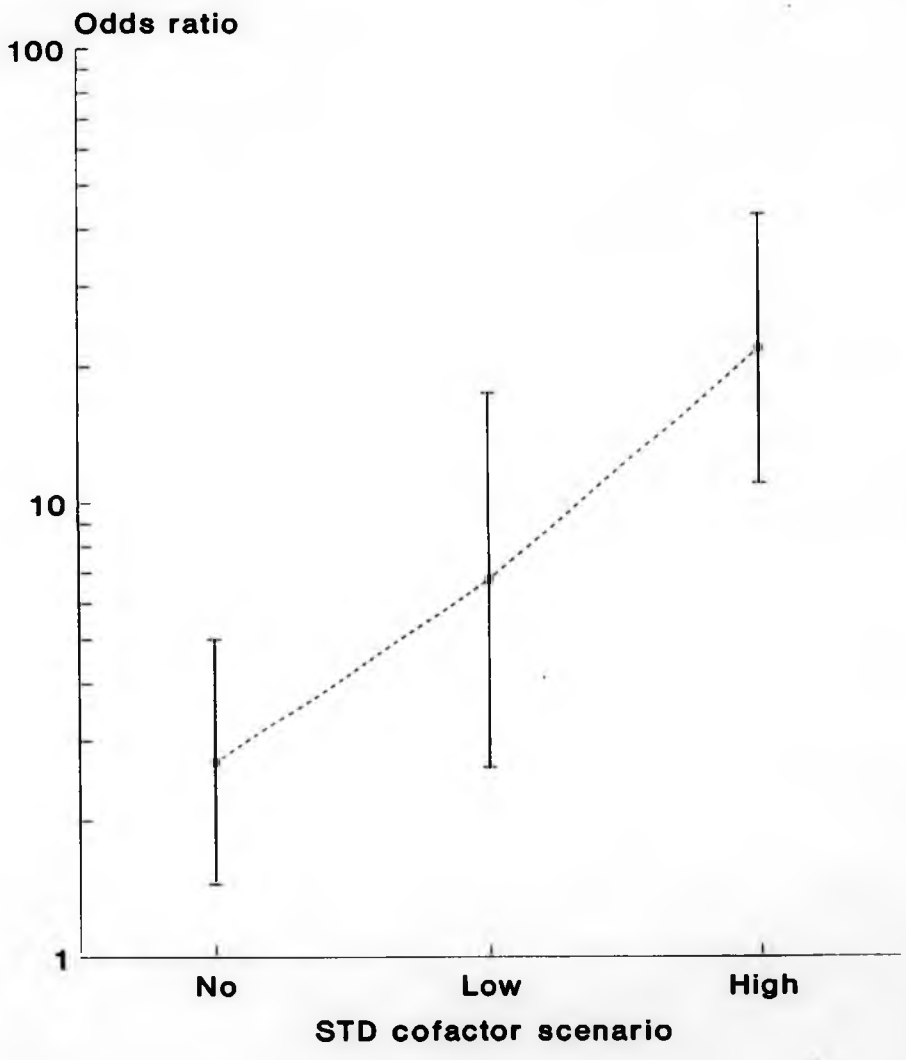



Figure 5.5 Odds ratios for history of ulcerative STDs in females (cohort study)

STDs were no stronger for the high cofactor scenario than for the low cofactor scenario. This results from increased confounding of associations by ulcerative STDs. This is discussed further in 5.3.5.

Tables 5.2 - 5.4 draw formal statistical comparisons for the respective associations between all and high risk populations, follow-up and cross-sectional studies, and, for the no cofactor scenario, history of non-ulcerative and ulcerative STDs.

In table 5.2 all mean ratios of ORs are greater than one, and most are significantly greater, ie CIs exclude unity. This reflects higher OR estimates observed in the general adult populations compared with high risk populations. This, in turn, reflects the confounding effect of greater heterogeneity in sexual behaviour in the general adult population.

In table 5.3 most mean ratio of OR estimates are greater than unity, reflecting a general trend for higher associations in cohort studies. Though most CIs do include unity, ratios of ORs tend to increase with the cofactor scenarios.

Comparing ORs for history of non-ulcerative and history of ulcerative STDs for the no cofactor scenario (table 5.4), the mean ratios of OR estimates are, in all cases, greater than one. CIs, however, do in all cases include unity. Comparisons for low and high cofactor scenarios are not particularly meaningful and so have not been included in the table. An explanation of this perhaps surprising result is given in 5.3.5.

### 5.2.2 LOGISTIC REGRESSION

Results from logistic regression analyses are shown in table 5.5. Results for geometric means of ORs are given with 95% confidence intervals calculated from the ten runs for each scenario. Results are again shown separately for a one-year history of ulcerative and non-ulcerative STDs in all females and males for cross-sectional and cohort designs by cofactor scenario, ie no, low and high. For each of these categories four OR estimates were calculated, reflecting unadjusted associations, and associations adjusted for the second STD, for current casual partnerships and one-off sexual contacts (represented by two binary

Table 5.2 Ratio of odds ratio estimates (and 95% CIs) from univariate analyses (All : High risk)

| | History of ulcerative STDs | | | History of non-ulcerative STDs | | |
|---|---|---|---|---|---|---|
| | STD cofactor scenario | | | STD cofactor scenario | | |
| | No | Low | High | No | Low | High |
| **Female X-sect** | | | | | | |
| All vs HR* | 1.68 (1.04-2.72) | 2.12 (1.48-3.03) | 1.55 (0.89-2.72) | 1.77 (1.28-2.44) | 2.32 (1.65-3.25) | 1.97 (1.13-3.46) |
| **Female Cohort** | | | | | | |
| All vs HR* | 1.86 (0.85-4.06) | 2.03 (1.05-3.94) | 1.84 (1.03-3.29) | 2.18 (1.32-3.60) | 3.03 (1.80-5.10) | 2.12 (0.81-5.53) |
| **Male X-sect** | | | | | | |
| All vs HR* | 1.88 (1.01-3.49) | 2.12 (1.70-2.64) | 2.89 (2.14-3.90) | 2.16 (1.14-4.10) | 2.03 (1.45-2.86) | 2.86 (2.12-3.86) |
| **Male Cohort** | | | | | | |
| All vs HR* | 2.18 (1.27-3.74) | 1.73 (1.01-2.97) | 3.49 (1.73-7.03) | 2.41 (0.67-8.67) | 1.73 (1.26-2.39) | 3.46 (2.18-5.47) |

* HR (high risk), in this context, represents males engaged in one-off sexual contacts and females with current casual partners.

Table 5.3 Ratio of odds ratio estimates (and 95% CIs) from univariate analyses (Cohort : Cross-sectional)

| | History of ulcerative STDs | | | History of non-ulcerative STDs | | |
|---|---|---|---|---|---|---|
| | STD cofactor scenario No | Low | High | STD cofactor scenario No | Low | High |
| **All Females** | | | | | | |
| Cohort vs X-sect | 1.22 (0.73-2.05) | 1.58 (0.87-2.89) | 3.16 (2.16-4.62) | 1.27 (0.92-1.75) | 1.39 (0.97-1.99) | 1.88 (1.03-3.42) |
| **HR* Female** | | | | | | |
| Cohort vs X-sect | 1.11 (0.59-2.05) | 1.65 (1.06-2.56) | 2.69 (1.57-4.62) | 1.03 (0.61-1.73) | 1.06 (0.64-1.75) | 1.73 (0.93-3.22) |
| **All Male** | | | | | | |
| Cohort vs X-sect | 1.14 (0.78-1.67) | 0.98 (0.51-1.90) | 2.18 (1.15-4.14) | 1.07 (0.70-1.63) | 1.11 (0.66-1.86) | 1.27 (0.63-2.56) |
| **HR* Male** | | | | | | |
| Cohort vs X-sect | 0.99 (0.49-1.99) | 1.20 (0.45-3.19) | 1.80 (0.73-4.44) | 0.96 (0.31-2.94) | 1.30 (0.71-2.36) | 1.05 (0.45-2.44) |

* HR (high risk), in this context, represents males engaged in one-off sexual contacts and females with current casual partners.

Table 5.4 Ratio of odds ratio estimates (and 95% CIs) from univariate analyses (Non-ulcerative : Ulcerative STDs)

| | STD cofactor scenario No |
|---|---|
| **All Female: X-sect** | |
| Non-ulcerative vs Ulcerative | 1.13 (0.79-1.62) |
| **HR* Female: X-sect** | |
| Non-ulcerative vs Ulcerative | 1.07 (0.57-2.03) |
| **All Female: Cohort** | |
| Non-ulcerative vs Ulcerative | 1.17 (0.59-2.32) |
| **HR* Female: Cohort** | |
| Non-ulcerative vs Ulcerative | 1.00 (0.35-2.89) |
| **All Male: X-sect** | |
| Non-ulcerative vs Ulcerative | 1.26 (0.95-1.67) |
| **HR* Male: X-sect** | |
| Non-ulcerative vs Ulcerative | 1.09 (0.42-2.86) |
| **All Male: Cohort** | |
| Non-ulcerative vs Ulcerative | 1.17 (0.77-1.79) |
| **HR* Male: Cohort** | |
| Non-ulcerative vs Ulcerative | 1.06 (0.28-3.97) |

* HR (high risk), in this context, represents males engaged in one-off sexual contacts and females with current casual partners.

## Table 5.5 Odds ratio estimates (and 95% CIs) adjusted for other STDs and current sexual relationships

| | History of ulcerative STDs STD cofactor scenario | | | History of non-ulcerative STDs STD cofactor scenario | | |
|---|---|---|---|---|---|---|
| | No | Low | High | No | Low | High |
| **Female, X-sect** | | | | | | |
| Unadjusted | 2.20 (1.48-3.29) | 4.26 (2.20-8.25) | 6.82 (3.82-12.18) | 2.51 (2.05-3.06) | 3.56 (2.48-5.10) | 4.22 (2.56-6.96) |
| Adjusted for other STD | 1.55 (1.02-2.36) | 3.03 (1.34-6.89) | 4.85 (2.36-9.97) | 2.16 (1.70-2.75) | 3.03 (2.03-4.53) | 3.35 (1.80-6.23) |
| Adjusted for partnerships | 1.82 (1.27-2.61) | 2.46 (1.20-5.05) | 4.66 (2.23-9.78) | 2.10 (1.68-2.61) | 2.20 (1.54-3.16) | 2.94 (1.65-5.26) |
| Adjusted for STD & partnerships | 1.45 (0.97-2.16) | 2.14 (0.96-4.76) | 3.86 (1.73-8.58) | 1.88 (1.42-2.48) | 2.03 (1.36-3.03) | 2.51 (1.27-4.95) |
| **Female, Cohort** | | | | | | |
| Unadjusted | 2.65 (1.45-5.00) | 6.75 (2.64-17.29) | 21.54 (10.91-42.52) | 3.25 (2.32-4.57) | 4.95 (2.83-8.67) | 7.92 (3.63-17.29) |
| Adjusted for other STD | 1.73 (0.84-3.56) | 4.39 (1.49-12.94) | 14.30 (6.96-29.37) | 2.61 (1.58-4.31) | 3.82 (2.14-6.82) | 4.62 (1.70-12.55) |
| Adjusted for partnerships | 2.08 (1.09-3.94) | 3.63 (1.42-9.30) | 14.01 (5.47-35.87) | 2.44 (1.92-3.10) | 2.75 (1.70-4.44) | 4.71 (1.80-12.30) |
| Adjusted for STD & partnerships | 1.62 (0.82-3.19) | 3.10 (1.16-8.25) | 11.13 (4.81-25.79) | 2.03 (1.31-3.16) | 2.44 (1.45-4.10) | 3.29 (1.14-9.49) |
| **Male, X-sect** | | | | | | |
| Unadjusted | 2.08 (1.48-2.92) | 3.00 (1.97-4.57) | 5.31 (3.03-9.30) | 2.59 (1.99-3.35) | 3.10 (2.03-4.71) | 4.35 (2.80-6.75) |
| Adjusted for other STD | 1.35 (0.92-1.97) | 2.14 (1.35-3.39) | 3.56 (1.92-6.62) | 2.23 (1.72-2.89) | 2.48 (1.48-4.18) | 3.13 (1.97-4.95) |
| Adjusted for partnerships | 1.35 (0.79-2.32) | 1.60 (0.81-3.16) | 2.23 (1.32-3.74) | 1.90 (1.27-2.83) | 1.75 (1.13-2.72) | 1.95 (1.26-3.03) |
| Adjusted for STD & partnerships | 1.20 (0.73-1.97) | 1.48 (0.78-2.80) | 2.01 (1.15-3.53) | 1.84 (1.28-2.64) | 1.67 (1.07-2.59) | 1.80 (1.12-2.92) |
| **Male, Cohort** | | | | | | |
| Unadjusted | 2.39 (1.21-4.71) | 2.97 (1.42-6.23) | 11.59 (5.42-24.78) | 2.72 (1.72-4.31) | 3.16 (1.54-6.49) | 5.53 (2.80-10.91) |
| Adjusted for other STD | 1.57 (0.73-3.35) | 2.03 (0.68-6.11) | 7.85 (2.56-24.05) | 2.16 (1.34-3.49) | 2.48 (0.86-7.17) | 2.64 (0.88-7.92) |
| Adjusted for partnerships | 1.51 (0.66-3.42) | 1.86 (0.44-7.85) | 4.85 (2.23-10.59) | 1.82 (1.13-2.94) | 1.97 (1.00-3.90) | 2.20 (0.79-6.11) |
| Adjusted for STD & partnerships | 1.35 (0.61-3.00) | 1.70 (0.38-7.61) | 4.39 (1.97-9.78) | 1.72 (1.06-2.77) | 1.82 (0.85-3.90) | 1.70 (0.57-5.10) |

variables), and adjusting for both history of second STD and current casual partnerships and one-off sexual contacts.

Results for unadjusted associations are, as expected, virtually identical to those obtained for all females and males from univariate analyses (table 5.1). Results obtained adjusting for the second STD and/or for current sexual partnerships give weaker associations, which reflect the confounding effect of sexual behaviour on unadjusted associations. In general, adjusting for only current casual partnerships and one-off sexual contacts results in weaker associations than adjusting for only the second STD. However, by including both factors in analyses associations are further reduced. This reflects residual confounding effects of sexual behaviour not measured by current casual partnerships and one-off sexual contacts, ie the second STD is a marker for sexual behaviour. The effect of including the second STD having already adjusted for sexual behaviour appears to consistently have a greater effect in females than males. This, in part, is likely to reflect the particularly important role of sexual behaviour of the partners of women in determining their risk of HIV infection.

Results adjusting for sexual behaviour and the second STD are not dissimilar to results shown in table 5.1 for high risk females and males. Thus choosing appropriate high risk groups to study should help minimise the confounding effect of sexual behaviour.

## 5.3 DISCUSSION

This section looks at the results generated, and further explores reasons for many of the findings. To facilitate this, it is useful to consider the odds of HIV infection in individuals with and without a recent history of ulcerative and non-ulcerative STD episodes.

An individual's history of STDs can be categorised into one of four mutually exclusive and exhaustive groups: (1) history of both ulcerative and non-ulcerative STDs, (2) history of ulcerative STDs only, (3) history of non-ulcerative STDs only and, (4) no history of either ulcerative or non-ulcerative STDs.

When an individual reports a history of, say, ulcerative STDs in the last year this may mean one of two things. Either they have had a history of both ulcerative and non-ulcerative STDs or a history of only ulcerative STDs. When an individual reports no history of ulcerative STDs this may also mean one of two things, ie that they have had no ulcerative or non-ulcerative STD episodes or that they have had no history of ulcerative STDs but have had episodes of non-ulcerative STDs.

### 5.3.1 MISCLASSIFICATION OF NON-ULCERATIVE STDs

Simulated odds ratios for a history of non-ulcerative STDs (table 5.1) were generally higher than reported in studies and, for the no cofactor scenario, higher than the respective ORs for ulcerative STDs. The reason simulated ORs are substantially greater than unity, even for the no cofactor scenario, is due to confounding by sexual behaviour. However, the reason why associations from empirical studies are usually much smaller than those simulated is probably due to substantial misclassification of non-ulcerative STDs, ie under-reporting due to non-recognition of non-ulcerative STDs. This might result either from asymptomatic episodes of STDs or since non-ulcerative STDs may have been masked by episodes of symptomatic ulcerative STDs. The strength of observed associations will depend on the extent of misclassification.

An illustrative example of the effect of misclassification of non-ulcerative STDs is shown in

table 5.6. This table shows results of misclassifying non-ulcerative STDs when individuals have both a history of ulcerative and non-ulcerative STDs. In practise, even though not all non-ulcerative STDs will go unreported among individuals who also have a history of ulcerative STDs (and especially since in many cases they will not have both STDs simultaneously), these results are unlikely to reflect the true extent of misclassification since there is often also likely to be considerable misclassification of non-ulcerative STDs in individuals with no history of ulcerative STDs. For high risk males, ORs (adjusted for some misclassification of non-ulcerative STDs) from cross-sectional and cohort studies of 1.08 (95% CI: 0.70-1.68) and 0.63 (95% CI: 0.14-2.94) respectively are reasonably consistent with empirical studies (*Mertens et al 1990*). Note, however, that in closely monitored cohort studies the effects of misclassification are likely to be smaller. Misclassification of ulcerative STDs is also likely to occur, but to a lesser extent.

Because of the considerable misclassification that, in practise, may occur, most of the following discussion has been focused on ulcerative STDs. Misclassifying non-ulcerative STDs has no effect on univariate associations between HIV and ulcerative STDs.

### 5.3.2 PREVALENT AND INCIDENT HIV INFECTIONS

The number of incident HIV infections in general population cohorts will usually be small over short time intervals, of say one year, even in large studies carried out in high prevalence regions. For cohort studies in general populations, estimates of associations are therefore likely to be imprecise and confidence intervals large.

Cross-sectional and cohort studies use prevalent and incident HIV infections respectively. Higher associations would, in general, be expected from cohort studies for the same duration of reference period (table 5.3), since incident HIV infections are likely to be more strongly associated with recent history of STDs than prevalent infections. This is more pronounced for higher cofactor effects, since more incident infections are attributable to other STDs, and the risk of HIV infection in the absence of STDs is reduced.

Table 5.6 OR estimates (and 95% CIs) for history of non-ulcerative STDs with adjustment for some misclassification of non-ulcerative STDs

| | History of non-ulcerative STDs, adjusted STD cofactor scenario | | | History of non-ulcerative STDs, unadjusted STD cofactor scenario | | |
|---|---|---|---|---|---|---|
| | No | Low | High | No | Low | High |
| **Female X-sect** | | | | | | |
| All | 1.80 (1.36-2.39) | 2.80 (1.84-4.26) | 3.35 (1.99-5.64) | 2.51 (2.05-3.06) | 3.56 (2.50-5.09) | 4.22 (2.56-6.96) |
| HR* | 1.19 (0.81-1.73) | 1.34 (0.83-2.16) | 1.79 (0.89-3.60) | 1.42 (1.05-1.92) | 1.54 (0.99-2.39) | 2.16 (1.09-4.26) |
| **Female Cohort** | | | | | | |
| All | 2.01 (1.32-3.06) | 3.67 (2.18-6.17) | 5.26 (2.46-11.25) | 3.19 (2.18-4.66) | 4.97 (2.85-8.65) | 7.92 (3.63-17.29) |
| HR* | 1.05 (0.49-2.25) | 1.26 (0.57-2.80) | 2.72 (0.89-8.33) | 1.45 (0.78-2.69) | 1.63 (0.76-3.49) | 3.71 (1.42-9.68) |
| **Male X-sect** | | | | | | |
| All | 1.84 (1.36-2.48) | 2.27 (1.27-4.06) | 2.89 (2.14-3.90) | 2.64 (2.03-3.42) | 3.10 (2.08-4.62) | 4.31 (2.77-6.69) |
| HR* | 1.11 (0.63-1.93) | 1.17 (0.62-2.23) | 1.08 (0.70-1.68) | 1.21 (0.66-2.20) | 1.52 (0.94-2.46) | 1.51 (0.91-2.48) |
| **Male Cohort** | | | | | | |
| All | 1.77 (1.19-2.64) | 2.03 (0.60-6.89) | 2.20 (0.63-7.77) | 2.80 (1.73-4.53) | 3.42 (1.57-7.46) | 5.47 (2.77-10.80) |
| HR* | 0.99 (0.50-1.95) | 1.09 (0.22-5.42) | 0.63 (0.14-2.94) | 1.16 (0.31-4.35) | 1.97 (0.84-4.66) | 1.58 (0.57-4.39) |

* HR (high risk), in this context, represents males engaged in one-off sexual contacts and females with current casual partners.

### 5.3.3 AGE OF STUDY SAMPLE

The age groups 15-49 for females and 20-49 for males were selected since, in the modelling scenarios, they represented the main sexually active populations. 15-19 males and all adults over 49 were assumed to have fewer sexual partners, resulting in lower incidence levels of HIV infection. By including these groups, heterogeneity in sexual behaviour is increased resulting in stronger associations between HIV and other STDs. 15-19 females are included since females were assumed to begin sexual activity at younger ages than males. This is consistent with data from the study population, and was necessary in order to replicate high rates of HIV infection in 15-19 year old females, and virtually none in the 15-19 males.

To illustrate this consider table 5.7, which shows mean estimates of odds of HIV infection (from 10 simulations) in all males by STD status and age group in a cross-sectional design for the no cofactor scenario. Odds estimates were derived from the ratio of the mean number of infected to the mean number of uninfected males. Incident infections were too few to consider the cohort design. The OR estimate for the 20-49 age group is identical to the result in table 5.1 (2.1). ORs are higher in the 15-19 and 50-74 age bands.

The main reason for higher ORs in 15-19 males compared with 20-49 males was that in the no STD history group, the odds of HIV infection was much smaller (over 20-fold) by the inclusion of a large group of males with no HIV infection and no history of other STDs (many of whom would not have reached sexual debut). This results in high observed ORs, even though odds are lower in the groups with history of STDs. ORs are also higher in the 50-74 age band, but not so markedly. This is because sexual behaviour characteristics do not change so dramatically in males; ie men still continue to engage in one-off sexual contacts.

Observed associations between HIV and other STDs are dependent on the age of the sample since age reflects sexual behaviour characteristics. In general, compared with males in the age range 20-49, associations are higher in 15-19 and 50-74 males. Similarly, compared with females in the age range 15-49, associations between HIV and other STDs are higher in older females.

Table 5.7 Estimates of odds+ of HIV infection in all males by STD status and age group for no cofactor scenario from cross-sectional study design

| | Age band 15-19 | 20-49 | 50-74 |
|---|---|---|---|
| Odds of HIV infection for history of: | | | |
| Both ulcerative and non-ulcerative STDs | 0.081 (3:37) | 0.28 (69:246) | 0.16 (7:44) |
| Only ulcerative STDs | 0.037 (0.3:8) | 0.27 (14:51) | 0.19 (3:15) |
| Only non-ulcerative STDs | 0.062 (2:30) | 0.28 (54:193) | 0.15 (6:40) |
| No STDs | 0.0038(2:416) | 0.093(61:638) | 0.032(11:359) |
| Odds of HIV infection for history of#: | | | |
| Ulcerative STDs | 0.072 (3:45) | 0.28 (83:297) | 0.17 (10:59) |
| No ulcerative STDs | 0.0078(3.5:446) | 0.14 (115:851) | 0.043(17:399) |
| ORs for ulcerative STDs | 8.5 | 2.1 | 4.0 |

+ Odds estimates have been derived from the ratio of the mean number of infected to the mean number of uninfected males (from 10 simulations).

# Odds of HIV infection for history of "ulcerative STDs" are derived by combining the groups "both ulcerative and non-ulcerative STDs" with "only ulcerative STDs". Odds of HIV infection for history of "no ulcerative STDs" are derived by combining the groups "only non-ulcerative STDs" with "no STDs".

### 5.3.4 CONFOUNDING BY SEXUAL BEHAVIOUR

Sampling HIV/STD associations from a simulated population of sexually active adults assuming no STD cofactor effects results in observed ORs considerably greater than unity (table 5.1). This suggests that even in the absence of any true STD cofactor effects, one would expect to observe strong associations between HIV and other STDs. This reflects substantial confounding by sexual behaviour. Restricting observations to high risk groups results in associations less confounded by sexual behaviour and ORs closer to unity (tables 5.1 and 5.2).

When sexual behaviour characteristics were adjusted for in logistic regression, strong associations remained, even for the scenario with no true cofactor effects (table 5.5). These associations demonstrate the effect of residual confounding of sexual behaviour. This occurs because only crude measures of sexual behaviour have been used in analyses. If previous sexual history (ie non-current), frequency of sexual contact, or behaviour patterns of sexual partners (especially for females) were also well documented then additional adjustments for these factors in logistic regression analysis should further reduce confounding effects on observed associations. Clearly these are usually prohibitively difficult to ascertain with any accuracy. However, as was shown in table 5.5, also adjusting for the second STD further reduced the strength of associations, especially in females. In this case the second STD serves as a marker for sexual behaviour.

The main reason for stronger simulated associations in females than males (table 5.1) is that the sexual behaviour representation is more heterogeneous in the female population. Casual partnerships stop in the mid-twenties and women then either have only one-off sexual contacts or only regular partners. Males, however, can continue in regular, casual and one-off sexual contacts until they are 50.

To explain why associations are also markedly less in high risk males than high risk females consider table 5.8, which gives estimates of odds of HIV infection in high risk males and females by STD status for cohort studies from the high cofactor scenario. Odds ratios for ulcerative STDs, derived from the ratio of the mean number of infected to the mean number of uninfected, are similar to the respective ORs presented in table 5.1 (ie 11.8 for females

Table 5.8 Estimates of odds+ of HIV infection in high risk males and females by STD status from cohort studies for the high cofactor scenario

| | High risk* females | High risk* males |
|---|---|---|
| Odds of HIV infection for history of: | | |
| Both ulcerative and non-ulcerative STDs | 0.33 (2:6) | 0.22 (6:28) |
| Only ulcerative STDs | 0.48 (5:11) | 0.21 (5:26) |
| Only non-ulcerative STDs | 0.11 (6:51) | 0.074(4:55) |
| No STDs | 0.025(10:421) | 0.062(7:108) |
| Odds of HIV infection for history of#: | | |
| Ulcerative STDs | 0.43 (7:18) | 0.21 (12:54) |
| No Ulcerative STDs | 0.034(16:473) | 0.066(11:164) |
| Non-ulcerative STDs | 0.14 (8:57) | 0.12 (10:83) |
| No non-ulcerative STDs | 0.035(15:432) | 0.090(12:134) |
| ORs for ulcerative STDs | 11.5 | 3.3 |
| ORs for non-ulcerative STDs | 4.0 | 1.3 |

\+ Odds estimates have been derived from the ratio of the mean number of infected to the mean number of uninfected males (from 10 simulations).

* High risk, in this context, represents males engaged in one-off sexual contacts and females with current casual partners.

\# Odds of HIV infection for history of "ulcerative STDs" are derived by combining the groups "both ulcerative and non-ulcerative STDs" with "only ulcerative STDs". Odds of HIV infection for history of "no ulcerative STDs" are derived by combining the groups "only non-ulcerative STDs" with "no STDs". Similarly odds of HIV infection for history of "non-ulcerative STDs" are derived by combining the groups "both ulcerative and non-ulcerative STDs" with "only non-ulcerative STDs", and odds of HIV infection for history of "no non-ulcerative STDs" are derived by combining the groups "only ulcerative STDs" with "no STDs".

and 3.3 for males). Odds of HIV infection are lower in males than females for individuals with a history of STDs but higher for those with no history of STDs. This results in less heterogeneity in odds of HIV infection among males with different histories of STDs, and leads to weaker OR estimates among males. The reason for this principally reflects the different HIV prevalence levels among partners of high risk males and females, and the duration of partnerships. Higher risk partners of high risk females (ie men with casual partners) generally have lower HIV prevalence rates than higher risk partners of high risk males (ie females with one-off sexual contacts). Thus high risk males are more likely to have contacts with HIV infected partners than high risk females, which leads to more HIV infections in the absence of STDs among high risk males. Although most high risk males acquire STDs from their one-off sexual contacts, on average, only one contact is likely to take place with a one-off partner in the presence of a single STD episode. This is in contrast to high risk females, who tend to acquire STD infections from casual male partners who concurrently have occasional one-off contacts. Thus compared with high risk males, high risk females are likely to have many more sexual contacts during STD episodes with their casual partners. Although these casual male partners have lower HIV prevalence levels than females in one-off sexual contacts, the higher frequency of contacts with casual partners in the presence of STDs results in higher levels of incident HIV infections in females with history of STDs.

### 5.3.5 CONFOUNDING EFFECTS OF STDs ON ONE ANOTHER

For the no cofactor scenario, associations for non-ulcerative STDs were generally slightly stronger than comparative associations for ulcerative STDs (tables 5.1 and 5.4). This results from less confounding by sexual behaviour for associations between HIV and ulcerative STDs. To explain this consider, for example, results presented in the first column in table 5.9, which give mean odds of HIV infection in all females by STD status from cohort studies for the no cofactor scenario. ORs for ulcerative and non-ulcerative STDs were 2.8 and 3.2 respectively, which, as expected, are similar to estimates in table 5.1 (ie 2.7 and 3.2 respectively).

The reason for higher associations with non-ulcerative STDs can be understood by looking

Table 5.9 Estimates of odds* of HIV infection in all females by STD status from cohort studies for the no and high cofactor scenarios

| Odds of HIV infection for history of: | Cofactor scenario No | High |
|---|---|---|
| Both ulcerative and non-ulcerative STDs | 0.11 (18:163) | 0.33 (4:12) |
| Only ulcerative STDs | 0.072 (5:69) | 0.38 (8:21) |
| Only non-ulcerative STDs | 0.075 (22:295) | 0.11 (9:84) |
| No STDs | 0.024 (25:1036) | 0.012 (17:1433) |
| ORs for both ulcerative and non-ulcerative STDs\| | 4.6 | 28.1 |
| ORs for only ulcerative STDs\| | 3.0 | 32.1 |
| ORs for only non-ulcerative STDs\| | 3.1 | 9.0 |
| Odds of HIV infection for history of#: | | |
| Ulcerative STDs | 0.099 (23:232) | 0.36 (12:33) |
| No ulcerative STDs | 0.035 (47:1331) | 0.017 (26:1517) |
| Non-ulcerative STDs | 0.087 (40:458) | 0.14 (13:96) |
| No non-ulcerative STDs | 0.027 (30:1105) | 0.017 (25:1454) |
| ORs for ulcerative STDs | 2.8 | 21.2 |
| ORs for non-ulcerative STDs | 3.2 | 7.9 |

\+ Odds estimates have been derived from the ratio of the mean number of infected to the mean number of uninfected males (from 10 simulations).

| "ORs for only non-ulcerative" represent the ratio of odds of HIV infection for history of "only non-ulcerative STDs" with odds of HIV infection for history of "no STDs". Similarly "ORs for both ulcerative and non-ulcerative STDs" and "ORs for ulcerative STDs" both make comparisons with odds of HIV infection for history of "no STDs".

\# Odds of HIV infection for history of "ulcerative STDs" are derived by combining the groups "both ulcerative and non-ulcerative STDs" with "only ulcerative STDs". Odds of HIV infection for history of "no ulcerative STDs" are derived by combining the groups "only non-ulcerative STDs" with "no STDs". Similarly odds of HIV infection for history of "non-ulcerative STDs" are derived by combining the groups "both ulcerative and non-ulcerative STDs" with "only non-ulcerative STDs", and odds of HIV infection for history of "no non-ulcerative STDs" are derived by combining the groups "only ulcerative STDs" with "no STDs".

at odds of HIV infection by STD status. Firstly, odds of HIV infection are similar in individuals with a history of only ulcerative STDs and in individuals with a history of only non-ulcerative STDs (0.072 and 0.075 respectively). Secondly, a history of non-ulcerative STDs is much more common than a history of ulcerative STDs (317 and 74 females respectively). The result is that, in females who have no history of ulcerative STDs, there is a substantial proportion (317/1378) with a history of only non-ulcerative STDs. Since these females tend to be more sexually active than those with no history of STDs, this serves to increase the odds of HIV infection in women with no history of ulcerative STDs (0.035), compared with females with no history of any STDs (0.024). In comparison, the odds of HIV infection in women with no history of non-ulcerative STDs is 0.027. The overall effect is that ORs are smaller for history of ulcerative STDs, principally because the no ulcerative group is more sexually active and therefore at higher risk of HIV infection than the no non-ulcerative group.

Clearly just the presence of a second STD in the population (even in the absence of assumed cofactor effects) confounds associations between HIV and the first STD. One way to look at associations not confounded by the second STD is to compare odds of HIV infection with a history of only ulcerative STDs or a history of only non-ulcerative STDs with those with no history of either ulcerative or non-ulcerative STDs. These are also shown in table 5.9. ORs for only ulcerative and only non-ulcerative STDs are similar for the no cofactor scenario (3.0 and 3.1 respectively), and reflect associations that would be expected if the second STD was absent from the population altogether. The difference between these associations and ORs of 2.8 and 3.2 for history of ulcerative and non-ulcerative STDs respectively (table 5.9) reflect the distorting effect of one STD on the other in the absence of any assumed cofactor effects.

For scenarios assuming STD cofactor effects, it is likely that the confounding effects of STDs on one another will be stronger. For the high cofactor scenario the derived OR for only ulcerative STDs (table 5.9, 32.1) is much higher than that for only non-ulcerative STDs (9.0), and both are higher than respective ORs for ulcerative and non-ulcerative STDs (21.2 and 7.9). Higher ORs for ulcerative than non-ulcerative STDs principally reflect the higher cofactor effects for ulcerative STDs. Higher ORs for history of only ulcerative and only non-ulcerative STDs reflect the effect of negative confounding of STDs on one another. This may

principally be explained by the lower odds of HIV infection in the no STD group (0.012) than the no ulcerative STD group (0.17) and the no non-ulcerative STD group (0.017), which include individuals with a history of only non-ulcerative and only ulcerative STDs respectively.

To further illustrate the confounding effects of STDs on one another, a second approach was employed by setting up further STD cofactor scenarios, comparable to the low and high cofactor scenarios but with no cofactor effects for non-ulcerative STDs. These scenarios were denoted by [10,1] and [100,1] respectively. The difference in ORs compared with the low and high cofactor scenarios respectively gives a further measure of the distorting effect of non-ulcerative STDs on associations between HIV and ulcerative STDs.

Comparing results from the low and high cofactor scenarios (table 5.1) with results from the scenarios [10,1] and [100,1] (table 5.10), further clarified the negative confounding effect of non-ulcerative STDs on associations with ulcerative STDs. Thus for lower prevalence levels of non-ulcerative STDs one would expect to observe higher associations between HIV and ulcerative STDs. Similarly, if ulcerative STDs had a particularly low prevalence in a population, then one might expect to observe higher associations between HIV and non-ulcerative STDs. The low prevalence of ulcerative STDs in the female prostitute population studied by *Laga et al (1993)* may have contributed to the strength of their findings. Note that the association from table 5.9 for history of only ulcerative STDs for the high cofactor scenario (32.1) is consistent with the comparable result from table 5.10 (31.2).

Although there are no assumed cofactor effects for non-ulcerative STDs in any of the scenarios in table 5.10, associations for history of non-ulcerative STDs are generally positive and increase with increasing cofactor effects for ulcerative STDs. This not only reflects confounding by sexual behaviour by also positive confounding by ulcerative STDs.

One further striking feature in table 5.9 is the interaction effect of ulcerative and non-ulcerative STDs. For the high cofactor scenario, females with a history of both STDs do not appear to be at higher risk of HIV infection than those with a history of only ulcerative STDs. This reflects the large differential in assumed cofactor effects for ulcerative and non-ulcerative STDs. Looking at interaction effects in the logistic regression models was not,

Table 5.10 Odds ratio estimates (and 95% CIs) from univariate analyses assuming no cofactor effects for no-ulcerative STDs in the low and high cofactor scenarios

| | History of ulcerative STDs | | | History of non-ulcerative STDs | | |
|---|---|---|---|---|---|---|
| | STD cofactor scenario | | | STD cofactor scenario | | |
| | No | [10,1] | [100,1] | No | [10,1] | [100,1] |
| **Female X-sect** | | | | | | |
| All | 2.20 (1.48-3.29) | 4.39 (3.00-6.42) | 8.67 (4.31-17.46) | 2.51 (2.05-3.06) | 3.60 (2.66-4.85) | 3.78 (2.64-5.42) |
| HR* | 1.32 (0.71-2.46) | 2.14 (1.40-3.25) | 4.53 (1.67-12.30) | 1.42 (1.05-1.92) | 1.65 (1.08-2.51) | 2.01 (1.04-3.90) |
| **Female Cohort** | | | | | | |
| All | 2.69 (1.45-5.00) | 8.75 (4.62-14.73) | 31.19 (14.59-66.69) | 3.19 (2.18-4.66) | 4.31 (2.27-8.17) | 5.70 (2.41-13.46) |
| HR* | 1.45 (0.61-3.42) | 3.46 (1.68-7.10) | 15.33 (4.01-58.56) | 1.45 (0.78-2.69) | 1.67 (0.72-3.86) | 2.97 (0.73-12.06) |
| **Male X-sect** | | | | | | |
| All | 2.10 (1.46-3.00) | 3.32 (2.05-5.37) | 6.75 (3.49-13.07) | 2.64 (2.03-3.42) | 3.29 (1.99-5.42) | 4.85 (3.25-7.24) |
| HR* | 1.12 (0.49-2.53) | 1.43 (0.92-2.23) | 2.03 (1.23-3.35) | 1.21 (0.66-2.20) | 1.77 (1.07-2.92) | 1.65 (1.11-2.46) |
| **Male Cohort** | | | | | | |
| All | 2.39 (1.21-4.71) | 3.74 (1.90-7.39) | 11.82 (4.01-34.81) | 2.80 (1.73-4.53) | 4.31 (2.27-8.17) | 5.58 (2.36-13.20) |
| HR* | 1.11 (0.51-2.41) | 1.52 (0.74-3.13) | 2.64 (0.83-8.41) | 1.16 (0.31-4.35) | 2.03 (1.26-3.29) | 1.57 (0.79-3.10) |

* HR (high risk), in this context, represents males engaged in one-off sexual contacts and females with current casual partners.

however, pursued since numbers were small and statistical tests for interaction lack power.

### 5.3.6 DURATION OVER WHICH A HISTORY OF STDs IS RECORDED

Throughout this chapter a one-year history of STDs has been considered. It is important, however, to look at the effect of duration over which a history of STDs is recorded on associations between HIV and other STDs.

Positive associations between HIV and other STDs recorded from follow-up studies have provided the strongest evidence supporting the hypothesis that STDs enhance HIV transmission. However it is clear here that OR estimates do not necessarily provide good estimates of true cofactor effects. For very different scenarios for true cofactor effects, simulated OR estimates from individual studies may overlap widely. But how does the period over which a history of STDs is recorded influence the results? This is perhaps also best explained via an example.

Let us consider just one STD circulating in a population. Suppose there is no enhancing effect of this STD on HIV transmission, and that there is no heterogeneity in sexual behaviour or frequency of sexual contact. Then, on average, the OR for the association between HIV and a history of STD episodes would be one irrespective of whether a history of STDs was recorded over one week or ten years. That is, individuals with and without a history of STDs would be equally likely to have acquired HIV infection over the period. Of course, in practise, a history of STDs is usually a marker for sexual activity and so we would expect proportionately more HIV infections in the group with a history of STDs. This would give rise to positively confounded ORs.

Now assume that the true STD cofactor effect is 100 per sexual contact and that there is no heterogeneity in sexual behaviour or frequency of sexual contact. In this case the period over which a history of STDs is recorded is critically important for our understanding of the relationship between the cofactor effect and observed associations. If HIV transmission from a single sexual contact with a seropositive partner could be accurately determined then, on average, we would find the risk of HIV infection to be 100 times greater for a single sexual

contact in the presence of an STD episode.

However, such a study is very difficult to implement. The main problems are: (1) to know that individuals in the study sample are truly uninfected prior to the sexual contact; and (2) to be able to attribute incident HIV infections to this particular single sexual contact. The reason that these issues prove problematic is that HIV antibody tests can not normally accurately detect HIV infection until at least three months have elapsed since the time of exposure. Thus for an HIV test result to be reliably negative at least three months need to have elapsed since the last sexual contact. Similarly if sexual contacts are then protracted over weeks or months, rather than just a single sexual contact, then, when a second test is carried out about three months later, it would not be clear that infections had arisen from one particular contact. There are of course other problems, including ascertaining the type of STDs (if any) present at the time of sexual contact.

In practise cross-sectional and follow-up studies are carried out to assess risk of HIV infection among people with and without a history of STD episodes over usually a 6-month or 1-year period. In this case only a few, if any, sexual contacts for any individual over this period are likely to be in the presence of STDs and it is only in these contacts that transmission of HIV is enhanced (assuming a true STD cofactor effect). Thus the observed association reflects a dilution of the per contact cofactor effect, which depends on the duration of the STD episodes, the number of STD episodes, and the duration of the period in which a history of STDs is recorded. In theory the shorter the observation period the more likely we should be able to detect true cofactor effects.

By making a few simple assumptions, a probabilistic model can be used to illustrate the relationship between per contact cofactor effects and observed associations. Let us assume that the probability of HIV transmission per sexual contact in the absence of the STD, p, is 0.001 (*Robinson et al 1994*). Let us also assume that individuals experience only one STD episode during any observation period, that duration the average duration of an STD episode is 2 weeks and on average an individual has two sexual contacts a week with an infected partner. Then the probability that an individual becomes infected with HIV in the absence of any STD episodes over the observation period can be described as: $P_c = 1-(1-p)^c$, where c is the total number of sexual contacts in the absence of STDs during this period.

Similarly the probability that an individual with a history of an STD episode becomes infected with HIV over the observation period is: $P_+ = 1-((1-p)^c(1-fp)^k)$, where f is the STD cofactor effect and k is the number of sexual contacts in the presence of STDs. Dividing $P_+$ by $P_-$ gives the relative risk of HIV infection.

Table 5.11 shows the results of applying this probability model to different observation periods for different assumed STD cofactor effects. For the no cofactor scenario risk ratios are always one. For an STD cofactor effect of 10 the relative risk declines from 5.4 to 1.3 as the duration over which STDs are recorded increases from four weeks to one year. For an STD cofactor effect of 100 the relative risk declines from 43.3 to 4.1 as the follow-up period increases from four weeks to one year. These relative risks of 1.0, 1.3 and 4.1 for a follow-up period of one year are consistent with OR estimates in high risk males for the no, low and high cofactor scenarios respectively (table 5.1).

The inability to detect the magnitude of per contact STD cofactor effects is likely to be due to the relatively long observation time compared with the duration of an STD episode.

### 5.3.7 HIV ENHANCING OTHER STDs

SimulAIDS allows for STDs to enhance the transmission of HIV. There is now also evidence to suggest that HIV infection can increase susceptibility to STDs, and also affect the clinical expression of STDs given infection (*Wasserheit 1992*). This is a consequence of an individual's weakened immune system as a result of HIV infection. If this is so then one might expect stronger associations than those simulated (especially in cross-sectional studies) since the proportion of HIV infected people with a history of STDs would probably increase.

### 5.3.8 SUMMARY

Focusing on high risk males, which best reflect empirical study samples, simulated associations for the no cofactor scenario were rather lower than those published, with results most consistent with the high cofactor scenario. Observed associations between HIV and

## Table 5.11 Risk of HIV infection by duration of recorded history of STD

| | Period over which history of STDs are recorded | | | | |
|---|---|---|---|---|---|
| | 1/2 week (1 contact) | 4-weeks (8 contacts) | 3-months (26 contacts) | 6-months (52 contacts) | 1-year (104 contacts) |
| Risk of HIV infection for no STD history | 0.001 | 0.0080 | 0.026 | 0.051 | 0.099 |
| Risk of HIV infection for STD history with cofactor effect: | | | | | |
| 1 | 0.001 | 0.0080 | 0.026 | 0.051 | 0.099 |
| 10 | 0.01 | 0.043 | 0.060 | 0.084 | 0.131 |
| 100 | 0.1 | 0.347 | 0.358 | 0.375 | 0.406 |
| RR of HIV infection with cofactor effect: | | | | | |
| 1 | 1 | 1 | 1 | 1 | 1 |
| 10 | 10 | 5.4 | 2.3 | 1.7 | 1.3 |
| 100 | 100 | 43.3 | 13.8 | 7.3 | 4.1 |

other STDs principally reflect a weighted average of the cofactor effect (over a relatively short duration of an STD episode) and the no cofactor effect (over a relatively long duration).

There are many other complex issues governing observed associations between HIV infection and other STDs. The most important seem to concern the positive confounding of sexual behaviour, both positive and negative confounding of STDs on one another (the extent of which will depend on prevalence levels of other STDs), misclassification of STDs, and type of study design, sample drawn and analyses carried out.

CHAPTER 6

# ESTIMATING THE PROPORTION OF HIV INFECTIONS ATTRIBUTABLE TO OTHER STDs

# 6. ESTIMATING THE PROPORTION OF HIV INFECTIONS ATTRIBUTABLE TO OTHER STDs

The objective was to assess the proportion of HIV infections attributable to other STDs using population attributable fractions (PAFs).

## 6.1 METHODS

Why does HIV spread so much more rapidly and extensively in some populations than others? This question is fundamental to our understanding of the dynamics of HIV transmission, and subsequently to the control of the spread of HIV infection. Many characteristics of populations are likely to play some part in the way HIV spreads, but are there one or two overriding factors? Sexual behaviour mixing patterns and sexual practises have, in theoretical exercises, been shown to be particularly important in determining the spread of infection (*Anderson et al 1991*, *Robinson et al 1993c*). In sub-Saharan Africa high levels of other STDs have consistently been documented (*Over and Piot 1991*). It is widely believed that other STDs may also contribute substantially to the spread of infection, and could play a major role in explaining the different rates and extent of spread of infection in different populations.

This chapter investigates the role that other STDs may play in the spread of HIV infection. Simulated scenarios described in chapter 4 are employed to address this. Under the assumption that other STDs do enhance the transmission of HIV infection, three questions are considered of particular interest. Firstly, if there were no other STDs circulating in this population, how would HIV have spread during the years immediately following its introduction, ie how much of infection to date is attributable to other STDs? Secondly, given that an epidemic is already established and widespread, what role are other STDs likely to play in the future transmission of HIV, ie what proportion of new infections from today will be attributable to other STDs? Thirdly, and related to the first two, how does the proportion of HIV infections attributable to other STDs depend on the phase of the epidemic?

The population attributable fraction (PAF) is an epidemiologic measure that has been used

to address these questions. *Last (1988)* defines the PAF in the following way. "With a given outcome, exposure factor, and population, the attributable fraction among the population is the proportion by which the incidence rate of the outcome in the entire population would be reduced if exposure were eliminated. It may be estimated using the formula: PAF = ($I_p$ - $I_u$) / $I_p$, where $I_p$ is the incidence rate in the total population and $I_u$ is the incidence rate among the unexposed. It is assumed that causes other than the one under investigation have had equal effects on the exposed and unexposed groups."

In this context, PAFs are rather difficult to estimate directly from empirical studies, since this requires information on the incidence of HIV infection in a population when other STDs are removed, and all else remains unchanged.

This simulation exercise, however, provides a very useful tool to examine the role that STDs may play in the spread of HIV infection. By setting up a theoretical controlled experiment, the spread of infection can be simulated both with and without STD cofactor effects operative, with all other factors remaining unchanged. With regard to the contribution that other STDs make to HIV transmission, this is identical to assuming that STDs are either present or absent in the population.

For this exercise, runs for each scenario were replicated ten times from a single recorded population and results expressed as averages of these replications.

### 6.1.1 PAFs FOR CUMULATIVE HIV INFECTIONS TO 1990

To address the question of what proportion of all HIV infections in the first ten years were attributable to other STDs, the spread of HIV infection was simulated from its introduction both with and without STD cofactor effects operative. This gives rise to four different scenarios representing: no STD cofactor effects; STD cofactor effects for ulcerative STDs only; STD cofactor effects for non-ulcerative STDs only; and STD cofactor effects for both ulcerative and non-ulcerative STDs.

PAFs associated with non-ulcerative STDs were then assessed by comparing the mean

cumulative number of adult HIV incident cases for the scenario with both cofactor effects operative with the mean number of incident cases for the scenario with only ulcerative STD cofactor effects operative. The difference represents the estimated number of cases that would additionally have been generated had cofactor effects for non-ulcerative STDs been operative. PAFs associated with ulcerative STDs and both STDs were similarly assessed using the scenarios with only non-ulcerative STD cofactor effects operative and no STD cofactor effects operative respectively, instead of the scenario with only ulcerative STD cofactor effects operative.

Confidence intervals for PAFs were derived using the log(-log) transformation (often referred to as the complementary log-log transformation). In this way, limits for confidence intervals were bound by 0% and 100%.

Define $$\hat{PAF} = \frac{\bar{y} - \bar{x}}{\bar{y}} = 1 - \frac{\bar{x}}{\bar{y}},$$

where $\bar{y}$ represents the mean cumulative number of HIV infections, assuming STD cofactor effects are operative for both ulcerative and non-ulcerative STDs, and $\bar{x}$ represents the mean cumulative number of infections, assuming either no STD cofactor effects are operative, or one or other of ulcerative or non-ulcerative STD cofactor effects are operative.

Then $$1 - \hat{PAF} = \frac{\bar{x}}{\bar{y}}.$$

Let $$\text{Var}\,[\log\,[-\log\,(1 - \hat{PAF})]] = \text{Var}\,[\log z],$$

where $$z = -\log\,[1 - \hat{PAF}] = -\log\,[\frac{\bar{x}}{\bar{y}}].$$

Then $$\text{Var}\,[\log\,[-\log\,(1 - \hat{PAF})]] = \frac{\text{Var}\,(z)}{z^2},$$

since $\text{Var}\ [f(z)] = [f'(z)]^2 * \text{Var}\ (z)$ .

But $\text{Var}\ (z) = \text{Var}\ [-\log(\bar{x}) + \log(\bar{y})]$

$= \text{Var}\ [\log(\bar{x})] + \text{Var}\ [\log(\bar{y})]$ ,

since $\bar{x}$ and $\bar{y}$ are independent,

And so $\text{Var}\ (z) = \frac{\text{Var}\ (\bar{x})}{\bar{x}^2} + \frac{\text{Var}\ (\bar{y})}{\bar{y}^2}$ ,

where $\text{Var}\ (\bar{x}) = \frac{s_x^2}{n_x}$

and $\text{Var}\ (\bar{y}) = \frac{s_y^2}{n_y}$

Thus Var [log [-log (1 - PAF)]] was estimated from sample means and variances for $n_x = n_y = 10$, and approximate 95% confidence intervals for log [-log (1 - PAF)] were calculated as: $\log [-\log (1 - \hat{PAF})] \pm 2 * \sqrt{\text{Var}\ [\log [-\log (1 - \hat{PAF})]]}$ . Confidence intervals for PAFs were then found by taking anti-logs.

### 6.1.2 PAFS FOR CUMULATIVE HIV INFECTIONS FROM 1990

For estimating the proportion of HIV infections attributable to other STDs after 1990, the spread of HIV infection from recorded populations in 1990 was simulated both with and without STD cofactor effects operative, and the number of cumulative infections was compared both 5 and 10 years later. PAFs were again estimated from the mean of ten runs and 95% confidence intervals calculated.

### 6.1.3 RELATIONSHIP BETWEEN PAFS AND STAGE OF EPIDEMIC

The third issue was to investigate the relationship between the proportion of incident infections attributable to other STDs and the stage of the epidemic. It has, for example, been hypothesized that STDs are likely to play a more important role in seeding an epidemic than in maintaining one. This would be supported if PAFs were larger in the earlier stages of the epidemic. This was addressed by running simulations for just one year both with and without STD cofactor effects operative from the introduction of HIV, and for one year from populations recorded 10 and 20 years after introduction of HIV (with cofactor effects operative up to these one year periods). PAFs were calculated as previously by comparing the mean number of infections generated both with and without the respective cofactor effects operative.

## 6.2 RESULTS

### 6.2.1 PAFs FOR CUMULATIVE HIV INFECTIONS TO 1990

Table 6.1 presents results for PAFs estimating the proportion of all adult HIV incident cases in the ten years to 1990 that were found to be attributed to non-ulcerative STDs, ulcerative STDs and both STDs. PAFs are given with 95% confidence intervals for the two different STD scenarios.

For both scenarios it is clear that ulcerative STDs contributed substantially to the spread of HIV infection over the initial ten years. Even for the low STD cofactor scenario, over 80% of new infections were found to be attributable to ulcerative STDs. This includes infections both directly and indirectly acquired, ie all subsequent infections, including all infections generated from a person who acquired HIV in the presence of other STDs. For the high cofactor scenario, over 95% of infections were attributed to ulcerative STDs.

As illustrated in figures 6.1 and 6.2 for the low and high cofactor scenarios respectively, mean prevalence levels for HIV infection were much lower in 1990 in the absence of ulcerative STDs, but only slightly lower in the absence of non-ulcerative STDs. For the high cofactor scenario and in the absence of both STDs, HIV infection remained at very low levels, if it was maintained at all.

The contribution made by non-ulcerative STDs was, at under 10%, relatively small.

### 6.2.2 PAFs FOR CUMULATIVE HIV INFECTIONS FROM 1990

Table 6.2 gives estimates of the proportion of new HIV infections, in both the 5 and 10 year periods from 1990, that were attributed to other STDs. PAFs are given with 95% confidence intervals for the two different STD scenarios.

The difference in PAFs between the five and ten year estimates was relatively small, with PAFs generally larger for ten year simulations. This seems reasonable since by averting

## Table 6.1 PAFs (%) for cumulative HIV infections to 1990

| STD cofactor scenarios | Non-ulcerative STDs | Ulcerative STDs | Both STDs |
|---|---|---|---|
| Low | 9 (3-24) | 83 (77-88) | 93 (91-95) |
| High | 2 (0-87) | 97 (95-99) | 100 (99-100) |

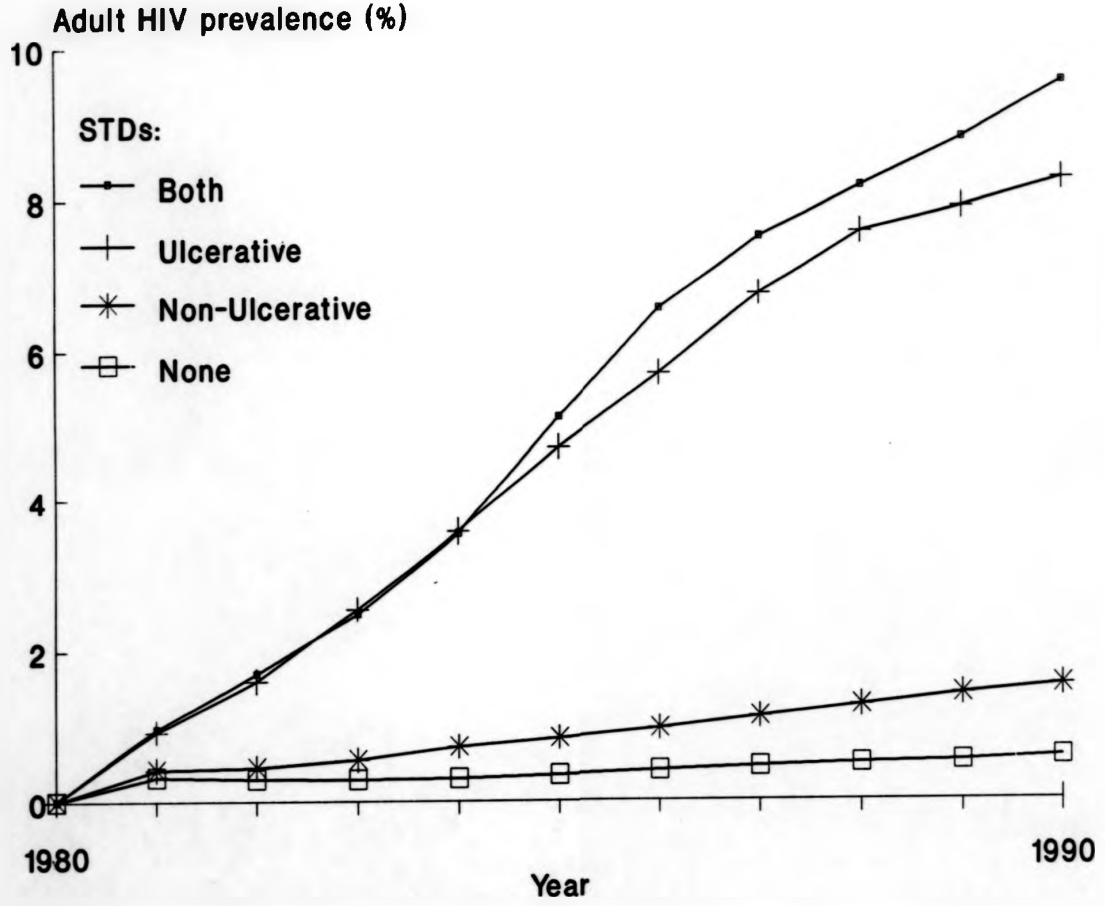



Figure 6.1 Mean HIV prevalence levels (10 replications) in the presence and absence of other STDs (low cofactor scenario)

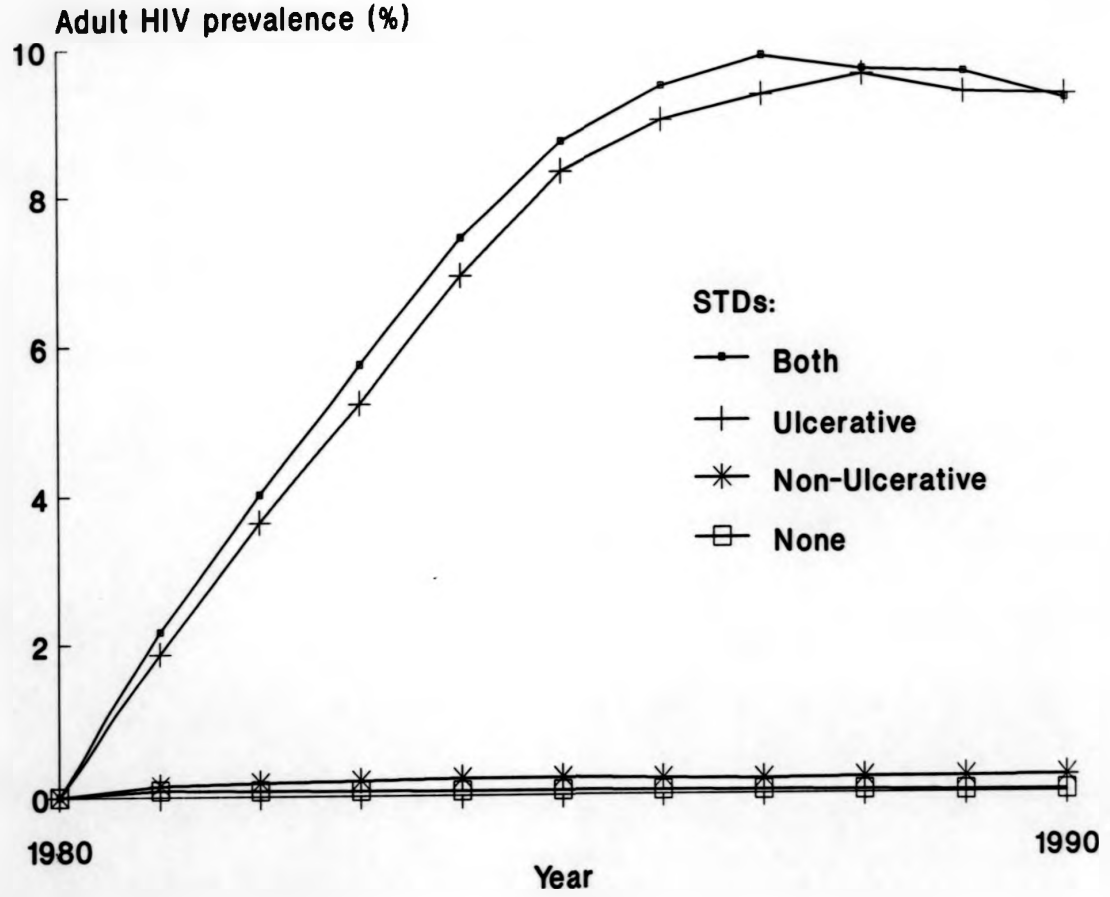



Figure 6.2 Mean HIV prevalence levels (10 replications) in the presence and absence of other STDs (high cofactor scenario)

## Table 6.2 PAFs (%) for cumulative HIV infections from 1990

| STD cofactor scenarios | Non-ulcerative STDs | Ulcerative STDs | Both STDs |
|---|---|---|---|
| Low | | | |
| 5 years from baseline | 5 (2-14) | 23 (19-26) | 30 (26-33) |
| 10 years from baseline | 6 (2-16) | 28 (24-33) | 38 (34-42) |
| High | | | |
| 5 years from baseline | 12 (5-25) | 71 (68-74) | 78 (75-80) |
| 10 years from baseline | 6 (1-25) | 77 (75-79) | 83 (81-85) |

primary infections, this also indirectly averts all subsequent infections arising from these source cases. Thus PAFs will increase over longer observational periods. If, in the extreme case, HIV is eventually removed from the population by removing other STDs (but would have remained otherwise), then the PAF would tend to 100%.

For the low cofactor scenario, about 20% of all new infections were found to be attributed to ulcerative STDs in the five years from 1990. For this scenario, this suggests that when HIV infection becomes widespread in the population, the contribution that ulcerative STDs make in generating new infections may be relatively small. Similarly for non-ulcerative STDs which were found to contribute to about 5% of new infections. For the high cofactor scenario ulcerative STDs still appear to play a very important role, with about 70% of new infections attributed to ulcerative STDs in the five years from baseline.

The implications of these results for STD control activities are important. The results suggest that, at these HIV prevalence levels, the effect of STD interventions in preventing HIV infections will depend on the real STD cofactor effects.

### 6.2.3 RELATIONSHIP BETWEEN PAFs AND STAGE OF EPIDEMIC

Table 6.3 gives PAFs for the proportion of adult HIV incident cases in a one year period, at various time points after the introduction of HIV. The proportion of infections attributable to non-ulcerative STDs is less than that for ulcerative STDs at all time points.

The most striking feature of the table is the generally declining PAFs with time since introduction of HIV. The proportion of new infections attributable to ulcerative STDs in a one year period is considerably greater in the first year of the epidemic than ten years on. Similarly PAFs are larger 10 years after introduction of HIV than 10 years later.

The wide confidence intervals for non-ulcerative STDs (and in particular at year one), reflect the generally small number of incident infections generated in a one year period in the absence of enhancing effects of ulcerative STDs, together with a striking stochastic element especially in the early phase of the epidemic.

Table 6.3 Relationship between PAFs (%) and stage of epidemic

| STD cofactor scenarios | Non-ulcerative STDs | Ulcerative STDs | Both STDs |
|---|---|---|---|
| Low | | | |
| Year 1 | 17 (1-99) | 68 (52-83) | 86 (78-92) |
| Year 11 | 10 (4-20) | 22 (16-31) | 29 (23-36) |
| Year 21 | 3 (1-12) | 16 (13-20) | 17 (12-23) |
| High | | | |
| Year 1 | 4 (0-100) | 95 (92-98) | 100 (98-100) |
| Year 11 | 15 (4-50) | 71 (66-75) | 81 (77-85) |
| Year 21 | 4 (0-57) | 51 (47-55) | 58 (55-62) |

## 6.3 DISCUSSION

To date many studies have demonstrated observed associations between HIV and other STDs, and some have concluded that STDs probably do enhance the transmission of HIV (*Cameron et al 1989, Plummer et al 1991b, Laga et al 1993*). However, very few have attempted to quantify the proportion of infections that may be attributable to other STDs (*Hunter 1993, Hayes et al 1994*). It is possible that both ulcerative and non-ulcerative STDs could contribute substantially to the spread of infection. Although STD cofactor effects are generally thought to be smaller for non-ulcerative STDs, their contribution in terms of total number of attributable infections may be substantial, since prevalence levels are often high.

### 6.3.1 PAFs FOR CUMULATIVE INFECTIONS TO 1990

In these simulated scenarios STDs play a very major role in initiating the spread of HIV infection. Even though prevalence of ulcerative STDs in 1990 among adults was not especially high at about 0.5%, their contribution to the spread of infection was substantial. Even for the low cofactor scenario over 80% of infections over the next decade were attributed, both directly and indirectly, to the presence of ulcerative STDs. In their absence, levels of HIV infection at baseline remained low.

The implications are important, for this would suggest that other STDs could almost entirely explain the rapid and widespread transmission of HIV infection in the population. This exercise demonstrates that it is plausible that other STDs could have played a critical role in the spread of HIV infection.

It has been suggested that just by including dynamic STDs in the modelling process, this must obviously make STDs important in the spread of HIV infection. This is certainly not so. At prevalence levels generated for ulcerative STDs it was not at all evident that over 80% of infections by 1990 would be found to be attributed to ulcerative STDs.

### 6.3.2 PAFs FOR CUMULATIVE INFECTIONS FROM 1990

The contribution that other STDs play in generating incident HIV infections once HIV has become established and levels have reached an endemic phase is also an important question. Perhaps most striking was that, for the low cofactor scenario, STDs played a relatively minor role in maintaining HIV infection. About 30% of all new infections in the 5 year period after baseline were attributed to other STDs, and less than 40% in the 10 years from baseline. For the high cofactor scenario other STDs do still play a critical role in maintaining HIV infection. About 80% of infections in the 5 years following baseline were attributed to other STDs. Again for these scenarios non-ulcerative STDs were found to play a relatively minor role. If true cofactor effects are closer to those represented by the low scenario, even if STDs were eliminated today, levels of HIV would still remain high over the following decade. This is the consequence of intervening only when the epidemic is already established and HIV infection already widespread.

PAFs give us a feel for the total disease burden attributed to other STDs. In practice it is highly unlikely that other STDs would be eliminated from the population, but these figures do give an upper bound for the proportion of infections that may be averted if STD control were introduced (see chapter 7).

### 6.3.3 RELATIONSHIP BETWEEN PAFs AND STAGE OF EPIDEMIC

By investigating the proportion of HIV infections attributable to other STDs in a one year time period at various points in the epidemic, it was clear that STDs contribute more to the spread of HIV infection in the earlier stages of the epidemic than later on, when HIV becomes more established. The message for STD control is again clear. Many more infections may be averted if STD control programmes are introduced at the earliest possible time. Note that the small decrease in STD prevalence levels after introduction of HIV (table 4.5) will have a small contributing effect to the decline of PAFs with time since introduction of HIV.

### 6.3.4 SUMMARY

Three questions of particular interest have been raised here. For each of them other STDs do make a substantial contribution to the spread of HIV infection. The contributions made, however, depend on the particular question of interest. In all cases, even though non-ulcerative STDs are more prevalent than ulcerative STDs, their contribution was found to be considerably smaller. This is a feature of the particular scenarios employed. If cofactor effects for non-ulcerative STDs had been assumed higher and/or the prevalence of non-ulcerative STDs had been assumed higher then their contribution would have been greater.

In the study population the prevalence of non-ulcerative STDs was observed to be roughly two times that of ulcerative STDs (*Wagner et al 1993*). In other populations this may be higher, and in some cases considerably so. Assuming higher cofactor effects for non-ulcerative STDs may also be reasonable. A recent follow-up study investigating associations between HIV and other STDs has demonstrated relatively strong associations with non-ulcerative STDs compared with earlier cross-sectional and case-control studies, which tended to show little, if any, association (*Laga et al 1993*). This lack of association in non-prospective studies may be explained by misclassification (see chapter 5), since many individuals with a history of non-ulcerative STDs may not have reported them. This might have resulted from non-ulcerative STDs being truly asymptomatic and therefore having passed unnoticed, or that the symptoms present in an individual were common and painless and not associated with "an STD", or that in the presence of concurrent ulcerative STDs they were not recognised. In all these cases the result would be a dilution of observed associations.

What is there to gain by introducing intervention measures as early as possible? In the extreme case when other STDs are removed altogether prior to the introduction of HIV, it was shown that HIV epidemics were substantially smaller. In some cases, an epidemic failed to take place at all since HIV never became established in the population. This is the optimal hypothetical scenario, and in practice is, of course, very difficult to implement and maintain.

The knowledge that HIV epidemics would almost certainly be smaller, and may be averted

altogether, if action was taken to control other STDs even before HIV infection had been acknowledged in a community, should strengthen our resolve to find resources to undertake and implement STD control programmes in all populations, not only those in which infection is already established. The sad reality however is that in many parts of sub-Saharan Africa (and now an increasing, but as yet still small, number of places in Asia), the situation is now not "how to avert an epidemic" but "how to control the further spread of HIV infection once it has become established".

CHAPTER 7

# SIMULATING INTERVENTION PROGRAMMES

# 7. SIMULATING INTERVENTION PROGRAMMES

The objective was to assess the impact of simulated interventions on the incidence of HIV infection after 1990.

## 7.1 METHODS

To model the effect of interventions, simulations were run for 10 years from one chosen baseline population for each cofactor scenario, ie from 1990 to 2000. For each simulated intervention, 10 runs were generated and results have been presented as arithmetic means of these repetitions.

The effect of various interventions on HIV incidence have been assessed. Simulated interventions include STD treatment programmes, improved condom use, modifications in sexual behaviour and combinations of these. The effect both of interventions targeted at specific core groups, and of those applied to the general population have been examined. All simulated interventions have been introduced at one time point, namely 1990. Note that for the no cofactor scenario simulated STD interventions clearly have no effect in reducing HIV incidence.

### 7.1.1 NO INTERVENTIONS

Simulations were continued for ten years for the no, low, and high cofactor scenarios to assess model projections in the absence of any specific interventions.

### 7.1.2 STD INTERVENTIONS

Interventions designed to improve the diagnosis and treatment of STDs were simulated by assuming:

50% or 100% of all STD episodes in males and females had their duration reduced by 50%.

Similar STD intervention scenarios were also generated for the core group of females with only one-off sexual partners.

### 7.1.3 (MALE) CONDOM INTERVENTIONS

It is clear, even without application of complex models, that the widespread and regular use of condoms would have a substantial effect on reducing HIV incidence levels. This, however, is likely to be infeasible at present and thus this exercise principally seeks to explore the likely impact of focused condom use in only one-off sexual contacts. In a rural population, where HIV infection is already established and widespread, this is unclear.

In SimulAIDS condom use for one-off sexual contacts may be specified in various ways. This is perhaps best illustrated with an example. If, say, we wish to specify that 50% of one-off sexual contacts are protected by condom use, SimulAIDS can handle this in one of four distinct ways; that is: (1) 50% of males always use condoms with their one-off partners; (2) 50% of females always demand use of condoms with their one-off partners; (3) All males use condoms with probability 0.50 for each one-off sexual contact; and (4) All females demand use of condoms with probability 0.5 for each one-off sexual contact.

In the first two cases use of condoms by males or females will be referred to as a characteristic of the male or female. Thus if an individual has this characteristic they will always use (or, for females, demand use) of condoms. Examples (3) and (4) lie at the other extreme such that each one-off sexual contact is equally likely to be protected by condom use. In this case condom use will be referred to as being random.

Clearly reality is likely to lie somewhere between these two extremes of characteristic and random use of condoms, with a few individuals using condoms all the time, some occasionally, and others not at all (*Pickering et al 1993*).

Simulated interventions have assessed both characteristic and random use of condoms by males and females for one-off sexual contacts to assess the extreme cases.

The range of simulated interventions aimed at either males or females in one-off partnerships include:

25%, 50%, 75% or 100% of males always use condoms with their one-off partners;
25%, 50%, 75% or 100% of females always demand use of condoms with their one-off partners;
For one-off sexual contacts, all males use condoms with probability 0.25, 0.50, 0.75 or 1.0 for each sexual contact; and
For one-off sexual contacts, all females demand use of condoms with probability 0.25, 0.50, 0.75 or 1.0 for each sexual contact.

Simulated interventions were also generated both assuming males use condoms and females demand use of condoms with one-off partners. These included:

25% of males always use condoms and 25% females always demand use of condoms in one-off sexual contacts;
50% of males always use condoms and 50% females always demand use of condoms in one-off sexual contacts;

For one-off sexual contacts, all males use condoms with probability 0.25 and all females demand use of condoms with probability 0.25; and
For one-off sexual contacts, all males use condoms with probability 0.50 and all females demand use of condoms with probability 0.50.

In the text in sections 7.2 and 7.3, "females demand the use of condoms" is sometimes shortened to "females use condoms".

### 7.1.4 OTHER BEHAVIOURAL INTERVENTIONS

Assumed changes in other sexual behaviour characteristics have been assessed for their influence on HIV incidence. Simulated modifications in sexual behaviour have independently assessed:

A reduction by 50% or 100% in the proportion of males with one-off partners;
A reduction by 50% or 100% in the number of sexual contacts of males with one-off partners;
A reduction by 50% or 100% in the proportion of males with casual partners; and
A reduction by 50% or 100% in the number of sexual contacts of males with casual partners.

### 7.1.5 PACKAGE OF INTERVENTIONS

Scenarios were set up to look at the combined effect of: (1) increased condom use; (2) STD treatment; and (3) a reduction in both the proportion of males having one-off contacts and

in the average number of contacts with one-off partners. There are clearly a large number of possible combinations for simulated interventions and the examples below illustrate just one set of simulated combined interventions. Simulations were run from 1990 assuming:

25% of all STD episodes had their duration reduced by 50%, and 25% of males and females always used condoms with one-off partners, and the proportion of males with one-off partners was reduced by 25%, and the number of sexual contacts of males with one-off partners was reduced by 25%; and

50% of all STD episodes had their duration reduced by 50%, and 50% of males and females always used condoms with one-off partners, and the proportion of males with one-off partners was reduced by 50%, and the number of sexual contacts of males with one-off partners was reduced by 50%.

Scenarios were also set up to assess all combinations of the individual and combined effects of each of the three components of the full package of interventions at both the 25% and 50% level, ie $2^3$ intervention scenarios (including none and full package). The remaining six intervention scenarios have been referred to as part package interventions. Of these the STD and condom interventions are identical to those described in sections 7.1.2 and 7.1.3.

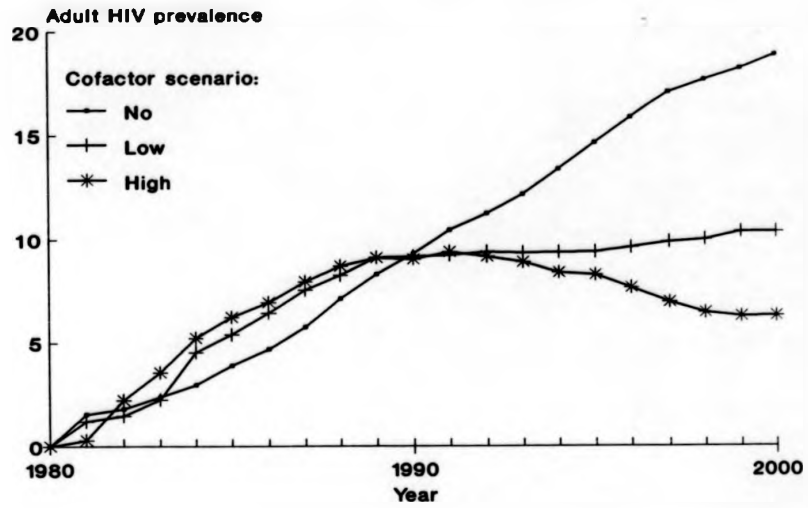
## 7.2 RESULTS

For each simulated intervention the mean annual HIV incidence from 10 runs has been presented graphically with time. Confidence intervals have not been given since number of events are generally small and intervals wide and overlapping. The mean number of 5 and 10 year cumulative HIV infections (and 95% CIs) for each simulated intervention have, however, been presented in table 7.1.

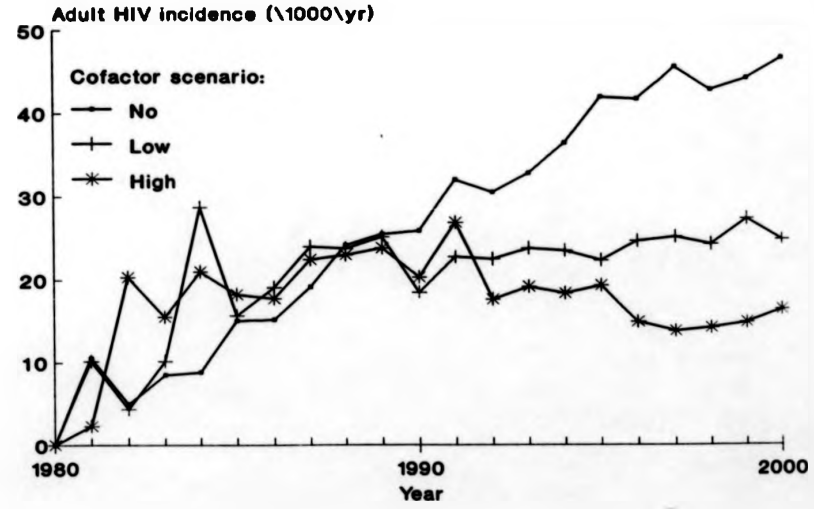
### 7.2.1 NO INTERVENTIONS

Figures 7.1a and 7.1b show results for HIV prevalence and incidence respectively from 1980 to 2000, assuming no simulated interventions for the three cofactor scenarios. Results to 1990 are those of single runs whereas from 1990 results are presented as the mean of ten runs. The results are striking in that HIV prevalence and incidence level off much earlier and at lower levels for both the low and high cofactor scenarios, compared with the no cofactor scenario. For all scenarios input parameter values were specified to give an average HIV prevalence of about 9.5% in adults in 1990. HIV prevalence levels peaked at about 10% by 1990 for the high cofactor scenario before declining slightly. HIV prevalence also peaked at about 10% for the low cofactor scenario, but was maintained at this level. These levels reflected an HIV incidence among adults of about 2%. For the no cofactor scenario HIV prevalence approached 20% by the year 2000, reflecting an incidence in the adult population of between 4% and 5%, and was still increasing. The mean number of cumulative HIV infections for the 10 years to 2000, in the absence of interventions for the no, low and high cofactor scenarios, were approximately 1780, 1110 and 770 respectively (table 7.1, page 197).

For the high cofactor scenario mean HIV incidence declined slightly after 1990, even in the absence of any specific intervention. This is a consequence of the rapid removal of the most sexually active males, without their immediate replacement. The increase in HIV incidence and prevalence from 1990 for the no cofactor scenario reflect the higher standard transmission probabilities assumed for the no cofactor scenario, which facilitate wider spread of HIV infection in the general population (and especially via casual partnerships). For the low and high cofactor scenarios standard HIV transmission probabilities are too low to




(a)




(b)

**Figure 7.1** Simulated projections for mean adult (a) HIV prevalence and (b) incidence, assuming no interventions for the no, low and high cofactor scenarios

generate rapid spread of HIV infection outside one-off partnerships, where other STDs have a relatively low incidence.

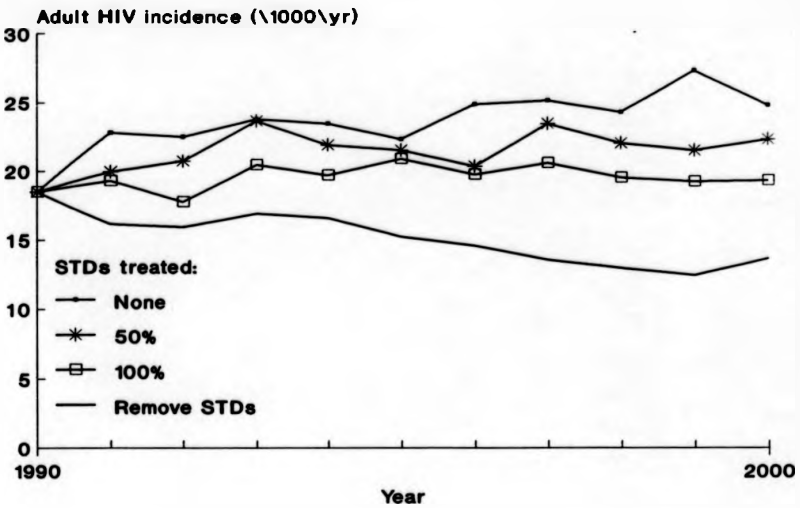
### 7.2.2 STD INTERVENTIONS

Figures 7.2a and 7.2b look at simulated STD treatment interventions, and the impact of reducing the duration of both ulcerative and non-ulcerative STD episodes in all males and females by 50% for the low and high cofactor scenarios respectively. For comparison, results representing the hypothetical removal of all STDs from the population are included.

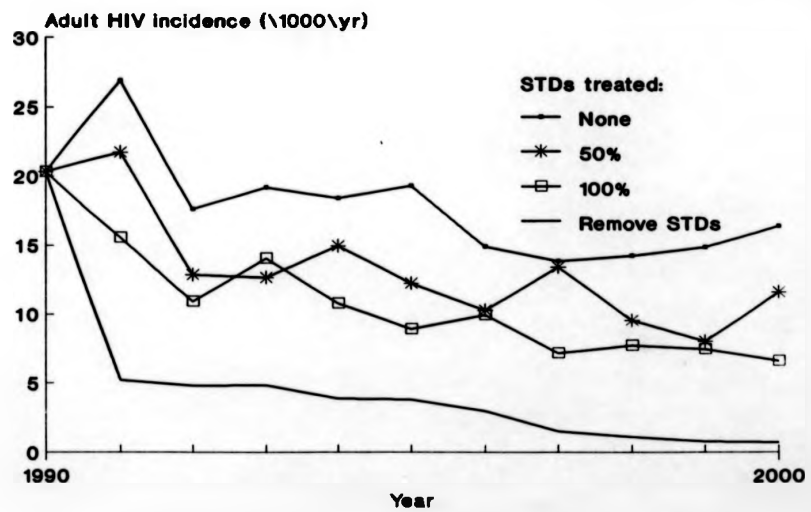
Figure 7.2a gives results for the low cofactor scenario assuming, after 1990, that 0%, 50% and 100% of all STD episodes were reduced by 50%. Compared with no intervention, assuming half of all STD episodes had their duration reduced by 50%, HIV incidence was reduced by about 10% by the year 2000. The widely overlapping confidence intervals for the cumulative number of incident infections in the 10 years from 1990 for no intervention [1112 (927-1297)] and 50% STD intervention [1004 (837-1171)] (table 7.1) suggest that, in this case, even by taking 10-year cumulative incidence in an adult population of about 5000, it would be difficult to detect differences in HIV incidence rates resulting from the effective intervention.

Figure 7.2b shows results for the same STD interventions as in figure 7.2a, but for the high cofactor scenario. In this case, the effect of the same intervention is stronger. Compared with no interventions, reducing the duration of half of all STD episodes by 50% results in about a 30% reduction in HIV incidence. The mean cumulative number of incident infections are reduced by a similar amount (table 7.1). The effect of removal of all STDs reflects the role that STDs play in maintaining HIV infection. In this case, in the absence of STDs, HIV may well not be maintained at all.

When it was assumed that STDs were still maintained at a minimum level of about 10% in females with one-off contacts, the impact of reducing the duration of STD episodes in only females with one-off contacts was negligible, since STD prevalence in this group was not reduced from 10%. The reduced duration in STD episodes therefore resulted in an




(a)




(b)

Figure 7.2 Simulated projections for mean adult HIV incidence, assuming the duration of all STD episodes is reduced by 50% in a specified proportion of cases for the (a) low, and (b) high cofactor scenarios

increased incidence of STDs.

When STD prevalence in females with one-off sexual contacts was allowed to be reduced to a minimum of about 2% then, by treating only this core group of females with one-off contacts, resulting levels of HIV incidence were similar to those for treating all STD episodes in the whole population.

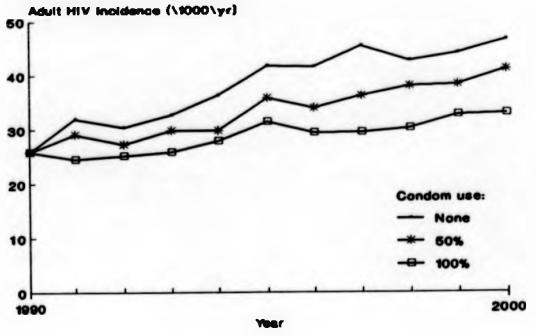
### 7.2.3 CONDOM INTERVENTIONS

For all simulated interventions the efficiency of condoms in preventing transmission of both HIV and other STDs has been assumed to be 100%.

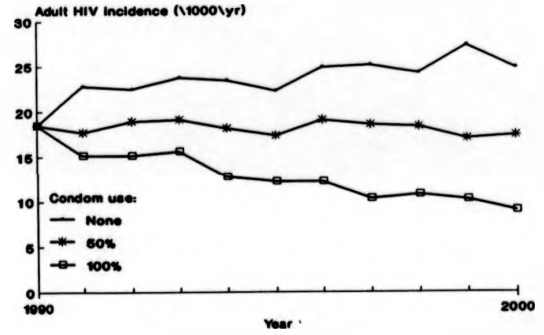
Figures 7.3a-c look at the impact of introducing condom use in only one-off sexual contacts for the no, low, and high cofactor scenarios respectively. They all show results assuming 0%, 50% and 100% of males always use condoms for all one-off sexual contacts. For 50% condom use HIV incidence was reduced by about 10%, 30% and 50% respectively by the year 2000. The 10-year cumulative proportion of HIV infections averted for each of these scenarios were approximately 13%, 26% and 40% respectively (table 7.1). For the no cofactor scenario, even when all transmission of HIV via one-off sexual contacts is ceased, HIV incidence still increases. Thus, in this case, once an epidemic is established, regular and casual partnerships must contribute substantially to the further spread of HIV infection.

Similar results to these for all three scenarios were obtained assuming 50% of all one-off contacts with males were protected by random use of condoms, and for both characteristic and random demand for use of condoms by females in one-off sexual contacts. This results from similar reductions in HIV incidence among females engaging in one-off sexual contacts for these different simulated interventions.

Simulations assuming characteristic condom use in both males and females engaging in one-off sexual contacts demonstrate the additional benefits associated with regular use of condoms by both a proportion of males and females. Figures 7.4a-c illustrate this for characteristic condom use in males and females. Results assuming 25% of characteristic




(a)

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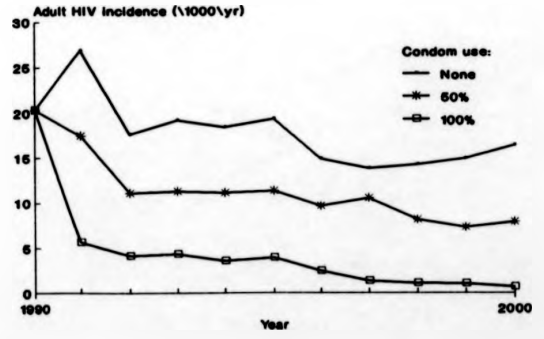
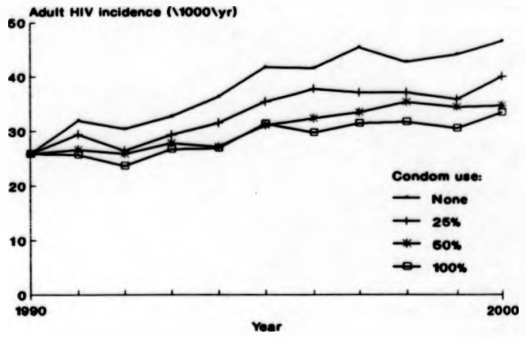
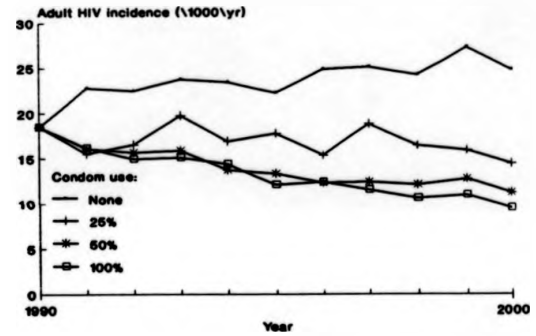



(c)

**Figure 7.3** **Simulated projections for mean adult HIV incidence, assuming a proportion of males always use condoms in one-off sexual contacts, for the (a) no, (b) low, and (c) high cofactor scenarios**




(a)

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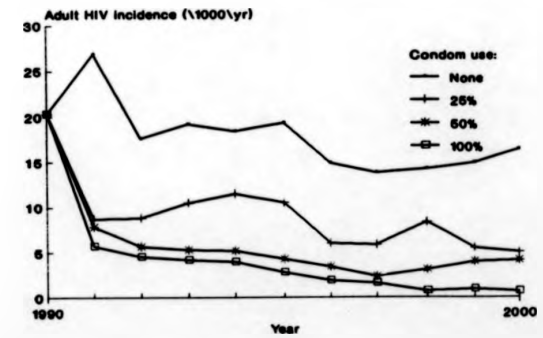



(c)

**Figure 7.4** Simulated projections for mean adult HIV incidence, assuming a proportion of males always use condoms and a proportion of females always demand use of condoms in one-off sexual contacts, for the (a) no, (b) low, and (c) high cofactor scenarios

condom use in both males and females are roughly equivalent to results assuming 50% condom use in either males or females, and results assuming 50% condom use in both males and females achieve a reduction in HIV incidence almost as effective as 100% use of condoms. This is not unexpected for independence of condom use in males and females since:

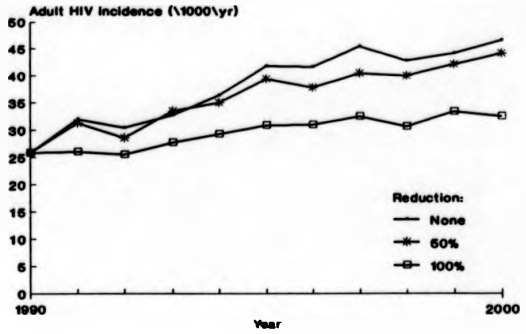
Prob (male or female uses a condom) = 1 - [prob (male does not use a condom) * prob (female does not use a condom)].

Similar results were obtained for random use of condoms among both males and females.

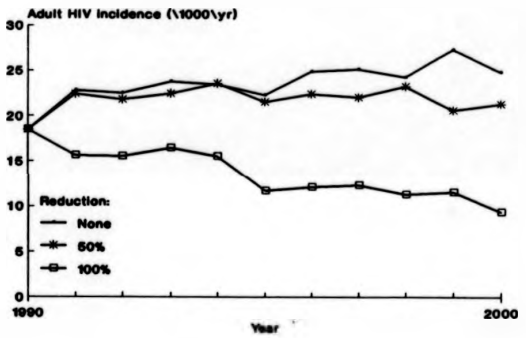
### 7.2.4 OTHER BEHAVIOURAL INTERVENTIONS

Scenarios reflecting other behavioural changes have focused on reducing proportions of males having one-off sexual contacts or casual partnerships, and reducing the number of sexual contacts with one-off or casual partners. Figures 7.5a-c show results assuming a reduction in the proportion of males having one-off sexual contacts for the no, low, and high cofactor scenarios respectively. Figures 7.6a-c show results assuming a reduction in the average frequency of one-off sexual contacts that males have. The most striking feature of these results is that the role of one-off sexual contacts clearly becomes more important for scenarios assuming higher STD cofactor effects. For the no cofactor scenario, even cessation of contacts with one-off partners does not result in declining levels of HIV incidence after 1990. For the high cofactor scenario, even a 50% reduction in the number of sexual contacts males have with one-off partners has a very dramatic influence on HIV incidence after 1990. In just two years HIV incidence in adults was reduced by, on average, 50% to about 1%.

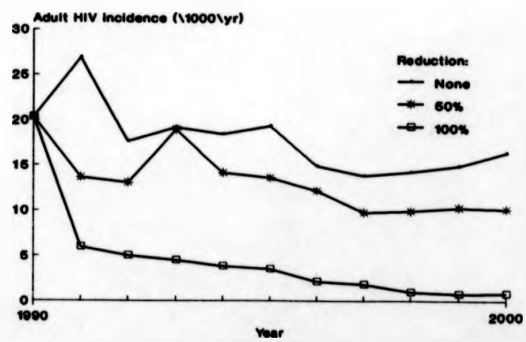
For all scenarios, results consistently showed that reducing number of contacts with one-off partners was more effective than reducing the proportion of males having one-off contacts. This is an important result and perhaps rather counter-intuitive. When the proportion of males in one-off contacts is reduced, the number of females engaged in one-off sexual contacts is also reduced since their average number of contacts with male partners is assumed to remain constant. This results in levels of HIV prevalence among males and females having one-off contacts remaining roughly constant. That there are fewer males and females engaging in one-off sexual contacts results in a reduction in HIV incidence levels




(a)

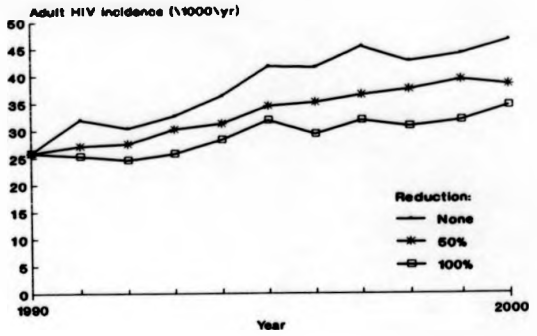



(b)

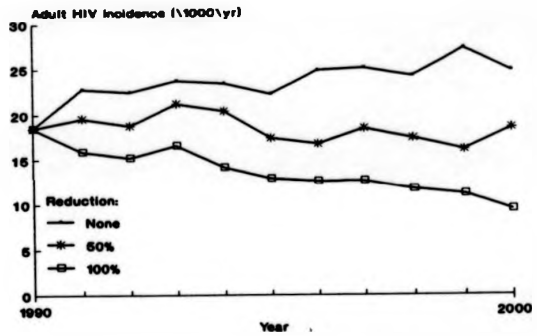



(c)

**Figure 7.5** Simulated projections for mean adult HIV incidence, assuming a reduction in the proportion of males engaging in one-off sexual contacts, for the (a) no, (b) low, and (c) high cofactor scenarios




(a)

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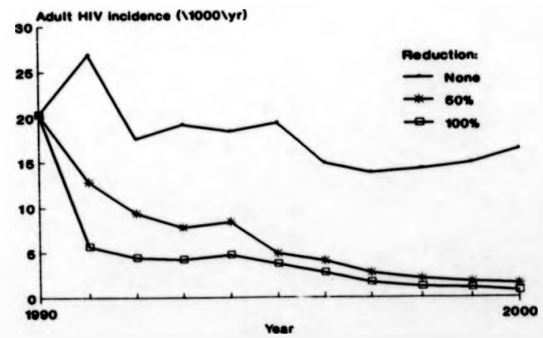



(c)

**Figure 7.6** Simulated projections for mean adult HIV incidence, assuming males reduce their frequency of one-off sexual contacts, for the (a) no, (b) low, and (c) high cofactor scenarios

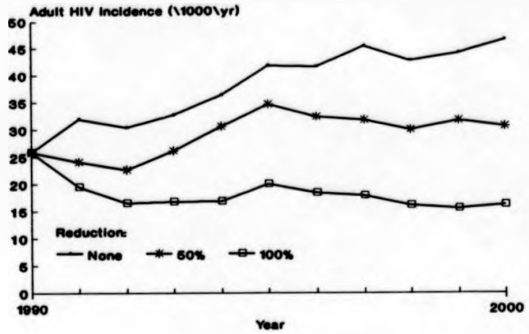
in the population. In contrast, by maintaining the proportion of males having one-off contacts and reducing their average frequency of contacts, the prevalence of HIV infection in this group of males is reduced, which consequently results in a reduction in HIV prevalence in females with one-off partners, which further leads to a reduction in HIV prevalence in males engaging in one-off sexual contacts, etc. This result is related to the cofactor scenario, with the difference more accentuated for the high cofactor scenario.

Figures 7.7a-c present results assuming a reduction in the proportion of males having casual partnerships for the no, low and high cofactor scenarios respectively, and figures 7.8a-c show results assuming a reduction in the average number of contacts with casual partners. It is clear that the role of casual partnerships is much more important than that of one-off sexual contacts for the no cofactor scenario. This, however, is reversed for the high cofactor scenario, where casual partnerships play a more minor role in the spread of HIV infection, due to much lower STD prevalence levels amongst casual than one-off partners.

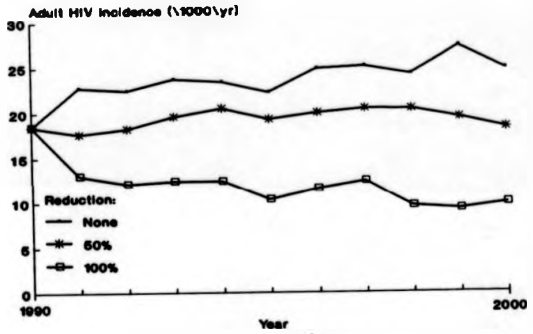
### 7.2.5 COMBINED INTERVENTIONS

Figures 7.9a-c present results for the full package of interventions described in 7.1.5. The results are again most striking for the high cofactor scenario, where even the package of interventions introduced at the 25% level has an immediate and dramatic effect on reduction of HIV incidence after 1990, with, on average, more than a halving of HIV incidence in the first year.

Figures 7.10a-c and 7.11a-c show results of part package interventions. Condom and behavioural interventions (focusing on one-off sexual contacts) were generally more successful in reducing HIV incidence levels than STD treatment interventions (aimed at the general population). In particular, interventions combining both STD and condom strategies were similar to those obtained for the condom only strategy, emphasising the important role that condoms can play in STD prevention programmes.




(a)

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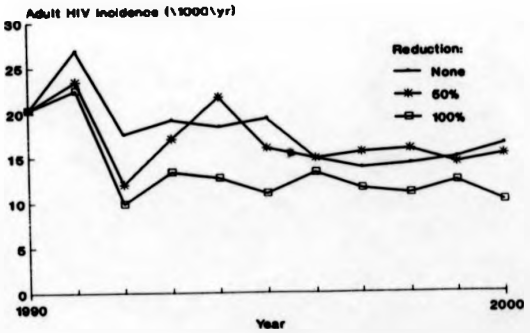
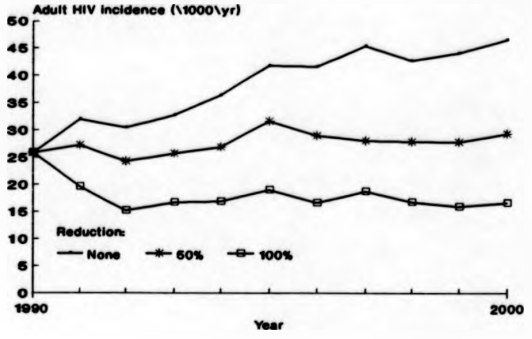
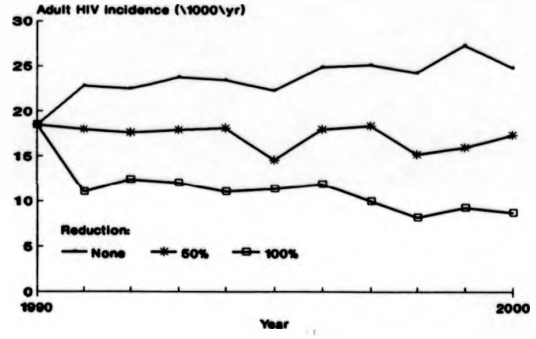



(c)

**Figure 7.7** Simulated projections for mean adult HIV incidence, assuming a reduction in the proportion of males engaging in casual partnerships, for the (a) no, (b) low, and (c) high cofactor scenarios




(a)

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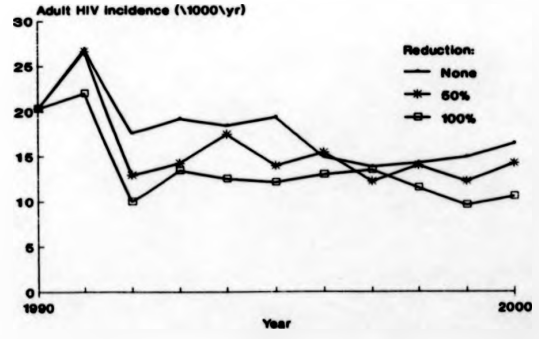
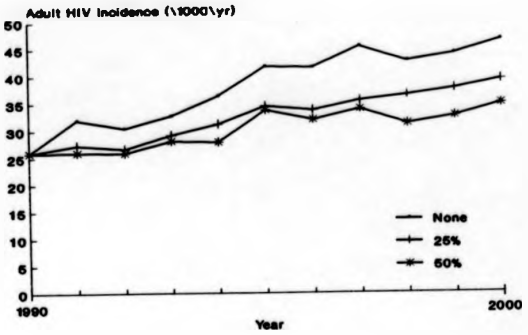
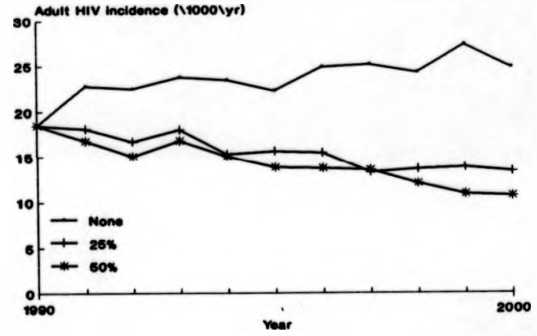



(c)

**Figure 7.8** Simulated projections for mean adult HIV incidence, assuming males reduce their frequency of contacts with casual partners, for the (a) no, (b) low, and (c) high cofactor scenarios




(a)

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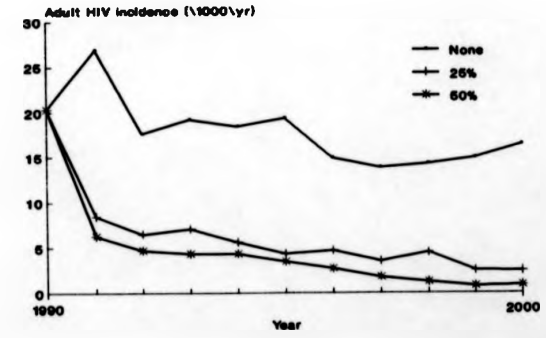


(c)

**Figure 7.9** Simulated projections for mean adult HIV incidence, assuming a full package of interventions, for the (a) no, (b) low, and (c) high cofactor scenarios

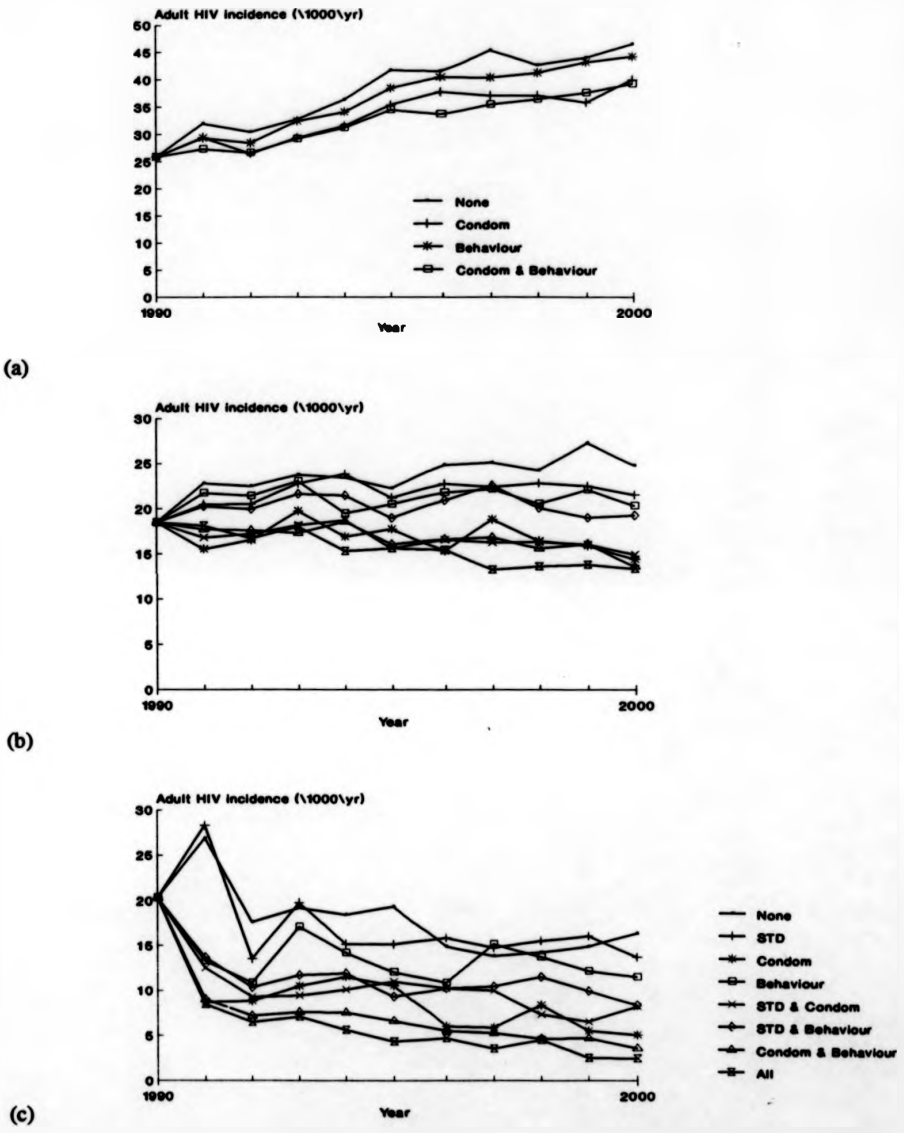


**Figure 7.10** Simulated projections for mean adult HIV incidence, assuming a part package of interventions at the 25% level, for the (a) no, (b) low, and (c) high cofactor scenarios

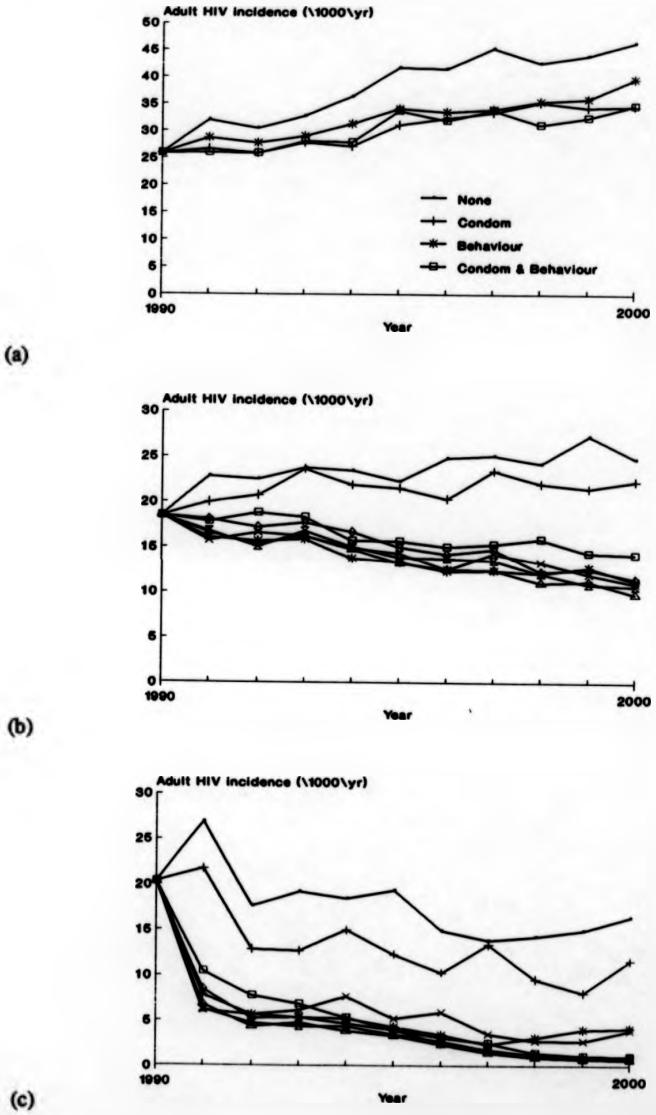


**Figure 7.11** Simulated projections for mean adult HIV incidence, assuming a part package of interventions at the 50% level, for the (a) no, (b) low, and (c) high cofactor scenarios

## Table 7.1 Mean number of cumulative HIV infections (95% CIs) after 5 and 10 year simulated interventions

| Cofactor scenario | NO | | LOW | | HIGH | |
|---|---|---|---|---|---|---|
| Years | 5 | 10 | 5 | 10 | 5 | 10 |
| Intervention | | | | | | |
| NONE *(fig 1)* | 811 (726-896) | 1780 (1652-1907) | 531 (469-594) | 1112 (927-1297) | 445 (349-540) | 769 (593-945) |
| STD TREATMENT *(fig 2)* | | | | | | |
| 50% | - | - | 497 (413-583) | 1004 (837-1171) | 327 (222-431) | 561 (413-709) |
| 100% | - | - | 454 (408-500) | 910 (781-1039) | 265 (149-382) | 439 (225-653) |
| remove | - | - | 375 (339-411) | 689 (595-784) | 99 (71-127) | 131 (98-164) |
| CONDOM USE | | | | | | |
| Male characteristic *(fig 3)* | | | | | | |
| 50% | 713 (636-810) | 1548 (1374-1722) | 423 (361-485) | 843 (737-950) | 274 (224-324) | 468 (392-544) |
| 100% | 633 (579-686) | 1330 (1213-1447) | 329 (288-369) | 576 (511-641) | 96 (79-112) | 126 (111-140) |
| Male & Female *(fig 4)* characteristic | | | | | | |
| 25% | 713 (638-789) | 1540 (1336-1743) | 401 (312-490) | 780 (623-937) | 220 (94-346) | 358 (93-623) |
| 50% | 651 (593-709) | 1416 (1293-1538) | 347 (294-399) | 633 (485-780) | 125 (60-189) | 202 (89-316) |
| 100% | 630 (561-699) | 1336 (1196-1476) | 337 (311-363) | 597 (557-636) | 94 (77-111) | 120 (93-148) |
| BEHAVIOUR CHANGE | | | | | | |
| Reduce % of males *(fig 5)* in one-off contacts | | | | | | |
| 50% | 785 (685-886) | 1684 (1503-1869) | 517 (426-608) | 1021 (837-1206) | 322 (232-412) | 554 (345-763) |
| 100% | 654 (609-698) | 1371 (1276-1466) | 347 (305-388) | 612 (517-708) | 101 (81-120) | 131 (98-163) |
| Reduce no. of *(fig 6)* one-off contacts | | | | | | |
| 50% | 707 (636-778) | 1540 (1414-1665) | 451 (374-527) | 856 (723-989) | 191 (85-296) | 246 (114-377) |
| 100% | 637 (589-685) | 1348 (1264-1432) | 346 (311-382) | 616 (546-686) | 101 (81-121) | 135 (108-161) |
| Reduce % of males *(fig 7)* with casual partners | | | | | | |
| 50% | 648 (586-709) | 1352 (1262-1442) | 442 (381-503) | 911 (797-1026) | 397 (268-525) | 730 (572-889) |
| 100% | 423 (386-461) | 813 (724-903) | 280 (213-347) | 529 (397-661) | 305 (211-399) | 564 (420-708) |
| Reduce no. of contacts *(fig 8)* with casual partners | | | | | | |
| 50% | 637 (567-706) | 1276 (1172-1381) | 399 (361-437) | 796 (658-933) | 374 (292-456) | 673 (493-853) |
| 100% | 412 (337-487) | 805 (708-902) | 268 (237-299) | 496 (383-608) | 308 (174-441) | 566 (383-748) |
| FULL PACKAGE *(fig 9)* | | | | | | |
| 25% | 698 (624-772) | 1513 (1300-1726) | 388 (326-450) | 713 (631-796) | 140 (71-210) | 220 (45-395) |
| 50% | 664 (594-734) | 1402 (1288-1517) | 360 (311-408) | 645 (535-755) | 102 (90-114) | 135 (113-158) |
| PART PACKAGE *(fig 10)* AT 25% LEVEL | | | | | | |
| STD | - | - | 504 (432-576) | 1021 (880-1162) | 403 (263-543) | 736 (497-974) |
| Condom | 713 (638-789) | 1540 (1336-1743) | 401 (312-490) | 780 (623-937) | 220 (94-346) | 358 (93-623) |
| Behaviour | 762 (661-863) | 1689 (1516-1863) | 492 (407-576) | 985 (833-1136) | 297 (191-403) | 579 (473-684) |
| STD & condom | - | - | 401 (318-484) | 776 (625-927) | 230 (140-321) | 419 (309-530) |
| STD & behaviour | - | - | 474 (433-514) | 945 (855-1034) | 250 (130-370) | 476 (251-701) |
| Condom & behaviour | - | - | 404 (329-479) | 772 (576-969) | 167 (81-253) | 273 (55-491) |
| PART PACKAGE *(fig 11)* AT 50% LEVEL | | | | | | |
| STD | - | - | 497 (413-583) | 1004 (837-1171) | 327 (222-431) | 561 (413-709) |
| Condom | 651 (593-709) | 1416 (1293-1538) | 347 (294-399) | 633 (485-780) | 125 (60-189) | 202 (89-316) |
| Behaviour | 707 (645-769) | 1505 (1376-1634) | 400 (332-468) | 751 (611-891) | 151 (87-215) | 192 (113-271) |
| STD & condom | - | - | 361 (324-398) | 657 (585-729) | 135 (92-179) | 221 (153-288) |
| STD & behaviour | - | - | 392 (341-443) | 697 (589-806) | 122 (81-162) | 155 (103-206) |
| Condom & behaviour | - | - | 353 (297-409) | 621 (524-718) | 101 (80-122) | 129 (102-157) |

## 7.3 DISCUSSION

This modelling exercise can only give a guide to the possible extent of reductions in HIV incidence that may be achieved through control programmes. In practise the impact of interventions clearly depends on many features, and especially the feasibility of introduction and application of such approaches.

### 7.3.1 NO INTERVENTIONS

In the absence of interventions, projections with and without assumed STD cofactor effects give very different results for the future spread of HIV infection. This difference is much greater than that between the low and high cofactor scenarios. As discussed below HIV prevalence and incidence levels observed in the study population peaked by 1990, which is highly inconsistent with the no cofactor scenario.

### 7.3.2 REDUCTION IN DURATION OF STDs

The STD dynamics assumed in the model for the simulation of the baseline characteristics of the study population reflected the presumed low availability of STD treatment in the study population prior to 1990. Intervention scenarios have been used to assess the likely impact of an increase in STD treatment after 1990.

Published reports have highlighted chancroid and syphilis as the major STDs responsible for genital ulcer disease in sub-Saharan Africa (*Over and Piot 1991*). The assumed dynamics of STDs in the model were therefore based on these reports. Follow-up data from the study population now also implicate herpes simplex virus type 2 (HSV-2) as possibly also being responsible for a substantial proportion of ulcerative STDs in the study population (*Wagner et al 1993*). Though HSV-2 is initially sexually transmitted, episodes of ulcerative STDs attributable to HSV-2 can then occur in the absence of further sexual transmission. This may be more common during periods of immunodeficiency, and may therefore be more prevalent among individuals with HIV infection, even after adjusting for behavioural differences. This

has not been explicitly accounted for in this modelling exercise.

The impact of STD control measures are likely to depend on the proportion of viral STDs in the population, since these are likely to be little affected by treatment regimens. However, STD interventions should also be aimed at educating individuals to avoid sexual contact in the presence of STD episodes. To explicitly assess the impact of this, the duration of treated STD episodes in SimulAIDS could be reduced, which would reflect a reduced number of sexual contacts in the presence of STDs.

Results from simulations suggest that STD interventions are strongly dependent on the true STD cofactor effects. Clearly the stronger these are, the greater the impact of interventions in reducing HIV incidence. For the high cofactor scenario the majority of cumulative HIV infections even after 1990 were attributable to other STDs. Thus if feasible STD interventions could reduce STD incidence levels, one might expect to see a substantial decline in HIV incidence in the general population. Even if STDs could be controlled in just the core group of females with one-off sexual contacts, this would also be important. However, in such a rural population, this group is not easily identifiable and in this exercise was assumed to include bar girls and CSWs from nearby trading villages and towns.

Note that in this exercise prevalence levels for other STDs were not assumed to be particularly high. For scenarios assuming higher STD prevalence levels the impact of equivalent STD interventions would be greater. These low estimates were chosen so as to provide likely lower bound estimates for the proportion of HIV infections attributable to other STDs (see chapter 6).

### 7.3.3 INCREASED CONDOM USE

It has been shown here that it may be possible to substantially reduce HIV incidence levels by promoting condom use, even if only in the more irregular partnerships. Results were again dependent on the cofactor scenario; any given condom intervention (aimed at one-off partnerships) was more effective under the high cofactor scenario. The reason for this dependence is two-fold. Firstly condom use reduces STD incidence and prevalence in the

population, thus reducing the number of sexual contacts potentially exposed to increased transmission of HIV. Clearly this is not relevant for the no cofactor scenario.

Secondly since standard transmission probabilities are higher for the no cofactor scenario, and since there are no enhancing effects of STDs on HIV transmission, more infections are transmitted during casual and regular partnerships for the no cofactor scenario than for the other scenarios. Thus preventing transmission of HIV during one-off sexual contacts has a much stronger impact on reducing incidence of HIV infection in the low and high cofactor scenarios than for the no cofactor scenario.

Results were presented for both characteristic and random use of condoms among males and/or females with one-off contacts. Random and characteristic use of condoms were found to be equally effective for these scenarios in a rural population. This would probably not be so in groups of females practising CSW professionally in urban areas, where the average number of partners is likely to be much higher. In this case characteristic use of condoms by females would probably be more effective since this is likely to have more impact on reducing the very high levels of HIV infection in these women.

Use of condoms characteristically by both males and females demonstrated substantial additional benefits. Use of condoms is likely to be most effective in reducing HIV incidence if males can be encouraged to use condoms at least for one-off sexual contacts, and females engaging in one-off sexual contacts are empowered enough to be able to demand the use of condoms by their partners.

### 7.3.4 OTHER BEHAVIOUR INTERVENTIONS

In the study population, HIV incidence during the first year of follow-up yielded a rate of about 1% in adults of 13 years and over (*Mulder et al 1994b*), and has not been observed to increase since then (personal communication, Daan Mulder). (1% incidence in adults 13 years and over in the study population is equivalent to about 1.1% in the simulated population where adults are assumed to be 15 years and over.) This rate of about 1% is clearly lower than incidence rates generated from simulations to baseline in 1990. All three

scenarios are consistent in their prediction of about 2% HIV incidence in 1990, corresponding to a prevalence of about 10%. It is believed that the observed incidence of about 1% in adults since 1990 represents a decrease in incidence, possibly as a result of the presence of the MRC Programme in the study area (personal communication, Daan Mulder). Without marked changes in STD treatment or increased condom use, it is believed that this reduction is likely to be due mainly to a reduction in the number of contacts with irregular partners.

What simulated behavioural interventions could give rise to a 50% decrease in HIV incidence over one or two years? From results presented here, only simulated interventions for the high cofactor scenario could generate such a rapid reduction in HIV incidence. These interventions specifically focused on reducing frequency of one-off sexual partners amongst males. For the no cofactor scenario HIV incidence still increased from 2.5%, even when all one-off contacts were stopped in 1990. This is highly inconsistent with observed results from the study population.

The apparent benefits associated with reducing the frequency of contacts that males have with one-off partners compared with reducing the proportion of males in one-off contacts is an important message to be conveyed, especially since, in most cases, it is likely be easier to reduce frequency of sexual contacts with one-off partners than to stop them altogether.

### 7.3.5 COMBINED INTERVENTIONS

The benefits associated with a combined approach to intervention are clearly substantial. Even a "package of interventions" each effective at the 25% level resulted in a striking reduction in HIV incidence for the high cofactor scenario. Part package interventions demonstrate how condom and other behavioral change interventions also serve to act as STD interventions.

### 7.3.6 SUMMARY

Since confidence bounds for HIV incidence often widely overlap for intervention and no intervention simulations, this suggests that for actual intervention studies of this size, it may be difficult to detect the effect of any real interventions, especially over short follow-up periods, unless the effect is striking.

Both the future course of the HIV epidemic, and the effect of intervention strategies are strongly dependent on the assumed STD cofactor scenarios. However, only the high cofactor scenario is consistent with results observed from the study population at baseline and during the first years of follow-up. For simulations with no intervention, HIV incidence levels one year after baseline, ie 1991, were approximately twice that observed in the study population for all three scenarios, ie 2% rather than 1% in adults. It is believed that this lower level of incidence in the study population is probably the result of a reduction in the number of sexual contacts that males have with irregular partners. It is unlikely to have resulted from either increased treatment of STDs or increased use of condoms. This is only consistent with results from feasible interventions in the high cofactor scenario.

Results also suggest that it may be possible to substantially reduce HIV incidence levels by promoting regular condom use, even if only in the more irregular partnerships. Substantial gains may also be made if this message can be aimed at both men and women. But potentially the greatest gains may be made by combinations of interventions aimed at reduction in levels of STDs, more regular condom use in the more irregular partnerships, and a decrease in the number of irregular partnerships. Even for a package of interventions at the 25% level, HIV incidence might be substantially reduced within a few years.

CHAPTER 8

# CONCLUDING REMARKS

# 8. CONCLUDING REMARKS

SimulAIDS has been used in this exercise as an experimental tool, allowing various issues to be explored. Results should be treated with some caution, as they will depend on the model's assumptions and the input parameter values ascribed. Since these are based on our current empirical understanding, many uncertainties do still remain.

The uniqueness of this project lies in the fact that: (1) It focuses on a specific African population, rather than a typical population; (2) It focuses on a rural population, rather than an urban population; (3) It simulates the transmission dynamics of two other STDs as well as HIV, whereas most exercises have not explicitly considered other STDs at all; (4) It has enabled the proportion of HIV infections attributed to ulcerative and non-ulcerative STDs to be estimated; and (5) It assesses the effect of focusing a range of interventions specifically on the more irregular partnerships.

The extent to which sensitivity analyses can be carried out is usually limited, with time constraints proving the critical limiting factor. For this exercise sensitivity of results was assessed for three scenarios assuming very different cofactor effects for STDs on HIV transmission. Results from these scenarios have, however, generated further interest, and especially relating to the sensitivity of results to different representations of sexual behaviour characteristics for the high cofactor scenario, and to sensitivity of results for both simulated ORs for associations between HIV and other STDs, and simulated proportions of HIV infections attributable to other STDs assuming different combinations of STD cofactor effects (eg 100 and 10 for ulcerative and non-ulcerative STDs respectively). These and other issues are currently being addressed (see 8.2).

## 8.1 SUMMARY OF MAIN RESULTS

Some of the principal results of this project have been summarised below.

1) The no cofactor scenario is inconsistent with results from the study population for the following reasons: (a) In order to reach approximately 10% HIV prevalence in

adults by 1990, assumptions that had to be made about choice of input parameters were inconsistent with empirical results; (b) Spread of HIV infection among males and females with one-off sexual contacts was considerably less rapid than is usually observed amongst particular high risk groups; (c) Simulated odds ratios for associations between HIV and other STDs were considerably less than those documented from empirical studies; (d) For simulations continued to the year 2000, HIV prevalence continued to increase to nearly 20% among adults, and was still rising; this compares with results from prospective follow-up of the study population which showed prevalence levels not increasing since baseline, when it was about 10%; and (e) Even after introduction of implausibly high simulated interventions in 1990, it was not possible to replicate HIV incidence rates of about 1% in the general adult population two years later, as has been documented from the study population.

2) Results from the high cofactor scenario are most consistent with empirical results from the study population.

3) By including out-migration and refining sexual behaviour representations, documented characteristics of the study population in 1990 could be replicated with reasonable accuracy. Representations were only consistent with a mean AIDS incubation period of about 4 years. This has proved consistent with subsequent data from two-year follow-up of the study population (*Mulder et al 1994a*). It was not possible to mirror the spread of HIV infection in the study population in the absence of one-off sexual contacts.

4) Results of all modelling scenarios at baseline in 1990 suggest that the study population is already experiencing a severe impact from HIV infection. Since the assumed introduction of HIV in 1980, crude mortality rates are estimated to have increased by about 60%, with mortality in the 30-34 year age band increasing 10-fold. Life expectancy decreased by about 15 years. The results are consistent with empirical data from two-year follow-up of the study population (*Mulder et al 1994a*).

5) Prevalence of high risk sexual behaviour, STD incidence and HIV incidence may all decline even in the absence of any specific intervention measures, due to the rapid

removal of the most sexually active individuals without immediate replacement.

6) Simulated associations between HIV and ulcerative STDs, assuming per contact cofactor effects of 100, are consistent with published reports of observed associations between HIV and ulcerative STDs. Many factors influence observed associations including: type of study design; choice of study sample; prevalence of respective STDs; misclassification of STDs; duration over which a history of STDs is recorded; and sexual behaviour characteristics.

7) Results are consistent with other STDs playing a critical role in establishing an HIV epidemic, but the role of STDs decreases with progression of the epidemic, making early STD intervention programmes particularly important. Even if other STDs are not especially prevalent in a general population, it seems possible that they may have an enormous impact on HIV and AIDS epidemics.

8) It should be possible to substantially reduce HIV incidence levels in the general population with the improved use of condoms, even if only in the more irregular sexual partnerships. STD treatment interventions should also provide a means to aid the control of HIV infection. Greatest gains may be made by combinations of interventions aimed at reducing levels of STDs, increasing regular condom use in the more irregular partnerships, and decreasing both the proportion of males having irregular partnerships and their frequency of contacts with irregular partners.

9) Interventions which reduce frequency of sexual contacts with irregular partners may be more effective than those focused on reducing proportions of males engaging in irregular partnerships. This is perhaps rather counter-intuitive, and clearly has important implications. *

10) This study supports the critical role of core groups in the dynamics of HIV transmission.

* Note, however, that this conclusion depends on the assumption that women with one-off sexual partners have a fixed number of sexual contacts per month.

## 8.2 FURTHER WORK BEING ADDRESSED

While this initial period of research has produced useful results, further work is needed both in terms of model development and application to additional research questions. These are now being addressed during a period of "postdoctoral" research with Professor Auvert in his Unit in Paris. During this period existing collaborations are being further strengthened and new links forged.

### 8.2.1 MODEL DEVELOPMENT

1) In SimulAIDS V5.02 enhancing effects of HIV transmission in the presence of an STD are specified for males and females per sexual contact. The cofactor effect for susceptibility to HIV infection for an individual with an STD has been assumed equal to the cofactor effect for infectivity of an individual with both HIV and an STD. At the outset, inclusion of separate terms for cofactor effects for susceptibility and infectivity was considered an unnecessary complicating factor. Today there may be evidence to suggest that, in the presence of other STDs, infectiousness with HIV and susceptibility to HIV may be quite different (*Hayes et al 1994*). This is now considered an important extension to the model to enable an assessment of the robustness of the results, and especially consistency with observed associations between HIV and other STDs.

2) SimulAIDS allows STDs to enhance the transmission of HIV. There is also now evidence that HIV infection may result in both increased numbers of episodes of STDs and in an increased duration of STD episodes (*Wasserheit 1992*). This is a likely consequence of reduced immunity in HIV infected individuals resulting in increased susceptibility to infection with STDs. For an individual infected with both HIV and HSV-2, a weakened immune system may also give rise to more (and possibly prolonged) episodes of symptomatic ulcerations. The model could introduce this feature by allowing the probability of STD transmission to an individual and/or the duration of an STD episode to depend on the HIV status of the individual, and possibly also on time since infection with HIV.

3) Refine sexual behaviour structure. One priority is to stratify frequency of sexual activity of married men having one-off contacts into two or three broad age bands. It would also be useful to have stratification of frequency of sexual activity within age bands, so as to better replicate the likely heterogeneity in number of sexual contacts of males with one-off contacts. Further recommendations may also be made on the basis of sexual behaviour data gathered from the general population cohort during the round 4 survey.

4) Allow for increased susceptibility to HIV infection in young sexually active females.

5) Development of vaccine component of the model, in order to enable evaluation of the effect of various vaccine policies for a rural setting in sub-Saharan Africa.

6) Development of tuberculosis component, to enable assessment of the likely impact of HIV on TB infection and disease.

### 8.2.2 FURTHER EVALUATION OF EPIDEMIOLOGIC ISSUES

Further work that is currently being addressed is briefly described below.

1) Use of already defined models to investigate further features and characteristics of the HIV epidemic.

   a) Investigate the future demographic consequences of the AIDS epidemic in this rural population, including effect on population growth rate, population pyramid, dependency ratio, mortality rates, fertility rates, life expectancy.

   b) Investigate the proportion of HIV infections attributable to different types of sexual partnerships.

   c) Investigate relationships between phase of HIV epidemic and ratio of male-to-female HIV prevalence, and phase of HIV epidemic and ratio of cases of

HIV infection to AIDS.

d) Assess the role that concurrent sexual partnerships, together with peaks of infectiousness both early and late in the AIDS incubation period, might play in the rapid spread of HIV infection in this rural population.

e) The effect of population structure and in- and out-migration patterns on the dynamics of HIV transmission.

2) Refine and update modelling scenarios in the light of model developments outlined in 8.2.1 and application of prospective data from the study population.

3) Apply IWGAIDS (an alternative mathematical deterministic model) to the same study population to assess the extent to which results may have been model-specific.

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