TREATMENT OF SEXUALLY TRANSMITTED DISEASES AS AN HIV PREVENTION STRATEGY?

Cofactor magnitudes, syndromic management and a reappraisal of the Muwanza and Rakai trials

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Treatment of sexually transmitted diseases as an HIV prevention strategy?

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Behandeling van seksueel-overdraagbare aandoeningen ter preventie van HIV?

Een herbeschouwing van cofactorgroottes, syndroom-benadering en de trials in Mwanza en Rakai

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VOOR MIJN OUDERS

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chapter 1

Introduction

THIS THESIS CONSISTS of studies assessing the extent to which the treatment of common sexually transmitted diseases (STD), such as gonorrhoea and syphilis, can help to prevent HIV infections and curtail the spread of the HIV epidemic in sub-Saharan Africa. Several types of observations have suggested that STD are a risk factor in the transmission of HIV, but the extent to which treatment of STD can contribute to HIV prevention is unclear. Knowledge of the latter helps determine the extent of HIV control measures and the amount of money that should be spent on STD treatment, relative to other prevention strategies such as education on behavioural risk reduction and the promotion of condom use.This is especially important in developing countries, where the HIV epidemic is most severe, where budgets for HIV control are most limited, and where STD are common.

This introductory chapter describes the background to our studies. It starts with an explanation of the HIV virus, of the HIV epidemic and of AIDS, the disease it causes (1.1). Next, prevention strategies for HIV are discussed, with particular reference to the options that are feasible in developing countries with widespread epidemics, such as those in sub-Saharan Africa (1.2). Section 1.3 gives a brief introduction to the natural history, epidemiology and treatment of STD. Sections 1.4 through 1.6 focus on the role of STD in HIV transmission, and examine how this has been investigated so far. Section 1.7 introduces the contribution this thesis makes to this research, and explains one of the main methods employed: the re-analysis of two STD treatment trials conducted in Uganda and Tanzania with an epidemiological transmission model. Finally (1.8), the specific objectives are detailed and the division of work over the chapters is outlined.

1.1 THE HIV/AIDS PANDEMIC

The pandemic of the acquired immunodeficiency syndrome (AIDS) is among the most pressing global issues in public health. The World Health Organization has estimated that, by the end of year 2000, 36 million people were infected with the human immunodeficiency virus (HIV), the underlying cause of AIDS. Thirty three million out of this total live in developing countries. Since the beginning of the pandemic in the late 1970s, 22 million people have died from AIDS. In 2000 alone, 5 million new HIV infections occurred, of which 3.8 million in sub-Saharan Africa (SSA) [UNAIDS & WHO 2000]. In 1999, AIDS was the fourth leading cause of death in the world, and it is moving up the tables.

The HIV retrovirus is thought to have originated from a simian (monkey) immunodeficiency virus (SIV) somewhere between 1930 and 1960 in West-Africa, but no major spread began until the late 1970s [Gao *et al.* 1999, Goldberg & Stricker 2000]. Both the timing and mode of its crossing to the human species and the role human played herein are subject to debate [Korber *et al.* 2000,

Hillis 2000]. Two types of HIV are distinguished, HIV-1 and HIV-2, which originated separately from different SIVs. HIV-2 occurs mainly in West-Africa, and is the cause of relatively little disease burden [Marlink *et al.* 1994]. In this thesis we focus on HIV-1, and all references to HIV should be understood to denote HIV-1.

HIV infection is acquired via direct exposure to the body fluids of infected patients; sexual intercourse is the most common mode of transmission. The infection can also be acquired during the transfusion of blood or blood products and, to the children of infected mothers, during birth or via breast feeding. The HIV virus causes AIDS by infecting the patient's white blood cells and impairing the immune system, the body's defence against infections and cancers. As yet, no cure has been found for AIDS. In the absence of specific care, patients develop AIDS within 8-10 years after HIV infection, and die 1-2 years thereafter. Death follows from opportunistic infections such as tuberculosis and other lung infections, from the development of fatal cancers, or due to general weakening and wasting [Colebunders & Latif 1991, Ambroziak & Levy 1999].

Around 1995, highly active antiretroviral combination therapies against HIV became available in Western countries. By reducing the level of the HIV virus in blood, these improve the patient's clinical status and life expectancy. Antiretrovirals are, however, no cure for AIDS, nor are they a light therapy: once the patient quits, as commonly happens due to the severe side effects of these drugs, the beneficial effects cease. Even more important, after some time the virus becomes resistant to the drugs, so that their effect stops altogether. Due both to the need for lifelong continuation of the therapy and to its novelty, the therapy is very expensive. In addition, in order to establish toxicity, side effects and optimal drug dosage, antiretroviral therapy requires frequent patient check-ups, thereby posing a heavy burden on the health infrastructure, in particular on physicians and laboratory capacities. All in all, these factors mean that antiviral therapy is not available widely in all populations, except for in the most developed, Western countries where relatively few HIV patients live [Forsythe 1998].

1.2 HIV SPREAD AND CONTROL IN SUB-SAHARAN AFRICA

More than 80% of people infected with HIV (some 25 million out of the 36 million total) live in SSA, where the infection is spread mainly through heterosexual contact. In certain regions, including, for example, Botswana, Zambia and Zimbabwe, HIV prevalences (i.e. the proportions of the population infected) as high as 30% of adults in the general population have been recorded. Young adults are the main group affected. Over the whole of sub-Saharan Africa, HIV incidence (i.e. the numbers of new infections) appears to be stabilising or even to be falling slightly. This is due mainly to stabilisation and to the saturation of the epidemic in the countries first affected, such as Uganda. But in other countries, including

Nigeria and South Africa which up to the 1990s had 'escaped' the epidemic, HIV spread has not only begun, it is also rising to alarmingly high prevalence levels, 5% and 20%, respectively. At prevalences of over 20% in the adult population, which now apply to the majority of sub-Saharan African countries, today's 15-year olds have a 50% chance of dying from HIV/AIDS if current infection rates are not cut dramatically [Stover & Way 1998, Worldbank 1997, UNAIDS & WHO 2000].

By depleting both the vigour and the numbers of young adults at the height of their productivity in work and family, the AIDS epidemic impacts not only on the health of populations, but also on the socio-economic and demographic situation: current estimates of the impact of the epidemic include a cumulative 16 million orphans from parents who died from AIDS, an annual reduction in population growth of on average 2.6% to 2.2%, and parallel decreases in economic growth (e.g. by 0.3-0.4 percentage point per year in South Africa in the late 1990s). The HIV epidemic also indirectly affects the health of African populations. The care of AIDS patients not only poses an increased burden on the health system, HIV/AIDS also directly depletes the numbers of health care workers, thereby resulting in deterioriating care for other common diseases. Due to the frequent occurrence of severe, infectious tuberculosis as an opportunistic infection in AIDS patients, the prevalence of tuberculosis in HIV epidemic countries is also increasing in the general, non-HIV infected population. Decreases in child vaccination rates over the past decade have been associated with the HIV epidemic. As a combined result of lower levels of care and of HIV infection around birth, infant and child mortality have begun to rise back to the levels of before the 1970s; in several SSA countries, life expectancy is now 10 to 20 years shorter than it would have been without AIDS [Stover & Way 1998, Worldbank 1997].

Since no cure or vaccine is available and since effective antiretroviral therapy is not within reach of the greater number of patients, the main mode of HIV/AIDS control in Africa lies in preventing infection. The primary means of prevention is a reduction in unprotected sexual contact between infected and uninfected individuals. Governmental and health agencies try to promote this in health campaigns explaining the modes whereby the virus is acquired and the options for preventing infection, such as sticking to one sexual partner at a time, or the use of condoms with casual partners.

As a complement to the prevention of exposure, efforts may sometimes focus on reducing the probability of virus transmission during unprotected sexual contact. Generally, HIV is not very infectious; during heterosexual intercourse between an HIV-positive and an HIV-negative healthy partner, the risk of viral transmission is below 1 in 1000. However, this risk varies greatly between individuals, depending, among other things, on the disease stage of the HIV-positive partner (who is more infectious during the two months following infection, and during the late, symptomatic stages of disease, than in the long asymptomatic

stage), as well as on specific sexual practices, and possibly on the circumcision status of the male partner [Levy 1993, Mostad *et al.* 2000].

Among the preventable conditions that may aid the efficient transmission of HIV is concurrent infection with other STD [Cameron *et al.* 1989, Laga *et al.* 1991, Wasserheit 1992]. STD are therefore considered 'cofactors' in the transmission of HIV. Since STD are highly prevalent in African populations, and since their control and treatment is amenable to improvement, their role in HIV spread has received the attention of HIV prevention workers.

1.3 Sexually transmitted diseases

Sexually transmitted diseases comprise all those infectious diseases whose main or sole mode of transmission involves sexual contact with infected partners. The most common STD, and those that are probably the most important as cofactors in HIV transmission in African populations, are described below. The description focuses on aspects relevant to the role of STD in HIV transmission in African settings. In addition, the modes of STD treatment available to developing countries are discussed. For a more elaborate description of STD and their treatment, we refer to [Brunham & Plummer 1990, Brunham & Ronald 1991, Holmes *et al.* 1999, Morse *et al.* 1990]. This section may be skipped by readers who are familiar with STD epidemiology.

Gonorrhoea: Gonorrhoea is caused by the bacterium *Neissera gonorrhoea.* The disease causes inflammation of the urethra (in males) and *cervix uteri* (in females), which may cause urethral or cervical discharge, respectively, and pain at urination. Not all patients become symptomatic at every episode of gonorrhoea. Especially in females, physical signs of the infection often go unnoticed. Gonorrhoea is treatable with commonly available antibiotics, but in the absence of treatment the disease disappears spontaneously after an estimated 2-3 months. Prevalences of gonorrhoea in African adult populations typically range between 1% and 7%, and peak in the most sexually active age range (15-35 years).

Chlamydia: Chlamydia is caused by the bacterium *Chlamydia trachomatis.* The cervical/urethral infection may give non-ulcerative symptoms similar to those of gonorrhoea, but it is usually milder, meaning that even more infections go unrecognised. Chlamydia is curable with antibiotics, and, in the absence of treatment, will disappear spontaneously after 4-24 months. Due to its longer duration, prevalence is somewhat higher than for gonorrhoea, at 3-12%.

Trichomoniasis: This bacterial infection is caused by *Trichomonas vaginalis.* In females, the vaginal infection may cause inflammation and symptoms of vaginal discharge and itching which can last for years. The disease is sexually transmitted, but in males usually passes without either symptoms or complications, and

resolves soon. In line with this gender difference, prevalences are estimated to range between 10 and 30% in females, but to be only 1-5% in males. Trichomoniasis is curable with antibiotics.

Bacterial vaginosis (BV): BV is a vaginal disorder that is not sexually transmitted (and is thus, strictly speaking, not an STD), but is nonetheless associated with STD and sexual promiscuity. It is caused by an alternation in the vaginal flora, with replacement of the normally predominant bacteria (lactobacilli) by anaerobic bacteria, genital mycoplasms and *Gardnerella*, causing a rise in vaginal pH. Depending on its severity, BV can cause vaginal discharge and/or itching or go unnoticed. The alteration of vaginal milieu may render the patient more susceptible to infection with other non-ulcerative STD [van de Wijgert *et al.* 2000, Spiegel 1991]. BV is treatable with (a mixture of) broad-spectrum antibiotics, but this may require a multiple dose regimen. Even then, the clinical response - measured as the percentage of patients who no longer have the condition several months after therapy, and in whom it does not recur within this period - is often poor. Prevalence levels in populations of African women differ according to the definition used, but may be as high as 50%.

Syphilis: Syphilis is caused by the bacterium *Treponema pallidum.* In the majority of patients it causes one or two genital ulcers in the six months following infection. During the next 1-3 years, which are denoted the 'active phase', (smaller) ulcers may occasionally recur, but in the later phases of infection the genital symptoms disappear. Thereafter, while the patient is no longer infectious, the infection has lifelong persistence. 'Late syphilis' may have severe complications including cardiovascular and neurological disease, from which the patient may die. Syphilis can be cured with antibiotics at all stages. Its overall prevalence varies widely between African settings, e.g. between 0.5% and 12%. This depends in the first instance on the definition of positivity: some diagnostic tests are only positive for 'active syphilis', while others also detect 'late syphilis'. In addition, the actual prevalence may vary between populations, depending on the local intensities of screening and treatment programmes. The prevalence of syphilitic ulcers is not usually measured, but is likely to be much lower than the prevalence of active syphilis, at somewhere under 1%.

Chancroid: Chancroid is caused by the bacterium *Haemophilus ducreyi.* The disease causes painful ulcers lasting approximately 2-3 months, after which the infection dissolves. Chancroid is curable with antibiotics. As the disease is notoriously difficult to diagnose, prevalence levels are not known (except in populations of STD patients with ulcers). Estimates of the population prevalence of chancroidal ulcers range from 0.5 to 2%; recent observations in STD clinics in some African cities indicate that the disease is now becoming less common.

Genital herpes: Genital herpes is caused by infection with *Herpes simplex virus type 2* (HSV-2). The disease is recognisable in a proportion of patients by an initial painful genital ulcer lasting approximately three weeks. Thereafter, smaller, less severe ulcers will recur for several decades, e.g. 1-4 times every

year, although the frequency of recurrences varies widely between individuals. In immunocompromised HIV/AIDS-patients, herpetic recurrences may occur at a higher frequency and with increased duration, size and severity. In Western settings - but not yet in developing countries -, antiviral therapy is now available to limit bot the severity and duration of herpetic ulcers, and, for as long as the medication is taken, to reduce the frequency with which they recur.This therapy, however, does not cure the infection. In developing countries, HSV-2 seroprevalence (i.e. the prevalence of antibodies against HSV-2 in blood, which indicates past infection) ranges between 30% and 60%, increasing steadily with age. The prevalence of herpetic recurrences is not known, but is likely to be much lower.

All STD (including HIV) are more efficiently transmitted from men to women than vice versa, a fact that is due mainly to the larger area of genital exposure in women than in men. In line with this, prevalences are mostly higher in women [Brunham & Plummer 1990]. Several of the STD can, if untreated, have serious complications, including severe pelvic or abdominal inflammation, infertility, and, in pregnant and breast-feeding women, illness and death of their foetuses or infants. STD are therefore also an important cause of sociopsychological distress, including risks of stigmatisation, domestic violence and marital breakdown. In around 1995, about 340 million new STD episodes were occurring every year (even excluding viral STD), the majority in developing countries [WHO 1999]; here, STD were the cause of a substantial disease burden in adults [Murray & Lopez 1996]. Even apart from their possible role in HIV spread, improvement in STD treatment is considered an important and cost-effective public health intervention for developing countries [Piot & Tezzo 1990, Brunham & Ronald 1991, Over & Piot 1996,Adler 1996].

1.3.1 STD treatment

STD share most of their symptoms, but differ with regard to the drugs that are effective in curing them. The choice of treatment for patients seeking care for STD-related symptoms cannot therefore be based on clinical examination alone. The infection responsible needs first to be diagnosed, which is possible using blood or genital swab samples. Diagnosis and subsequent infection-specific treatment is common practice in STD clinics in Western, industrialised countries: patients are sampled and asked to return for a second clinic visit to receive the diagnostic result and corresponding treatment.

For several reasons, STD diagnostics is often not feasible in many developing settings. Diagnosis generally requires a well-equipped laboratory with skilled staff, the costs of which may be prohibitive. Especially in remote rural areas, it is risky to send patients away in the expectation that they will return to hear the outcome: they may not be able to return for the second visit, and will thus

have to forego treatment. In order to overcome this problem, the approach currently recommended for developing countries, and adopted in most of them, is so-called syndromic management [WHO 1994]. Syndromic management is based on the idea that a specific set of signs and symptoms constitutes a syndrome, and indicates the presence of a certain class of infection. A combination of treatments is then prescribed that is effective against the most common organisms underlying this syndrome - and these drugs are immediately given on the spot. For example, patients with abnormal genital discharge would be presumptively treated for gonorrhoea, chlamydia and trichomoniasis.

However, as an STD control strategy, the treatment of symptomatic patients seeking care in clinics has only a limited role. A majority of patients may not have symptoms, may not recognise them, or may otherwise fail to seek timely treatment. Even if patients seek and receive effective treatment, they may have already infected their partner before they are cured. To enhance the role of treatment in STD control, so-called mass treatment has been proposed. This consists of the presumptive treatment of a whole population, whether infected and/or symptomatic or not. The idea behind mass treatment is that it catches all STD, whether symptomatic or asymptomatic, and that reinfection by untreated sexual partners is delayed because the whole population is treated at the same point in time. While mass treatment is not a commonly implemented service, it is sometimes used temporarily to achieve a rapid reduction in STD burden, especially in high-prevalence populations or in epidemic outbreaks [Cutler *et al.* 1952, Olsen 1973, Steen & Dallabetta 1999].

1.4 STD AS COFACTORS IN HIV TRANSMISSION

Evidence for a so-called 'cofactor effect' of STD on HIV transmission stems from several observations. Generally speaking, individuals with STD also have the highest rates of HIV. If studied prospectively over time, individuals with STD at start of observation run a higher risk of subsequently acquiring HIV. Similarly, as yet uninfected partners of HIV patients have a higher risk of getting infected if the HIV-positive partner has STD. This suggests that STD enhance both the acquisition of HIV (in HIV-negative persons) and the transmission of HIV to sexual partners (in HIV-positive persons). These epidemiological correlations involve typically between two-fold and ten-fold increases in prevalence and transmission risks [Cameron *et al.* 1989, Laga *et al.* 1991], and they are the subject of numerous studies and literature reviews [Wasserheit 1992, Fleming & Wasserheit 1999]. Their interpretation, however, is not straightforward (see below).

Biological, laboratory or clinical observations have provided insight into the mechanisms by which STD may enhance HIV acquisition and infectivity [Kreiss *et al.* 1994, Mostad & Kreiss 1996, Cohen *et al.* 1997, Fiscus *et al.* 1998, Fleming

& Wasserheit 1999, Rotchford *et al.* 2000, McClelland *et al.* 2001]. STD can contribute to HIV transmission via several mechanisms:

- Ulcers or smaller ulcer-like skin lesions increase the permeability of the genital tract to the entry or excretion of the HIV virus, by disrupting the normal epithelial (i.e. skin) barrier. To a lesser extent, inflammation, which is associated with STD like gonorrhoea, also renders the genital mucosa more permeable to pathogens.
- Inflammation attracts (CD4-positive) white blood cells, the target cells for infection with the HIV virus, to the genital tract. The increased presence of HIV-susceptible or HIV-infected white blood cells in the genital tract increases the likelihood of infection or its transmission [Kreiss *et al.* 1994].
- Inflammation may also enhance HIV infectivity by increasing the levels of certain cytokines (i.e. biological messenger substances) in the genital tract, and thus by stimulating the replication of infectious HIV virus.
- A similar enhancement of replication of HIV may result from coinfection of genital epithelial cells by the viruses HIV and HSV-2; this is called viral upregulation [Albrecht *et al.* 1989].
- Another mechanism for enhanced HIV replication may be the co-infection of macrophages (a certain type of white blood cells) by *Treponema pallidum*, the bacterium causing syphilis [Theus *et al.* 1998].

On the basis of these biomedical mechanisms, ulcerative STD are seen as stronger cofactors in HIV transmission than non-ulcerative STD. Among non-ulcerative STD, cofactor strength probably varies with the extent of inflammation. According to this interpretation, gonorrhoea would be a more important cofactor than chlamydia and trichomoniasis [Jackson *et al.* 1997a, Mostad 1998]. In females, it has been suggested that BV, which does not cause inflammation but which alters vaginal flora and also lowers vaginal pH, enhances susceptibility to HIV infection. The importance of this putative cofactor effect is subject to debate, however [Taha *et al.* 1998, Martin *et al.* 1999, Sturm-Ramirez *et al.* 2000].

Laboratory studies have shown that treatment of STD reduces shedding of the HIV virus in the genital tract - a likely correlate of infectivity [Cohen *et al.* 1997, McClelland *et al.* 2001, Rotchford *et al.* 2000]. This observation provides important support for the causality of the relationship between STD and HIV. That is, it implies that the clustering between STD and HIV is indeed due to STD predisposing to HIV transmission, and not (entirely) to the reverse effect, i.e. that HIV infection predisposes to STD [Wald *et al.* 1993], or to confounding due to the many risk factors that STD and HIV share.

On the basis of these data, it is thus likely that the treatment of STD (and the improvement of such treatment) helps to limit the spread of HIV. But how much will STD treatment help to prevent HIV transmission? If we are to determine the proportion of HIV prevention inputs that should be dedicated to improving STD treatment services - inputs that will inevitably be made at the expense of inputs

on other prevention strategies - this must be established.

This is not something we can learn directly from biological and epidemiological studies of the kind described above. Although the outcomes measured in biological studies are indicators of infectivity (such as genital HIV shedding) or of susceptibility, it is not known how they translate quantitatively into transmission rates. The translation of epidemiological HIV/STD correlations into STD cofactor effects is also problematic [Dickerson *et al.* 1996, Boily & Anderson 1996, Mertens *et al.* 1990, Nagelkerke *et al.* 1995, Hayes *et al.* 1995c]. Their most important cause is that STD and HIV are both acquired during unprotected sex with high-risk partners: the more high-risk sexual contacts an individual has, the more likely he or she is to contract both STD and HIV. This means that, even if STD cofactor effects did not exist, individuals who had STD would be more likely to have or contract HIV. Unless this phenomenon is properly 'corrected for' in data analysis - which is very difficult -, observed correlations cannot therefore tell us the magnitude of STD cofactor effects.

The role of STD in HIV spread can be better quantified on the basis of experimental studies that monitor the effect of improved STD treatment on HIV spread in actual populations. To date, a number of such 'intervention studies' have been conducted. The best evidence comes from community-randomised trials measuring the impact of STD treatment via comparisons between an intervention arm (i.e. group) and a 'comparison arm' that is not given the intervention. The impact is measured at the level of the population, rather than at the level of the individual participant. This is because the treatment of STD in trial participants may not only affect these participants' own susceptibility to acquiring HIV, but also their chances of infecting their partners, who may or may not be receiving STD treatment. At the community level, the impact of treatment is further multiplied by the indirect effects even on individuals who neither participate nor have contact with participants, since STD prevalences in the whole population fall, reducing everyone's exposure. In African settings in which HIV and STD spread throughout the population and are not confined to high-risk groups, the population is also the most logical level for evaluating interventions; in (rural) Africa, the village or community is the population level that is typically judged appropriate for the inclusion of most direct and indirect effects. In order to minimise the possibility that differences in outcomes between the study arms might be caused by unintended pre-existing differences in risk level rather than to the intervention under study, the participating communities are distributed at random between the intervention and comparison arm. This process is called (community-)randomisation.

At time of writing, two population-based randomised trials of improved STD treatment had been completed [Grosskurth *et al.* 1995a, Wawer *et al.* 1999]. Their interpretation and its implications form the main topic of this thesis. For an overview of the outcomes of other, less rigorously designed STD treatment studies,

the reader is referred to recent comprehensive reviews [Fleming & Wasserheit 1999, Merson *et al.* 2000].

1.5 Community-randomised STD treatment trials in Mwanza and Rakai

The community-randomised STD treatment trials were conducted in rural Uganda and Tanzania in the 1990s. Their design and main outcomes are summarised in Table 1.1. Both trials involved the improvement of STD treatment for the entire population in half of the (10 or 12) rural communities, and followed approximately 12,500 adults to monitor the effects. Communities were distributed at random between the intervention and comparison arms. For two years, each trial measured the prevalence of STD and the incidence of HIV in all participating adults. Subsequently, they calculated the impact of the intervention as relative reductions in these outcomes in the intervention arm as compared to the comparison arm.

Whereas the design of the trials was similar, the interventions tested differed. In Mwanza, Tanzania, the intervention involved an improvement of syndromic management for patients with STD symptoms who were seeking treatment in clinics (see 1.3). To encourage the population's use of the improved services, in addition, an outreach team made biannual visits to the communities served by the intervention clinics, giving health education on the availability of free, improved STD treatment and on the importance of prompt treatment [Grosskurth *et al.* 1995b, Grosskurth *et al.* 1995a, Hayes *et al.* 1995b]. In Rakai, Uganda, the intervention was home-based mass treatment of the entire adult population. The mass treatment and coinciding STD survey was repeated every ten months, so that the evaluation period between 1994 and 1996 covered three survey rounds and the epidemiological impact of the first two treatment rounds [Wawer *et al.* 1998, Wawer *et al.* 1999]. The difference between the trials in their treatment strategies paralleled a difference in their rationale. The Mwanza trial intended to test a feasible and sustainable STD intervention which, if effective, was to be actually implemented on a larger scale, preferably integrated into the general 'primary' health care system. The Rakai trial was a so-called 'proof-of-concept' study that aimed to test the maximum reduction in HIV incidence that could be brought about by a maximum reduction in STD rates; to achieve the latter, the intensive periodic mass treatment intervention was considered the best means.

After two years, both trials observed reductions in STD prevalences in the intervention arm relative to the comparison arm, although these seemed fairly limited, especially in Mwanza [Mayaud *et al.* 1997a, Wawer *et al.* 1999]. In Mwanza, an exceptionally large reduction was found in symptomatic urethritis (0.51, 95% CI 0.24-1.10 [Mayaud *et al.* 1997a]), but the interpretation of this out-

Table 1.1 **The design and outcomes of the randomised community-based STD treatment trials in Tanzania and Uganda.** Unless indicated, risk ratios were adjusted for (a) in Mwanza: Community pair, age, sex, history of STD ever prior to baseline survey, circumcision in men, travel during follow-up, STD prevalence in community pair at enrolment; and in case of HIV also for: HIV prevalence in community pair at enrolment; (b) in Rakai: Community pair, sex, age, marital status, religion, reported number of sex partner in previous year, partners resident $\geq$5km distance from respondent's house, and condom use; and, in case of STD and HIV, respectively, also for: STD or HIV prevalence in pair at enrolment [Grosskurth *et al.* 1995a, Hayes *et al.* 1995b, Hayes *et al.* 1995a, Mayaud *et al.* 1997a, Wawer *et al.* 1998].

	Mwanza, Tanzania	Rakai, Uganda
design	randomisation of 6 pairs of rural communities	randomisation of 5 pairs of rural communities
period	1992-4 (2 years)	1994-6 (20 months)
follow-up at 2 years	71% of 12,500 adults (15-54 years)	74% of 12,500 adults (15-59 years)
STD intervention	syndromic management of symptomatic STD in clinics + population-based health education	home-based mass treatment of whole adult population every 10 months
Risk ratio intervention/comparison arm after 2 years (95% confidence interval):		
(active) syphilis[1]	0.71 (0.54-0.93)	0.59 (0.32-1.09)[2]
gonorrhoea	0.96 (0.50-1.85)[3]	0.66 (p=0.44[4])
chlamydia		0.88 (0.50-1.53)
trichomoniasis in females	1.09 (0.92-1.28)	0.59 (0.38-0.91)
genital ulcers in past year	1.27[5]	1.02 (0.80-1.29)
incidence of HIV (over 2 years)	0.62 (0.45-0.85)	0.97 (0. 81-1.16)

[1] Defined as TPHA-positive and RPR-titer $\geq$1:8.
[2] Adjusted only for community pair and baseline prevalence.
[3] Men only.
[4] Statistical significance level in Wilcoxon test .
[5] Crude.

come is unclear, as symptomatic urethritis was diagnosed only among men with reported genital symptoms or signs, the number of which changed during the trial (see 10.2.1).

Impact on HIV incidence differed markedly between the trials. In Mwanza, STD treatment was associated with a 38% reduction (incidence ratio 0.62, with a 95% confidence interval of 0.45-0.85) [Hayes *et al.* 1995a], whereas in Rakai, HIV incidence was hardly reduced at all (incidence ratio 0.97, 95% confidence interval 0.81-1.16) [Wawer *et al.* 1999].

1.6 Explaining the contrasting outcomes of the Mwanza and Rakai trials

The two trials gave different answers to the question of whether STD control can contribute to HIV prevention. It is critical to understand why they produced such different results, as this determines their implications for practical HIV prevention policy. Specific questions include: *Why was the impact on HIV incidence relatively large in Mwanza while STD had decreased there relatively little? Why did the STD reductions in Rakai not translate into an impact on HIV incidence?* This section lists the hypotheses that have been advanced to explain the discrepancy in outcomes between the studies [Habbema & De Vlas 1995, Habbema & Korenromp 1999, Grosskurth *et al.* 2000, Hudson 2001].

Table 1.2 **Possible reasons for the difference in impact on HIV incidence between syndromic STD treatment (ST) in the Mwanza trial and mass STD treatment (MT) in the Rakai trial.**

Differences in the interventions
ST but not MT continually provides treatment, improving coverage of STD episodes
Mobility/migration disturbs periodic MT more than continual ST
Some cofactors, such as bacterial vaginosis, are more effectively treated by ST than by MT
Most STD episodes become symptomatic, therefore ST misses only few (asymptomatic) infections
Cofactor effects are higher for symptomatic STD, the focus of ST
The impact of ST on HIV in Mwanza is (in part) due to mechanisms other than a reduction in STD cofactor burden (like patient counselling on safe sex)
Differences in the study populations
Mwanza was in an earlier stage of the HIV epidemic, when STD cofactors are more important
Rates of incurable cofactor genital herpes (HSV-2) higher in Rakai
Preceding behavioural response to HIV epidemic in Rakai had reduced rates of curable STD
Greater mobility in Rakai than in Mwanza population
Differences in study design
Open cohort in Rakai included new participants enrolled halfway, diluting *apparent* impact, vs. closed cohort in Mwanza
The Rakai cohort but not the Mwanza cohort bordered non-intervention area, resulting in more dilution of impact due to (re-)infection from outside
Random chance
In Mwanza, intervention arm started out with lower HIV/STD rates than comparison arm, inflating *apparent* impact

Possible explanations can be divided into the following categories (Table 1.2):
- differences in the interventions
- differences in the study populations
- differences in study design
- random chance.

Interventions: mass vs. syndromic treatment

Because of their different accessibility and target groups, mass treatment and syndromic treatment may differ in the number of cofactor STD treated. For several reasons, syndromic, clinic-based treatment (the Mwanza intervention) may reduce STD cofactor burden more than mass treatment (the Rakai intervention). Under a syndromic approach, treatment can be sought by patients at all times and at their own convenience. With periodic mass treatment, in contrast, no treatment is possible in episodes that occur in between treatment rounds, or in residents who are temporarily absent at the moment of treatment. Since mass treatment derives its effect mainly from the simultaneous cure of a majority of infected persons, its effectiveness may be markedly reduced by high STD reinfection rates; this is to be expected in small-scale trials in which infections are reintroduced into the community soon after each round by infected immigrants or by residents who were temporarily absent. Another potentially relevant difference is that some STD respond better to syndromic treatment - which allows for multiple-dose drug therapies - than to the single-dose mass treatment regimen adopted in Rakai. In particular, syndromic treatment may be comparatively efficient at curing bacterial vaginosis.

As indicated in subsection 1.3.1, these advantages of syndromic treatment have to be weighed against its disadvantages: that it reaches only symptomatic patients, and that reinfection by partners is not explicitly combated (except in the rare case in which all sexual partners are co-treated). As additional explanations for the larger impact on HIV in Mwanza, these disadvantages of syndromic treatment have been put into question. In particular, it has been proposed that missing asymptomatic infections is actually a minor disadavantage. First, only a small fraction of episodes may be asymptomatic. Second, the supposed benefit of covering asymptomatic infections might, from the perspective of HIV prevention, be limited if the relative cofactor effect of asymptomatic STD is small in comparison to that of symptomatic STD. This hypothesis follows the line of reasoning that cofactor effects are in part mediated by mechanisms associated with symptoms, such as inflammation and ulceration (see section 1.4).

A different mechanism for a larger impact on HIV under the Mwanza approach may have been that this intervention package also affected HIV transmission by mechanisms other than the reduction of the STD cofactor burden, for example

through the STD health education offered to patients in conjunction with the antibiotic treatment.

Study populations

Three differences in the populations in which the trials were conducted may have contributed to their contrasting outcomes.

At time of the trial, Mwanza was at an earlier stage of the HIV epidemic than Rakai, and the role of STD cofactors is larger in earlier stages of the HIV epidemic [Robinson *et al.* 1997]. In Mwanza, at the start of the trial in 1992 (which was estimated to be the tenth year of the HIV epidemic), HIV prevalence among adults was 4% and rising (reaching 6% two years later). In the Rakai trial between 1994 and 1996 (which were estimated to be the 16th and 18th years of the epidemic), HIV prevalence was roughly stable, at around 16% throughout. Early in HIV epidemics, infections take place primarily in 'core groups' of highly sexually active individuals, who have high rates of STD. Later on, once HIV has spread into the general population, more HIV transmissions will occur in stable relationships between low-risk individuals, fewer of whom have STD. In addition, due to deaths from AIDS among high-risk groups, STD prevalences may fall during the HIV epidemic, further lowering the role of STD cofactors. An additional mechanism behind the decreasing cofactor role in advanced HIV epidemics for curable STD specifically, might be an increase in the prevalence of the incurable cofactor herpes (HSV-2) [O'Farrell 1999]. This would occur because herpetic ulcers are a symptom of HIV/AIDS, and thus become more common with the increasing occurrence of AIDS.

Furthermore, at the time of trial, Rakai had just experienced a behavioural risk reduction following the end of its civil war in 1986 [Serwadda *et al.* 1992, Konde-Lule *et al.* 1993, Konde-Lule *et al.* 1997, Kilian *et al.* 1999]. By reducing the prevalences of STD and the relative frequency of occurrence of high-risk sexual contacts in which STD are most important, this may have helped to decrease the importance of cofactor STD at time of the trial. In Mwanza, in contrast, risk behaviour had presumably been at a lower level than in Rakai during the 1980s - which would explain the fact that its HIV epidemic was less severe as compared to that in Rakai -, but this risk level seems to have been maintained throughout.

A final difference between Rakai and Mwanza that may have influenced the trial outcomes is their relative exposure to STD re-infection from people moving in and out of the trial area who had not previously benefited from the intervention. Living on the main trading route between Tanzania and Uganda where there are relatively many trading centres, the Rakai population may have been more mobile than the Mwanza population - which, in an area that is generally known for its poor infrastructure, included isolated fishing villages far away from major roads.

Study design

Whereas the trials were similar with respect to the unit of randomisation and the time interval of impact measurement, they differed in two other design aspects that may have contributed to the difference in the observed impact*. First, in Mwanza, impact on HIV incidence was measured in a closed cohort, which only included individuals who were present both at the start and the end of the trial. In Rakai, the cohort included individuals who were present in the study area between any two rounds, but not necessarily all three. The Mwanza cohort, therefore, excluded a relatively higher number of mobile individuals, limiting impact measurement to a lower-risk and more compliant part of the population. As a result, *apparent* impact may have been inflated as compared to what can be expected for actual target populations.

Second, in Mwanza the HIV incidence cohort was confined to communities in the inner part of the intervention area, whereas the Rakai cohort covered all intervention villages including those bordering the non-study area. The cohort selection in Mwanza may thus have reduced STD reinfection rates resulting from exposure of study participants to individuals from outside the intervention area, as compared to Rakai (over and above the possible differences in mobility levels between the *populations* described above).

Random chance

Since both the Mwanza and Rakai trials were single experiments that were performed on a subsample of the target population, their outcomes are subject to random chance. The level of uncertainty in the impact estimates is represented by the large confidence intervals surrounding them. For Rakai, impact was estimated at a 3% reduction in HIV incidence, but with the prediction that, in the hypothetical case that the trial should be repeated, the true impact could, with 95% certainty, lie anywhere in a range of between -16% and +19%. For Mwanza, the corresponding 95% confidence interval around its point estimate of 38% HIV incidence reduction ranged between 15% and 55%. It is therefore possible that, entirely by chance, the Mwanza trial found an unusually large effect, and the Rakai trial found an unusually small one.

Random chance may also have played a role in the baseline population characteristics co-determining their outcomes. In Mwanza, the communities randomised into the intervention arm by chance had, at the start of the trial, a lower average HIV prevalence than the communities in the comparison arm (3.8 vs.

* It is of note that these differences do not denote true differences in intervention effectiveness, but rather observation artefacts associated with small-scale trials.

4.4%) [Grosskurth *et al.* 1995a]. Because of this imbalance - which also held for some known HIV risk factors [Grosskurth *et al.* 1995a, Mayaud *et al.* 1997a] - the intervention arm could be expected to have a lower incidence of HIV during the trial, even apart from intervention effects.

1.7 Methods: simulation modelling of the Mwanza and Rakai trials

The above sections make clear that it is not yet understood to what extent STD treatment can contribute to HIV prevention in SSA. Observational studies on STD cofactor effects do not provide evidence on this, and the two STD treatment trials yielded contradictory results. In this thesis we have mainly used simulation (computer) modelling to further evaluate the outcomes of the Mwanza and Rakai trials. This section describes the rationale for simulation modelling, and the characteristics of the model we used.

Rationale for modelling

Empirical testing of the hypotheses that have been advanced to explain the differences in outcomes between the Mwanza and Rakai trials would require large numbers of additional trials. For example, to exclude the role of random chance in the Mwanza outcomes, new trials would need to be conducted, in a way that was as comparable as possible to the original trial. This is not possible, for several reasons. In the years since the original trial, the Mwanza HIV epidemic has developed; therefore, in any 'repeat Mwanza trial' the starting HIV prevalence would inevitably be higher. Similarly, empirical testing of, for example, mass treatment in Rakai at an earlier stage of the HIV epidemic would not be possible. One solution might be to replace Rakai with another population that was comparable in all respects except for the factor under study, but, for obvious reasons, the existence of such populations is unlikely. Some may have ethical objections against repeat trials of syndromic STD treatment: since the Mwanza trial found a positive impact on HIV, withholding such intervention from a comparison group would be unacceptable. Finally, even if additional trials could be done, they would be costly and their results would require a long wait.

A simpler, faster and cheaper way to extrapolate trial outcomes to other populations and to explore the impact of alternative interventions may be to do theoretical studies on the existing data. Theoretical models can predict systematically what would happen if only a single factor of interest were changed. For infectious diseases, this is commonly done with the aid of epidemiological transmission models [Yorke *et al.* 1978, Hethcote & Yorke 1984, Anderson & May 1991,

Habbema *et al.* 1992]. 'Dynamic' transmission modelling allows for the complex interactions between the infection status of different individuals or population groups, considering the non-linear effects in disease spread within populations over time. For example, a rise in STD prevalence brings with it increased exposure for STD-negative persons, and will therefore increase incidence [Anderson 1994]. As a result, a shortening of STD durations, thanks to for example improved treatment, can more than proportionally reduce STD rates. Another dynamic effect is changes in the population composition due to HIV/AIDS deaths. An example of a model study on the role of the type of STD treatment would be to simulate a Rakai-like mass treatment intervention in the Mwanza population and vice versa. Besides allowing the study of hypothetical alternative interventions, or combinations of such interventions, modelling allows us to look at outcomes that are not easily measured in empirical studies, such as the impact over a longer time period than a two-year trial duration, and such as savings in disability-adjusted life years - which allows for better comparison of STD interventions with other health interventions [Over & Piot 1992].

Simulation model *STDSIM*

The model studies in this thesis were performed with the microsimulation model *STDSIM*. This model describes the heterosexual spread of STD and HIV, and the effect of control measures upon it [Van der Ploeg *et al.* 1998]. *STDSIM* has been under development at Erasmus University Rotterdam since 1994, at the request of the Department of International Aid (Directorate-General 8) of the European Commission. The model is described in greater detail in Chapter 6. Below, we summarise its main features, considering the different types of models available and the requirements imposed by our research questions.

The simplest models used for studying the spread and control of STD [Anderson 1989,Anderson 1991] serve to describe the general mechanisms operating in disease spread and control at population level. Such models are commonly *deterministic*, i.e. they consist of a set of mathematical equations describing the flow of individuals between 'healthy' and 'infected' or 'diseased' groups; the outcomes obtained under a given set of input assumptions are fixed. Another type of model, including *STDSIM*, simulates the transmission of infections in a population at the level of individual persons (so-called microsimulation) [Habbema *et al.* 1996]. Each individual is represented by a number of characteristics, some of which remain constant (such as sex and date of birth), and some of which change (e.g. the disease status). Changes in personal characteristics result from stochastic events (such as getting infected); whether and when an event occurs is determined by Monte-Carlo sampling from probability distributions. As an example, for a single sexual contact between an HIV-infected and an HIV-uninfected partner, one may specify a 0.1% chance that the infection will be transmitted.

Repeated simulation runs of this model will differ in whether transmission actually occurred at this timepoint, and thereby in the subsequent course of the HIV epidemic. Microsimulation models thus give an indication of the stochastic variation in disease spread.

Modelling at the level of individuals is essential to the study of the relationship between HIV and STD spread: after all, interactions between these diseases occur at the level of individuals and their sexual contacts. One example is the effect of the HIV epidemic on STD epidemiology: due to deaths from AIDS among persons in high-risk groups, the average level of risk behaviour and of STD in the population is likely to decrease during the epidemic. This dynamic effect is much more difficult to represent in a group-compartmental model [Garnett & Anderson 1996a, Kretzschmar *et al.* 1995]. Similarly, the simulation of individuals who may or may not be (co-)infected with different mixtures of STD and HIV is the most intuitive, and technically the easiest, method of modelling biological interactions between STD and HIV [Boily & Anderson 1996, Koopman & Longini 1994]. Furthermore, so-called 'sexual network effects' are fully captured exclusively in individual-based models [Ghani *et al.* 1998, Morris & Kretzschmar 1998]. The term 'sexual network' denotes the patterns in sexual partnerships, including the heterogeneity in sexual behaviour within the population (most individuals have few partners and few have many); it also denotes the mixing between individuals differing in age or in their respective numbers of (concurrent) partners. These factors influence individuals' risk of infection, on top of their own risk behaviour. A final argument in favour of microsimulation is that such models are flexible with regard to the specification of input, and especially of output. Both can be chosen to optimally resemble real-world (trial) data, allowing, for example, for particular statistical analyses and facilitating meaningful comparisons between empirical data and model outcomes.

1.8 Aims and outline of the thesis

The overall aim of this thesis was to investigate the role of STD cofactors on HIV transmission, and of STD treatment in HIV prevention. We defined the following specific objectives:

- To estimate the magnitude of STD cofactor effects on HIV transmission;
- To quantitatively explore the importance of the explanations listed in Table 1.2 for the discrepancy in outcomes between the Rakai and Mwanza STD treatment trials.

The magnitude of STD cofactor effects (**Chapter 2**) had to be estimated because these values are input parameters to the trial simulations. At the same time, by explaining the difficulties and biases in estimating STD cofactor effects derived

from observational studies, this study served as a (retrospective) justification of the intervention trials. And it can be seen as a critical reappraisal of the earlier insight - deemed proven by the Mwanza trial and little disputed until after Rakai - that STD cofactor values are very large.

Of the categories of potential determinants in Table 1.2, our studies focused on the type of STD treatment and the type of population, because these were *a priori* thought to be most important. **Chapters 3 and 4** explored the probability with which episodes of gonorrhoea and chlamydia become symptomatic, a determinant of the impact of syndromic STD treatment (and as such also an input parameter to the simulation model *STDSIM*). This was done on the basis of survey data from the Rakai trial; the extent to which the outcomes are representative for the Mwanza population is addressed in the General Discussion (**Chapter 10**). As part of the studies on population differences, **Chapter 5** documents a systematic comparison of STD prevalences between the trials at their start. Both datasets had to be standardised for the relative sensitivities and specificities of the different diagnostic tests used, for differences in the age/sex composition of the tested subcohort, and for other eligibility criteria. **Chapter 6** describes *STDSIM*, with particular attention to its representation of sexual behaviour, which is one of the most difficult and critical aspects of the model. **Chapters 7 and 9** give more details on the *STDSIM* representations of STD, HIV and their biological interactions, which were especially relevant to their specific objectives. **Chapters 7 and 8** explore the importance of the type of STD treatment. This was done by simulating, besides the actual trials, the hypothetical impact of a Rakai-like mass treatment intervention in Mwanza (**Chapter 7**) and a Mwanza-like syndromic treatment intervention in Rakai (**Chapter 8**). The role played by the stage of the respective HIV epidemics was studied by simulating the impact of hypothetical STD treatment trials in Rakai at various stages of the HIV epidemic (**Chapter 8**). Among the mechanisms determining the outcomes of this study was the effect of HIV on the dynamics of the incurable cofactor STD HSV-2. The model representation of HSV-2 was derived from a separate, more theoretical simulation study, which is described in **Chapter 9. Chapters 8 and 9** also address the role behavioural risk reduction played in explaining the outcomes of the Rakai trial.

In the General Discussion (**Chapter 10**), the results of these studies are returned to the perspective of the full set of hypotheses proposed to explain the contradictory outcomes of the Mwanza and Rakai trial, as listed in Table 1.2. This chapter also summarises the results of additional studies not reported in the thesis. Some of these provide additional evidence for or against the hypotheses addressed in **Chapters 2 to 9**, and others shed light on the applicability and importance of the remaining hypotheses.

chapter 2

Estimating the magnitude of STD cofactor effects on HIV transmission – how well can it be done?

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2.1 Summary

Objective: To review possibilities for estimating cofactor effects of sexually transmitted diseases (STD) on HIV transmission based on observational studies.
Study design: We analyzed factors influencing associations between HIV and STD, which can bias STD cofactor estimations, from a sexual network perspective. We discuss study designs that reduce distortions and methods to improve estimates in the presence of confounding.
Results: Standard statistical adjustments of cofactor estimates are insufficient because they ignore clustering between HIV and STD in partners of study subjects, resulting from population heterogeneity in risk factors and assortative mixing. Reverse causation due to HIV-related immunosuppression may further inflate cofactor estimates. Misclassification of STD and clustering between STD can bias estimates in either direction. We quantitatively demonstrate that ignorance of sexual network effects may result in considerable overestimation of cofactor magnitudes.
Conclusion: The limitations of observational studies complicate quantitative inferences on the role of STD in HIV transmission.

2.2 Introduction

Observational studies have consistently shown the presence of sexually transmitted diseases (STD) to correlate with increased rates of sexual HIV transmission. Biological and clinical studies suggest that this association is in part caused by cofactor effects of STD on HIV transmission. STD may enhance the infectivity of HIV-positive patients, because they increase shedding of the HIV virus in the genital tract (the infectivity cofactor effect). Also, STD may increase the susceptibility to HIV infection, because they disrupt the mucosal integrity of the genital tract and increase the presence and activation of HIV susceptible leukocytes in the genital tract due to inflammation (the susceptibility cofactor effect) [Moss & Kreiss 1990, Laga *et al.* 1991, Wasserheit 1992, Mostad & Kreiss 1996, Vernazza *et al.* 1999, Fleming & Wasserheit 1999].

If STD cofactor effects are strong and STD are highly prevalent, STD control e.g. via improvement of STD management can be a strategy for HIV prevention. The effectiveness of STD treatment for HIV prevention has recently been tested in two trials in sub-Saharan Africa, with apparently contrasting outcomes [Wawer *et al.* 1999, Grosskurth *et al.* 1995a]. While community-randomized trials can provide evidence of the role of STD in HIV transmission in a particular population, their implications for prevention policy in other populations (external validity) are not straightforward. The population-attributable fraction (PAF) of HIV incidence which is due to cofactor STD varies between populations [Vittinghoff

& Padian 1996], for example with the type of sexual network and the stage of the HIV epidemic [Robinson *et al.* 1997]. Because of this, similar STD reductions may impact HIV incidence differently in different populations, and this needs consideration in the evaluation of cofactor effects and the implementation of interventions. For example, the lack of impact of STD reductions on HIV incidence in the mass treatment trial in Rakai, Uganda [Wawer *et al.* 1999] does not disprove the existence of cofactor effects, nor the possible effectiveness of mass treatment in populations with a larger PAF of STD in HIV spread [Gray *et al.* 1999, Korenromp *et al.* 2000c].

Besides external validity, other problems can complicate the interpretation of trial outcomes. Lack of impact on HIV may point at the non-existence of (strong) STD cofactor effects, but might as well simply be due to a failure to reduce STD rates. Conversely, if a trial showed a large reduction in HIV incidence but only little reductions in STD rates (as did the trial of syndromic case management in Mwanza, Tanzania [Grosskurth *et al.* 1995a, Mayaud *et al.* 1997a]), the impact of the intervention on HIV is not easily explained from a reduced STD cofactor burden, and other causal pathways cannot be excluded [Hudson 2001].

Prior to organizing STD intervention trials, and as a complementary approach to these trials, researchers have tried to infer the importance of STD in HIV transmission by estimating the magnitude of biological cofactor effects. Using cofactor magnitudes as input in epidemiological transmission models, the proportion of HIV transmission attributable to STD, and the impact of STD control relative to alternative HIV prevention strategies can be predicted for various settings [Stover & O'Way 1995, Robinson *et al.* 1995, Robinson *et al.* 1997, Bernstein *et al.* 1998, Korenromp *et al.* 2000c]. Provided good estimates of STD cofactor values are available, this approach would obviate the need to repeat effectiveness trials of every alternative STD control strategy in every new target population.

2.3 Estimating STD cofactor magnitudes

Cofactor values are commonly estimated from longitudinal observational studies monitoring HIV transmission in subjects or couples who had or did not have STD during or at start of an observation interval. (Often, the acquisition of STD is however measured retrospectively, as otherwise it would have to be treated.) Associations between HIV transmission and STD presence in these studies can be expressed in different ways: as odds ratios of cumulative transmission throughout the duration of follow-up intervals, as hazard rate ratios based on a survival analysis, or as relative risks per single sexual contact [Boily & Anderson 1996]. The interpretation of these cofactor measures is extremely difficult, as they are subject to a multitude of possible biases which may inflate or deflate their value [Mertens *et al.* 1990, Wasserheit 1992, Nagelkerke *et al.* 1995, Hayes *et al.* 1995c,

Boily & Anderson 1996, Dickerson *et al.* 1996].

Factors inflating STD cofactor estimates

Table 2.1 lists factors contributing to a positive association between STD and HIV, which may inflate cofactor estimates. The primary cause of spurious associations between STD and HIV is their common mode of acquisition, through sexual contact with an infected partner. Since individuals with many or promiscuous partners are at high risk for both STD and HIV, associations between STD and HIV incidence are expected even in the absence of biological interactions [Mertens *et al.* 1990, Wasserheit 1992, Boily & Anderson 1996]. In order to reduce confounding resulting from underlying same risk factors, cofactor estimates are commonly statistically adjusted for the presence of known risk factors, such as the number of partners of the subject at risk, e.g. by multivariate logistic regression or Mantel-Haenszel stratification. Such adjustment typically reduces the magnitude of the risk estimate [Telzak *et al.* 1993, Weir *et al.* 1994, Nelson *et al.* 1997, Nopkesorn *et al.* 1998], as would be expected in case of confounding. It may however not fully resolve confounding, because STD, HIV and risk behaviour cluster not only in study subjects, but also in the (unknown) partners of study

Table 2.1 **Factors enhancing the association between HIV and STD, which can inflate STD cofactor estimates.**

Factor	Applies to which STD:
Same underlying risk behaviour for STD and HIV	all
Heterogeneity in susceptibility to both STD and HIV, due to:	
- circumcision	esp. ulcerative STD
- general health, nutritional and immune status	all
- hormonal contraception	all
- young age in females	all
Heterogeneity in infectivity with both STD and HIV, due to:	
- circumcision	esp. ulcerative STD
- general health, nutritional and immune status	all
- HIV-related immunosuppresssion	esp. HSV-2 and chancroid?
Concurrent other cofactor STD, including entanglement of susceptibility and infectivity cofactors	all
Differential misclassification of STD status, due to:	
- misreporting of symptoms	all
- short duration of STD relative to observation interval	esp. STD of short duration like gonorrhoea

subjects, the partners of their partners, i.e. their sexual network at large. Associations between STD and HIV caused by common underlying risk behaviour are particularly strong because of heterogeneity in risk behaviour (for example, few individuals have many partners while the majority has few) and assortative mixing (high-risk individuals tend to choose high-risk partners) [Garnett & Anderson 1993a, Morris 1997]. Thus, having at least 1 unprotected contact in the form of an STD source partner may indicate a relatively large probability of unprotected contacts with other high-risk partners, which may confer a risk of HIV on top of that from the STD source partner.

Consider a cohort of HIV-susceptibles, some of whom experience an STD episode during the observation period, and some of whom do not. A subject experiencing an STD must have had an STD infected partner during follow-up, who has him-/herself earlier acquired this STD by risk contact and is therefore relatively likely to harbour HIV as well. Consequently, an STD-exposed subject is at increased risk of being exposed to HIV from the STD-infected partner, relative to subjects who do not experience STD. By enhancing the association between STD and HIV acquisition, this effect thus inflates susceptibility cofactor estimates. Importantly, since the window period till diagnostic detectability of STD (typically 1 week [Holmes *et al.* 1999]) is shorter than the window period till seroconversion for HIV (between 2-3 months [Horsburgh Jr. *et al.* 1989, Willerford *et al.* 1993]), the acquisition of HIV and STD in a single sexual contact from an HIV- and STD positive partner may in longitudinal studies appear as if the STD infection preceded HIV acquisition.

Non-behavioural risk factors that enhance either the infectivity with or the susceptibility to STD and HIV simultaneously also contribute to the association between STD and HIV. Lack of circumcision, for instance, probably contributes to the association between ulcerative STD and HIV by increasing the susceptibility to, and possibly the infectivity with those STD and HIV in males independently [Cameron *et al.* 1989, Jessamine *et al.* 1990, Moses *et al.* 1998, Lavreys *et al.* 1999, Quinn *et al.* 2000]. This effect may indirectly also inflate cofactor estimates in females, if male circumcision causes STD and HIV to cluster in their male partners and consequently in the women themselves. Other non-behavioural common risk factors include general immune and health status, nutritional/vitamin A status, hormonal contraception and young age in females [Clemetson *et al.* 1993, Mostad *et al.* 1997, John *et al.* 1997]. By causing heterogeneity among individuals in the fragility of the genital mucosa and hence in susceptibility to and infectivity with HIV and STD, these - and other unknown - factors will inflate STD cofactor estimates, unless they could be adjusted for in both study subjects and partners.

In the relation between HIV infectivity and STD, besides common risk factors, 'reverse causation', i.e. HIV predisposing to having STD, is a source of bias. A factor inducing such 'reverse causation' is HIV-related immunosuppression. Immunosuppression increases the presence and duration of STD in the later,

highly infectious stages of HIV/AIDS disease, due to a worse treatment response, prolongation of the episode duration if left untreated and an increased occurrence of (recurrent) ulcers [Nzila *et al.* 1991, Wasserheit 1992, Wald *et al.* 1993, Ghys *et al.* 1995, Kaul *et al.* 1997]. Evidence for this can be gleaned from the fact that treatment of HIV patients for STD coinfection reduces the level of HIV shedding, but commonly not to the low levels of non-STD infected HIV patients [Moss *et al.* 1995, Cohen *et al.* 1997, Ghys *et al.* 1997, Rotchford *et al.* 2000]. It has also been suggested on theoretical grounds that HIV disease might increase the susceptibility to STD infection by altering the host response [Wasserheit 1992], although empirical support for this is lacking.

Finally, clustering between different STD - which is plausible because of common underlying risk factors and has been observed empirically [Laga *et al.* 1993, Cameron *et al.* 1989, Mbizvo *et al.* 1996, Dada *et al.* 1998] - enhances the association between HIV and any single STD. Unless adjusted for, clustering may cause the effect on HIV transmission of each single cofactor to be overestimated. Clustering between a cofactor STD and a non-cofactor STD may cause the non-cofactor STD to be erroneously perceived as a cofactor itself. This effect may for instance play a role in observed associations between bacterial vaginosis (BV) and HIV [Cohen *et al.* 1995, Sewankambo *et al.* 1997, Taha *et al.* 1998, van de Wijgert *et al.* 2000], because BV has been shown to associate independently with trichomoniasis and other non-ulcerative STD [Sewankambo *et al.* 1997, Zenilman *et al.* 1999, Taha *et al.* 1999, van de Wijgert *et al.* 2000].

A special case of clustering of STD is in sexual couples. Due the high transmission efficiency of classical STD (in the order of 10-30% per sexual contact [Brunham & Plummer 1990, Holmes *et al.* 1999]), STD in HIV-discordant couples are often present in both partners during at least part of the follow-up period. Estimates of the susceptibility cofactor can then be inflated by an additional enhancement of HIV transmission by the infectivity cofactor, and vice versa. The likelihood and extent of inflation due to concurrent STD depends on the interaction between coexistent cofactors, which has not been studied empirically. Their effects can either multiply - e.g. if genital ulcer disease (GUD) increases HIV transmission 5-fold and chlamydia 3-fold, their combination increases HIV transmission 15-fold - , add up - e.g. the combination increases HIV transmission 7-fold - , or saturate - e.g. chlamydia on top of GUD does not further increase HIV transmission. If cofactors multiply, the concurrent STD can increase HIV transmission equally in GUD-positive and GUD-negative individuals, and, in case the concurrent STD clusters with GUD, its cofactor effect then enhances the association between HIV and GUD. If the cofactor effects add up or saturate, however, the net effect on the risk estimate for the STD of interest is not obvious and depends on the degree of clustering between STD in the study population. In the extreme case of no clustering between STD and saturating or additive cofactors, the concurrent STD might increase HIV transmission more in GUD-negative individuals than in GUD-positive individuals, thus deflating the risk estimate for GUD. If

cofactors result from different mechanisms, multiplication of their effects is biologically plausible. This may for example be the case if an ulcer in an HIV-negative person created a portal of entry for HIV, while a concurrent chlamydia infection increased the presence of HIV-susceptible inflammatory cells in the genital region. One same STD in both partners, e.g. genital ulcers which can create blood-blood contact, may also have a combined cofactor effect of at least the product of the individual cofactor effects (Heiner Grosskurth, p.c.). For cofactor effects resulting from the same underlying mechanisms, saturation would seem more likely. An example could be coinfection of an HIV-patient with chancroid and syphilis. Each alone, these infections enhance the infectivity with HIV [Fleming & Wasserheit 1999], but their combined effect probably saturates at some point.

Factors deflating STD cofactor estimates

Other mechanisms may dilute observed associations between STD and HIV and bias cofactor estimates downward (Table 2.2).

Non-differential misclassification of STD status will dilute any association, whether positive or negative. Misclassification is particularly likely for self-reported symptoms of non-ulcerative STD in females, which often cause only mild and aspecific symptoms that are not perceived at all [Holmes *et al.* 1999]. Also for laboratory-diagnosed infections, getting a complete track of STD occurrence during follow-up is often difficult. Poor sensitivity and specificity of diagnostic tests may cause misclassification. The time interval between follow-up visits in cofactor studies is typically longer than the duration of STD episodes, so that infections may appear and resolve in between two subsequent visits and hence go unnoticed.

Table 2.2 **Factors weakening the association between HIV and STD, which can deflate STD cofactor estimates.**

Factor	Applies to which STD:
(Non-)differential misclassification of STD status, due to:	
- misreporting of symptoms	esp. non-ulcerative STD in females
- limitations in diagnostic tests	all
- short duration of STD relative to observation interval	esp. STD of short duration like gonorrhoea
Non-differential misclassification of HIV status due to delayed seroconversion	all
Sexual abstinence during STD symptoms	esp. painful STD like ulcers

Differential STD misclassification, by contrast, can either dilute or enhance STD/HIV associations. As an example of enhancement, study participants experiencing frequent STD episodes may be more likely to be classified as STD-exposed than participants experiencing STD less frequently, because the former are better at symptom recognition and their chances of having at least one episode coinciding with a sampling moment are larger. In that case, the true difference in the number of STD episodes between the 'positive' and 'negative' group would be larger than apparent, leading to overestimation of per-episode or per-contact cofactor effects.

Like for STD, non-differential misclassification of HIV status at the beginning and end of follow-up intervals, due to a delay in seroconversion after HIV infection of about two months [Horsburgh Jr. *et al.* 1989, Willerford *et al.* 1993] deflates positive associations.

Finally, if STD patients abstain from having sex when symptomatic, actual associations would be lower than the theoretical cofactor effect, because the number of STD-enhanced HIV exposures is small.

2.4 Example of a cofactor estimation

The above summary of determinants of STD/HIV associations elucidates the complexity of estimating cofactor magnitudes from observational studies. While confounding due to common risk factors can be reduced by adjusting for as many subject attributes as possible, the confounding due to sexual network effects is however virtually impossible to completely control for. Even though the majority of studies taken as evidence for the existence of significant cofactor effects can be credited for using designs and statistical analyses that reduce confounding and other distortions as much as possible [Holmberg *et al.* 1988, Cameron *et al.* 1989, Plummer *et al.* 1991, Laga *et al.* 1993, Telzak *et al.* 1993, Hayes *et al.* 1995c, Nelson *et al.* 1997], none of these can be free of all bias. Theoretically, the ideal design for a cofactor study would be a trial randomizing (matched pairs of) individuals into two groups, of which one would be infected with STD and the other not. Both individuals in a pair would then be exposed either in a controlled way and at a controlled frequency to the same HIV-positive partner(s), or uncontrolled to a randomized set of HIV-positive partners. By controlling and/or randomizing both subjects and partners, distortions due to heterogeneity in susceptibility to and infectivity with STD and HIV are avoided. Controlling the mode and frequency of contact with HIV-positive partner(s) should ensure homogeneity in exposure. Obviously, such human experiments are for ethical and practical reasons never performed; imagining them however illustrates how observational studies inevitably fall short of the standards. The impossibility for observational studies to avoid all these biases would not be of such importance if this could

cause only small deviations. However, this is not true, as we will illustrate with data from an often quoted quantitative example.

The cofactor effect of GUD on female susceptibility was estimated [Hayes *et al.* 1995c] from a study of HIV-negative prostitutes in Nairobi who were followed for on average 21 months [Plummer *et al.* 1991]. In this cohort, of 68 prostitutes who reported one or more GUD episodes during follow-up, 72% seroconverted for HIV, while 55% of 49 prostitutes without GUD seroconverted. To avoid biases in the estimates due to the relatively long duration of follow-up, during only part of which the STD would be really present, the cofactor estimation focused on the effect per single sexual contact. Per-contact cofactors were derived from the observed cumulative risks, using estimates of the numbers of sexual contacts with HIV-positive client-partners during follow-up and the duration of STD episodes [Hayes *et al.* 1995c]. As summarized in Table 2.3, it was estimated that GUD enhances the per-contact risk of HIV acquisition by the women by a factor 23 [Hayes *et al.* 1995c].

In this calculation, HIV prevalence was assumed to be equal in clients of GUD-exposed and unexposed prostitutes. Because of clustering between the presence of HIV and STD and between HIV exposure and STD, which has for instance been observed in studies in Uganda [Carpenter *et al.* 1999] and Cameroon [Weir *et al.* 1994], the prevalence of HIV might however be higher among the clients of GUD-exposed prostitutes. In addition, STD- and HIV- exposed prostitutes may have more frequent clients contacts. In a subcohort of the same Nairobi population, HIV-positive prostitutes had a 22% higher client contact frequency than HIV-negative prostitutes [Kaul *et al.* 1997]. If we assume that, due to these effects, the number of HIV exposures was 20% lower among GUD-unexposed prostitutes relative to GUD-exposed prostitutes, the cofactor estimate reduces from 23-fold to 12-fold (Table 2.3).

Table 2.3 also shows the possible bias if the effect of GUD were confounded with that of lack of circumcision in clients. Based on circumcision rates in Nairobi males of about 91% in the general population [Hunter *et al.* 1994] and between 73-81% among STD clinic attenders [Simonsen *et al.* 1988, Cameron *et al.* 1989, Nasio *et al.* 1996], we estimated that about 20% of clients of GUD-exposed prostitutes, and 10% of clients of GUD-unexposed prostitutes were uncircumcised. If we assume that the per-contact infectivity with HIV is 3-fold higher in uncircumcised males [Cameron *et al.* 1989, Jessamine *et al.* 1990, Moses *et al.* 1998, Quinn *et al.* 2000], the cofactor estimate would be 14.

In a third scenario, we considered that the GUD-exposed prostitutes suffered not only a susceptibility cofactor effect due to their own GUD, but, preceding this, also a male infectivity cofactor effect during the client contact in which they acquired GUD. We estimated that GUD-exposed prostitutes, who each experienced on average 2.5 GUD episodes during follow-up [Hayes *et al.* 1995c], had on average 2.5 contacts with HIV-positive GUD source clients during follow-up, during which a cofactor effect of 5 applied; no such effect was assumed for GUD-

***Table 2.3* Quantitative illustration of the effect of confounding on a per-contact cofactor estimate for genital ulcer disease (GUD) on susceptibility to HIV, based on a cohort study of female prostitutes in Nairobi [Plummer *et al.* 1991, Hayes *et al.* 1995c].** Formulas adopted: $\pi_0 = 1-(1-P)^n$ (Eq. 1); $\pi_1 = 1-(1-P)^{n0} * (1-fP)^{n1}$ (Eq. 2), where: π_0 = the observed cumulative risk of HIV seroconversion for the STD-unexposed group; π_1 = the observed cumulative risk of HIV seroconversion for the STD-exposed group; n = the estimated average number of sexual exposures to HIV over the follow-up period for the unexposed group; P = the corresponding per-contact HIV transmission probability in the absence of STD; n_0 = the estimated average number of sexual exposures to HIV over the follow-up period for the STD-exposed group during the absence of the STD; n_1 = the estimated average number of sexual exposures to HIV over the follow-up period for the STD-exposed group during the presence of the STD; f = the calculated per-contact cofactor effect. The stratifications in brackets in columns n, n_0 and n_1 denote contributions of subgroups of client-partners. Explanation of calculation for Base-case scenario: At a reported average frequency of client contacts of 3.8 daily [Plummer *et al.* 1991], 10% of which were on average protected by condom use, $\pi_0 = 55\%$, $\pi_1 = 72\%$ and an estimated prevalence of HIV in the male client population of 11% [Hayes *et al.* 1995c], n was estimated at about 246, giving $P = 0.0032$ (Eq. 1). Assuming a fixed duration per GUD episode of 1 week, n_0 and n_1 were estimated at 242 and 6.6, respectively, giving $f = 23$ (Eq. 2) [Hayes *et al.* 1995c].

Confounder	Original (implicit) assumption	Alternative assumption	n†	*P*	n0†	n1†	f
Base-case scenario	All below	-	246.0	0.00324	242.4	6.6	23
1. Sexual network	Frequency of unprotected contacts with HIV$^+$ clients is equal for GUD$^+$ and GUD$^-$ prostitutes	Frequency of unprotected contact with HIV$^+$ partners is 20% higher for GUD$^+$ relative to GUD$^-$ prostitutes. Contacts with HIV$^+$ partners do not temporally cluster with GUD in the prostitutes.	220.4	0.00362	260.6	7.1	12
2. Circumcision	No cofactor effect of circumcision, and/or no clustering between GUD and circumcision	20% of partners of GUD$^+$ prostitutes and 10% of partners of GUD$^-$ prostitutes are uncircumcised. Transmission probability is 3x *P* in case of lack of circumcision. HIV exposures to uncircumcised partners do not temporally cluster with GUD in the prostitute.	246.0 (c 221.4; u 24.6)	0.00270	242.4 (c 193.9; u 48.5)	6.6 (c 5.3; u 1.3)	14
3. Clustering with STD in partner	No clustering in STD status between partners, and/or no cofactor effect of GUD in the 'source' client.	GUD-exposed prostitutes have an average of 2.5 contacts with GUD source partners, while GUD-unexposed prostitutes do not. GUD source partners are all HIV$^+$. GUD in source partner increases *P* 5-fold, and does not coincide with GUD in the prostitute.	246.0	0.00324	242.4 (GUD$^-$ 239.9; GUD$^+$ 2.5)	6.6	20
Combination of 1, 2 and 3.	See above	All above. GUD source partners are uncircumcised. The effect of circumcision multiplies with the cofactor effects of GUD.	220.4 (c 198.4; u 22.0)	0.00301	260.6 (c GUD$^-$ 208.5; u GUD$^-$ 49.6; u GUD$^+$ 2.5)	7.1 (c 5.7; u 1.4)	3

† c = circumcised; u = uncircumcised

unexposed prostitutes. This changed the cofactor estimate from 23 to 20.

Finally, as an illustration of the overall effect that residual confounding may have, we considered these three confounders in combination. In this combined scenario, the per-contact cofactor estimate for GUD on female susceptibility consistent with the Nairobi data was only 3 (Table 2.3).

In contrast to factors inflating cofactor estimates (Table 2.1), factors deflating cofactor estimates (Table 2.2) are unlikely to have played a large role in this example. Misclassification of ulcer incidence would seem uncommon in this group of prostitutes, who thanks to intensive and regular counselling on symptom recognition and health seeking were believed to report to the clinic for the majority of ulcer episodes [Plummer *et al.* 1991, Hayes *et al.* 1995c]. The long follow-up (21 months) relative to the HIV window period renders misclassification of HIV status during the first and last months of the observation interval relatively unimportant. A reduced frequency of sexual contact during GUD was however possible, and indeed taken into account in the original analysis, under the estimated number of HIV exposures during the presence of GUD [Hayes *et al.* 1995c].

2.5 Discussion

By considering all determinants of associations between STD and HIV, we showed that available study designs and methods of statistical correction are not sufficient to resolve all biases that can occur when estimating the magnitude of STD cofactor effects from observational studies. The most important source of bias is confounding due to the common mode of acquisition, and hence the multiple common risk factors, for STD and HIV (Table 2.1). In particular, ignorance of sexual network effects can result in considerable overestimation of cofactor effects. Our quantitative example hereof, in which the consideration of three plausible confounders reduced a per-contact cofactor estimate for GUD on female susceptibility from 23 to 3 (Table 2.3), by no means exhausts all possible levels and combinations of distortions. In more heterogeneous study populations, confounding is probably more severe than in the Nairobi prostitute cohort, where heterogeneity in risk behaviour was likely present in the client partners but probably not so much among the prostitutes themselves [Plummer *et al.* 1991].

In contrast to confounding, which besets all observational studies, a subset of cofactor studies is affected by STD misclassification (Table 2.2). The dilution of cofactor estimates that may result from this can be reduced by increasing the frequency of follow-up visits, as has been done in recent studies [Rakwar *et al.* 1999]. The availability of more reliable STD diagnostic tests may in future reduce this problem further.

Within the restriction of observational studies, a preferred study design may be the follow-up of monogamous HIV-discordant couples [De Vincenzi 1994, Gray *et al.* 1999, Carpenter *et al.* 1999, Quinn *et al.* 2000]. In such cohorts, partner attributes such as circumcision status and the level of immunosuppression can be taken into account, and heterogeneity in exposure to HIV and STD is relatively limited. Couple studies, however, have disadvantages as well. These relationships may not be representative for all partnerships. For example, stable relationships in which HIV has not yet been transmitted from the HIV-positive partner may disproportionally include recently initiated relationships, or partners who for some reason are relatively non-infectious. Furthermore, the validity of this design depends critically on whether the HIV-negative partners behave truly monogamously during follow-up, and the HIV-positive partners do not.

A further step can be the re-analysis of observational studies using dynamic individual-based transmission models that simulate the clustering between STD and HIV due to same underlying risk factors, patterns in sexual behaviour and STD cofactor effects. Projected STD/HIV associations in simulated individuals and couples can be compared with classical cofactor estimates by processing them statistically as commonly done with actual data, iteratively fitting them against those empirical estimates by varying the underlying model input cofactor values. By simulating a specific cohort study with respect to its design, the sexual network in which it was based and the statistical analysis, cofactor magnitudes can thus be indirectly estimated from these data, accounting for both commonly considered biases and sexual network effects. Network simulations have provided important theoretical insights into the determinants of STD/HIV associations [Koopman *et al.* 1991, Robinson 1994, Boily & Anderson 1996]. It must however be borne in mind that the added value of model-based cofactor estimates depends critically on the correctness of representation of the sexual network and of the quantitative effect of all other sources of bias. If the network or some sources of bias are not well known, model-based estimates may not be better than simpler estimates.

Previous overestimation of STD cofactor effects may be one of the reasons for the disappointing lack of impact of STD prevalence reductions on HIV incidence in the STD treatment trial in Rakai [Wawer *et al.* 1999]. The contrasting outcomes of the Mwanza trial, which showed a large impact of improved syndromic STD management on HIV incidence with apparently very limited STD reductions [Grosskurth *et al.* 1995a, Mayaud *et al.* 1997a] have been discussed elsewhere [Habbema & De Vlas 1995, Hudson 1999, Grosskurth *et al.* 2000]. Like intervention expectations, estimates of the fraction of HIV transmission attributable to STD calculated on the basis of classical cofactor estimates may as well be inflated [Otten Jr. *et al.* 1994, Laga *et al.* 1993, Fleming & Wasserheit 1999, Gray *et al.* 1999, Orroth *et al.* 2000]. Also, previous model projections, which have assumed cofactor effects of up to a 100-fold per sexual contact [Robinson *et al.* 1995, Rob-

inson *et al.* 1997, Bernstein *et al.* 1998, Korenromp *et al.* 2000c] may have exaggerated the importance of STD in HIV spread and prevention.

Besides biasing the overall value of cofactor estimates, the limitations of observational studies have other implications. The strength of distortions differs between populations, depending on the extent of heterogeneity in sexual behaviour and the local prevalence of additional confounders, such as AIDS-induced immunosuppression. This complicates the comparison between studies and populations of PAFs based on such population-dependent risk estimates. For instance, the PAF of STD in HIV transmission has been estimated as larger in the Mwanza trial population as compared to the Rakai trial population. This was however for a considerable part due to higher risk estimates in Mwanza, and not only to a higher fraction of HIV seroconverters exposed to STD [Gray *et al.* 1999, Orroth *et al.* 2000]. If the larger risk estimates in Mwanza related mainly to more (residual) confounding than in Rakai, e.g. due to the different follow-up scheme or to stronger clustering in Mwanza between STD and other risk factors, the site comparison would be flawed and the site difference in PAFs overestimated.

Furthermore, as some biases apply only to subsets of STD, it is unclear whether the observed strength of associations with HIV of different STD directly reflect their relative cofactor strengths. For example, the relatively strong association between HIV and ulcerative STD as compared to non-ulcerative STD may in part result from the strong association of ulcerative STD with lack of circumcision and HIV-related immunosuppression.

In conclusion, given the difficulty in estimating the magnitude of STD cofactor effects and the absence of solid and consistent evidence from STD intervention trials, it remains uncertain how much STD treatment can contribute to HIV prevention. Clearly, additional community-based intervention trials would help clarify this issue. As yet, for evidence-based HIV prevention policy, condom promotion and other forms of (targeted) primary prevention - which directly prevent the transmission of HIV as well as STD - remain the safest bet. However, even if STD cofactor effects on HIV transmission would be weaker than previously thought, improving STD management remains an important component of HIV prevention programmes. Any association between STD and HIV, whether causal or not, indicates that STD patients are at high risk of contracting and transmitting HIV. The education, counselling, condom provision and contact tracing that is part of comprehensive STD management can therefore be an effective means of targeting these HIV prevention strategies to those most in need.

chapter 3

The prevalence of self-reported discharge and dysuria in *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infection: a systematic review

Sudaryo MK, Korenromp EL, Arends LR, Habbema JDF. The prevalence of self-reported discharge and dysuria in *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infection: a systematic review. *Submitted for publication.*

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3.1 Summary

Objective: To estimate the point prevalence of self-reported discharge and dysuria among patients infected with *Neisseria gonorrhoeae* (NG) or *Chlamydia trachomatis* (CT), and to assess the influence of treatment seeking behaviour in the population hereon.
Methods: Literature review and pooling of prevalences across studies. Correlations in the occurrence of discharge and dysuria, and the relation between symptom prevalence and indicators of STD treatment patterns, were assessed as Pearson correlation coefficients.
Results: Pooled prevalences of discharge and dysuria were 23% and 17% for NG in females, 26% and 7% for CT in females, 18% and 22% for NG in males, and 6% and 6% for CT in males. For females with either infection, the prevalence of discharge varied considerably between studies. For males but less for females, the prevalences of discharge and dysuria tended to correlate positively, across populations and within individual patients. Symptom prevalence did not correlate with the proportion of cases seeking medical treatment ($p = 0.97$) or the patient delay interval in the population ($p = 0.6$).
Conclusions: The prevalence of self-reported symptoms is low among NG- and CT-infected subjects across a range of populations, in spite of variation in rates of STD treatment. Besides the pathogenicity of the infections and treatment patterns, geographical variation in (subjective) reporting behaviour and, for females, aspecific discharge may be important determinants of symptom prevalence. The prevalence of self-reported symptoms alone is not a good rationale for choosing between NG- and CT- control strategies, nor for evaluating the success of treatment services.

3.2 Introduction

Sexually transmitted diseases (STDs) are widespread and a major cause of acute and chronic morbidity among adults throughout the developing world; their control is considered important and highly cost-effective [Piot & Islam 1994, Over & Piot 1996]. The choice of the most appropriate STD control strategy should take into account how many cases are symptomatic. If most patients become symptomatic and seek treatment for these symptoms, high quality clinical case management would be an important component of control programmes. Even in settings where diagnostics on the aetiologic agent is not feasible, the syndromic approach, which consists of treating patients for the main possible causes of their symptoms [Adler 1996, Wilkinson 1997, Dallabetta *et al.* 1998], could guarantee adequate treatment. If most patients develop symptoms but fail to recognize these or do not seek treatment, education on symptom recognition and on

the importance of prompt treatment becomes essential. However, if the majority of infections pass without symptoms, more active intervention, such as screening or mass treatment, may be appropriate in addition. Therefore, knowledge on symptom frequency is important in STD-care decision making.

For *Neisseria gonorrhoeae* (NG) and *Chlamydia trachomatis* (CT) infection, the main acute symptoms, which form the entrance point for syndromic treatment, are genital discharge and dysuria. These infections are however thought to often pass without producing these symptoms, especially in women [Handsfield *et al.* 1974, Oates & Csonka 1990, Martin 1990, Holmes *et al.* 1999]. Symptom probability is usually estimated from cross-sectional studies measuring the proportion of STD infected persons reporting current symptoms. In this chapter, we present a systematic review on the prevalence of self-reported discharge and/or dysuria among NG- and CT-infected males and females in general populations from across the world that were recruited according to the same set of criteria. We assess the correlation between the occurrence of both symptoms, and how these rates relate to the extent of STD treatment in the population. We discuss the use and limitations of the prevalence of self-reported symptoms as the rationale for choosing between STD control strategies in the light of our results.

3.3 Methods

Literature search

A systematic review was performed of English language articles reporting any of the following outcomes of interest on infection with NG and/or CT in adult and adolescent males and females (with the exception of sexual abuse cases in adolescents):

- the proportion who experience current discharge (females: abnormal vaginal discharge; males: urethral discharge) and/or dysuria;
- the proportion seeking effective medical treatment;
- the patient delay interval, i.e. the time period between the onset of symptoms and the receipt of effective medical treatment (more properly, this is the sum of patient delay and health care delay, but we will use the term 'patient delay' for brevity).

We interpreted any treatment in modern health facilities providing recommended antibiotics as effective.

Eligibility criteria for studies on symptom prevalence were:

- The article contains quantitative information on the proportion of infected patients reporting genital or urethral discharge or dysuria. This could be either

a direct estimate of this proportion, or the possibility to derive this proportion from reported numbers or proportions with and without STD among symptomatic and non-symptomatic groups.

- The subjects have been recruited in such way that they are non-selective for the symptoms of interest, i.e. from general populations, antenatal and family planning clinic attenders or contacts referred by STD patients. Thus, we excluded studies involving subjects visiting clinics because of symptoms. Symptoms refer to those perceived and reported by subjects (as opposed to "signs" observed by physicians).
- The term 'current' refers to symptoms perceived at the time of study interview or within a period of maximally 6 months before the interview.

The search was done on Medline databases of between 1966 and 2000, with the search program *Ovid Search Software* version 3.0, by combining the subject headings *gonorrhoea, chlamydia, urethritis, vaginal discharge, urinary tract infection,* and *cervicitis* with the text words *discharge* and *dysuria.* For symptom prevalence, this search was combined with a search of text word *symptom**; for patient delay with subject heading *time factor* and/or text word *delay*; for the proportion seeking treatment with subject heading *patient acceptance of health care* and/or text words *health seeking, treatment seeking,* or *seek treat**. To increase specificity, searches from subject headings were limited to the fields diagnosis, drug therapy, epidemiology, etiology, and transmission. In addition, we identified eligible articles by back tracing from the reference list of articles already included, or upon suggestion by experts. These additional strategies served to reduce the probability of misssing papers due to limitations in our search strategy, incompleteness of the Medline database, and missing information in titles or abstracts of articles included in Medline and identified by our search strategy.

Data extraction

From each article, we extracted place and time period of the study, characteristics of the study population and sampling frame, method of diagnosis of the infection, time of experiencing symptoms, and if available the presence of concurrent other non-ulcerative STD and the prevalence of symptoms among uninfected controls. Data on patient delay were recorded as means or medians. For studies reporting only the distribution of patients over categories of delay intervals, we estimated the median assuming a homogeneous distribution of cases within each category, and assuming a mean duration of 1.5 times the lower limit for each uppermost category (e.g. 10.5 days for a category of '7 or more days'). Data were independently extracted by two investigators (MKS and ELK) and subsequently compared. Discrepancies were resolved by discussion and consensus.

Statistical analysis

We pooled "primary data" as if all patients in all studies combined were one big sample and calculated the overall symptom prevalence and the corresponding 95% confidence interval (CI). To analyse the relation between outcomes, Pearson correlation coefficients (r) and the corresponding p-values of statistical significance were calculated, using SPSS version 9.

3.4 Results

Articles identified

Using the criteria outlined above, we included 36 articles, published between 1969 and 2000 (Appendices I and II). The studies come from 5 continents and include both developing and industrialized countries. The number of subjects per study varied from 2 to 2570. Some articles were unclear about the time of experiencing symptoms (Appendix I); in these cases we interpreted symptoms as "current".

Symptom prevalences

Taking into account the sample sizes of studies, the prevalence of self-reported symptoms were reasonably similar across studies, except for discharge in females (Figure 3.1). For discharge, the range was zero to 100% in females and zero to about 50% in males, while the prevalence of dysuria ranged from zero to about 20% in females and zero to 40% in males. Studies reporting a 0% prevalence were mainly ones with small sample sizes, and this outcome may therefore in part relate to chance variation around a very low prevalence in the base-population from which the study population was sampled. No clear relations were apparent between symptom prevalence and the geographical location of the study (Appendix I).

Figure 3.1 also shows the pooled symptom prevalence. For females with either NG or CT, discharge was on average more common than dysuria. Oppositely, among males with NG, dysuria was more common than discharge. Among males, both symptoms are more common in NG than in CT, while for females, only dysuria was more common in NG than in CT infection. Discharge was more often seen in females than in males for both STD. On average, for NG, both symptoms were about as frequent in females as in males, while for CT, discharge was more prevalent in females than in males.

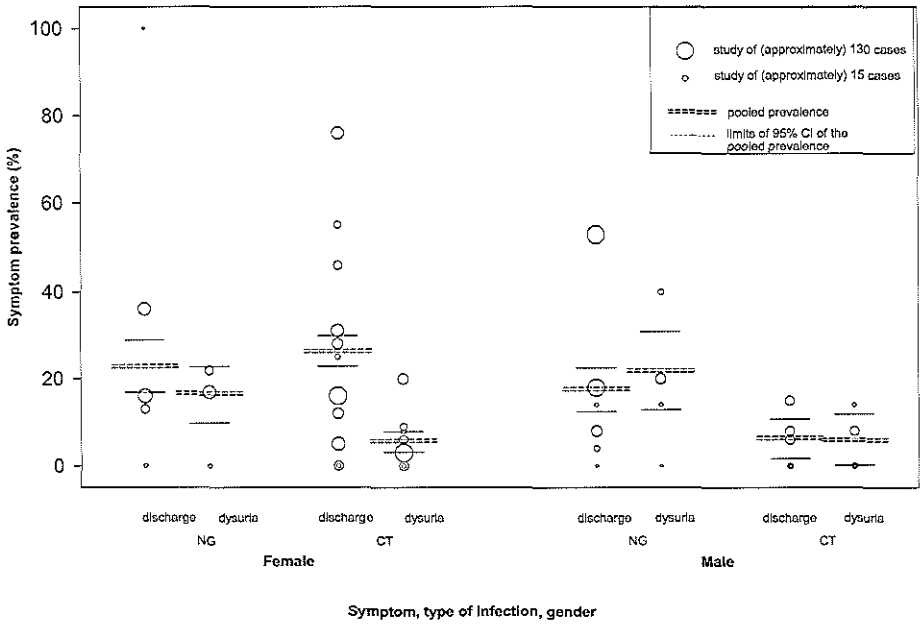

Figure 3.1 **Prevalence (%) of discharge and dysuria in females and males infected with *Neisseria gonorrhoeae* (NG) or *Chlamydia trachomatis* (CT), in individual studies and pooled across studies.** Each circle represents one individual study. Study sample size is proportional to the square of the circle surface area (see insert).

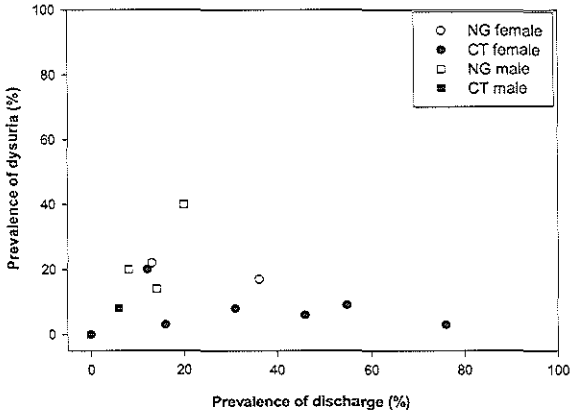

Figure 3.2
Correlation between prevalences (%) of dysuria and discharge, stratified by gender and type of infection, from studies reporting both categories of symptoms for the same population. Each symbol represents one individual study.

Correlations between discharge and dysuria within populations

Among studies reporting both discharge and dysuria separately (Figure 3.2), for males the proportion with discharge correlated positively with the proportion

with dysuria, for both NG and CT ($r = 0.92, p = 0.03$, and $r = 1.000, p < 0.001$, respectively). For females, however, discharge was more frequent than dysuria in all but one study, and these two proportions did not correlate ($r = 0.72, p = 0.28$, and $r = 0.07, p = 0.87$, for NG and CT respectively). While the proportion of female patients with discharge varied widely among these studies (between 0 and 76%), the proportion with dysuria was low (between 0 and 22%) in all.

Prevalence of either vs. both symptoms

In most countries, syndromic treatment guidelines use as criterion for non-ulcerative STD the presence of discharge *and/or* dysuria [Dallabetta *et al.* 1998]. For assessing the value of syndromic management, we therefore looked at the combined prevalence of at least one of these symptoms. Due to overlap in symptoms (some patients having both and others neither), the overall symptom prevalence will be less than the sum of the prevalences of discharge and of dysuria separately. This effect may be enhanced if the occurrence of both symptoms clusters within individual patients, due to variations in symptomaticity between bacterial strains or types, patients and ethnical groups [Crawford *et al.* 1977, Workowski *et al.* 1994, Alary *et al.* 1996, Royce *et al.* 1999]. In the studies in this review, clustering may be inferred from the correlation in prevalence between these 2 symptoms across populations (Figure 3.2). We therefore compared the prevalences of discharge, dysuria and the combination of either or both symptoms in the subset of studies reporting all 3 outcomes. For NG in females, this subset of studies had an average prevalence of 9% for discharge and 16% for dysuria [Catterson & Zadoo 1993, Colvin *et al.* 1998, Paxton *et al.* 1998b]. If both symptoms would occur independently, the combination of at least one symptom would be expected to occur in 24% of cases, i.e. in (100 - ((100-9)*(100-16))%. The observed prevalence of reporting at least one symptom was 25%, suggesting that these two symptoms did not correlate. Also in males with NG [John & Donald 1978, Mayaud *et al.* 1997a, Rees *et al.* 1977, Colvin *et al.* 1998, Paxton *et al.* 1998b], the observed prevalence of at least one symptom was similar to the expected combined prevalence (both 30%), suggesting no correlation between discharge and dysuria. In line with this, in 4 studies in NG-infected males that did not discriminate between discharge and dysuria [Arya *et al.* 1973, Fransen *et al.* 1985, Handsfield *et al.* 1974, Jackson *et al.* 1997b], the average prevalence of discharge and/or dysuria was 39% (Appendix I), similar to the sum of the averages for discharge (15%) and for dysuria (22%) over all studies included. For CT, however, the prevalences of at least one symptom were, at 5% and 14%, only 0.6 and 0.8 times the expected value in case of independence in males [Colvin *et al.* 1998, Paxton *et al.* 1998b, Harms *et al.* 1998, Matondo *et al.* 1995] and females [Catterson & Zadoo 1993, Colvin *et al.* 1998, Paxton *et al.* 1998b, Oriel *et al.* 1972], respectively, suggesting clustering between both symptoms.

Relation of symptom prevalence with treatment seeking and patient delay

If most symptomatic patients seek treatment and get cured, the prevalence of symptomatic infection falls; consequently, the point prevalence of symptoms is in general lower than the cumulative probability per episode of getting symptoms, and symptom prevalence would be expected to vary with treatment patterns in the population [McCormack 1981, Garnett *et al.* 1999]. In order to understand to what extent the observed variations in symptom prevalence (Figure 3.1) was due to variation between populations in treatment patterns, we assessed whether symptom prevalence correlated with treatment rates and average patient delay in the same population. Since very few studies reported both symptom prevalence and proportion treated or patient delay for NG- or CT-infected populations, we also correlated outcomes derived from different studies on closely related populations. For example, the patient delay interval among male STD clinic attenders with NG in London between 1973 and 1975 [Alani *et al.* 1977] was correlated with the symptom prevalence among males infected with NG who were identified as contacts of NG patients in clinics in London in 1977 [John & Donald 1978] (Appendix II). Where matching between closely related NG- or CT-infected populations was not possible, studies reporting patient delay or treatment seeking rates for STD in general (i.e. not only NG and CT) were used. Among 5 populations with information on symptom prevalence and the proportion seeking treatment, no correlation was apparent (r = -0.02, p = 0.97; Figure 3.3a). Among the 8 populations with data on symptom prevalence and patient delay, these two outcomes did not correlate either (r = -0.18, p = 0.6; Figure 3.3b).

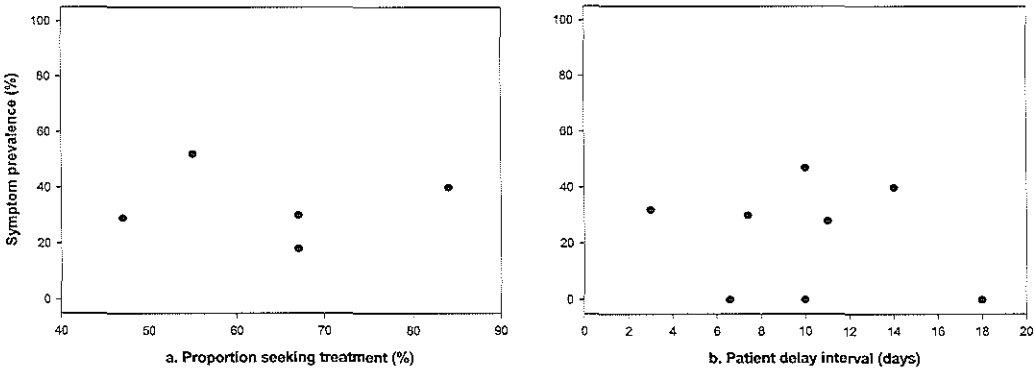

Figure 3.3 **Correlation between prevalence (%) of symptoms and (a) proportion (%) of patients seeking treatment; (b) average patient delay interval (in days), in the same or a similar population.** For matching of studies, see Appendix II.

3.5 Discussion

Our review of the prevalence of self-reported symptoms in NG and CT infection revealed two interesting findings. Discharge among females was on average the most prevalent symptom, although discharge prevalences varied widely between studies; unlike symptoms for either infection in males, discharge did in females not correlate with dysuria. Furthermore, for the other categories, prevalences were relatively similar (and low) across populations, despite likely variation in the intensities of treatment; and symptom prevalence did not correlate with indicators of the extent of STD treatment.

If we ignore the outcomes on discharge in females, the results confirm the general notion that infection with NG and CT is often asymptomatic [Handsfield *et al.* 1974, Oates & Csonka 1990, Martin 1990, Holmes *et al.* 1999]. Among males, dysuria was slightly more prevalent than discharge in either infection. These findings are in line with insights in the natural course of NG and CT infections [Holmes 1974, Schachter *et al.* 1975, Martin 1990, Oates & Csonka 1990, Holmes *et al.* 1999]. Among males, both symptoms were more prevalent in NG than in CT, and among females, dysuria was more prevalent in NG than in CT. These outcomes are as expected if NG infection produces more severe symptoms than CT does [Schachter *et al.* 1975, McCutchan 1984, Stamm *et al.* 1984, Martin 1990, Holmes *et al.* 1999]. Among NG patients, dysuria was about equally prevalent in males and females. This may seem inconsistent with the existing idea that non-ulcerative STD pass more mildly in females than in males [Oates & Csonka 1990, Wiesner 1981]. However, as explained above, symptom prevalences are not only determined by the pathogenicity of the infection, but also by the levels of treatment of symptomatic patients [McCormack 1981, Garnett *et al.* 1999]. If treatment rates are lower for females than for males, or if females who get treated do so less timely than males, as has been observed in many settings [Faxelid *et al.* 1998, Moses *et al.* 1994, Newell *et al.* 1993, Wilkinson *et al.* 1998], this dynamic effect may cause symptom prevalence to be higher in females than in males, even though per infection episode, symptoms are more likely to develop in males.

A likely explanation for the relatively high prevalence of discharge in females is aspecific discharge. Genital tract infections other than NG and CT, as well as pregnancy [Holmes *et al.* 1999] can also cause abnormal discharge, and may in fact be a more common cause of this syndrome than NG and CT [Dallabetta *et al.* 1998]. In our review, 6 studies [Chokephaibulkit *et al.* 1997, Edwards *et al.* 1985, Mayaud *et al.* 1997b, Saltz *et al.* 1981, Tait *et al.* 1980, Waters & Roulston 1969] reported on co-infections in female patients, with prevalences of trichomoniasis vaginalis, candidiasis, and bacterial vaginosis ranging between 6% and 51%. In line with this, prevalences of discharge among NG- or CT-negative controls were sometimes almost equally high as among infected subjects [Chokephaibulkit *et al.* 1997, Keim *et al.* 1992, Kovacs *et al.* 1987, Lim *et al.* 1989, Saltz *et al.* 1981]. In comparison, for males only one study reported on coinfection, at a 29% rate for

Trichomonas vaginalis [Watson-Jones *et al.* 2000]; no studies reported on symptom prevalences among NG- or CT-negative male controls (Appendix I). Because only a subset of the studies included reported symptom rates in control groups, we could not adjust for aspecific symptoms in the pooled analysis. This implies that the obtained symptom prevalences overestimate the proportion of NG- or CT-episodes that induce specific symptoms providing females with an incentive to seek care. Importantly, concurrent vaginal infection with other pathogens and pregnancy are most prevalent in those populations with least access to STD diagnostic and treatment facilities. Therefore, the overestimation of symptom prevalence, and consequently of the effectiveness of the syndromic STD treatment approach, may be especially large for resource-poor settings. Aspecific discharge may also have contributed to the observed population heterogeneity in the prevalence of discharge among NG- and CT-infected women, as the study populations, which came from a wide range of countries (Appendix I) likely differed in the rates of coinfection and pregnancy.

Contrary to the theory [McCormack 1981, Garnett *et al.* 1999], our correlation analyses did not confirm a dependency of symptom prevalence on treatment patterns (Figure 3.3), despite variation between the populations studied in the extent of STD treatment (Appendix II). Several factors may explain this finding. First, the matching between studies reporting on the different outcomes was far from perfect (Appendix II), and these analyses were based on small numbers of studies with often small sample sizes, limiting the power to detect patterns.

Perhaps more importantly, the effect of treatment may be obscured by, and possibly negatively confounded with that of reporting behaviour - which also differs between populations. Signs perceived as worrisome in some populations may be considered normal in others; conversely, reporting of symptoms unrelated to clinical signs may occur in some but not all populations [Paxton *et al.* 1998b, Mayaud *et al.* 1997b, Hawkes *et al.* 1999, Trollope-Kumar 1999]. More specifically, symptom reporting may be better in populations with higher treatment rates, as both depend on the general health care and developing standards of the country. Thus, in Western industrialized countries, the prevalence of signs in NG and CT infection may be relatively low thanks to high treatment rates, but symptom awareness is relatively high. In populations with low treatment rates as in many developing countries, the prevalence of disease signs among infected individuals is higher, but symptom recognition likely worse. This might result in comparable prevalences of self-reported symptoms in populations differing in the use and quality of STD treatment.

Several other limitations in the review methods and data used must be taken into account when interpretating the estimated symptom prevalences. For Gram stain, culture and leucocyte-esterase dipstick (LED) in the diagnosis of NG [Judson 1990a, Jackson *et al.* 1997b], sensitivities are higher in symptomatic infection than in asymptomatic NG infection; the same has been suggested for enzyme-

linked immunoassay (EIA) in the detection of CT. As these were the main tests used for diagnosis in the studies included (Appendix I), this may have biased symptom prevalences upward. Besides treatment patterns and pathogenicity, also the duration of the incubation period influences symptom prevalence. For example, a disease in which every patient would develop symptoms after 3 weeks and in which patients remained symptomatic for 1 week would, in the absence of treatment, be consistent with a symptom point prevalence of 25% only. However, since the incubation periods of chlamydia and females are short relative to the duration of symptoms and reasonably similar in both sexes [Holmes *et al.* 1999], this is unlikely to have influenced the ranking of symptom rates between the categories studied here. Despite large variation between individual studies in the prevalence of discharge among infected females, which is unlikely to be due to chance alone (although we did not formally test the homogeneity assumption), we used a fixed effect model and not a random effect model to pool all outcomes. Where the prevalences found in the largest studies are distributed in reasonable balance between and around the smaller studies, this is unlikely to have markedly biased the estimated means. Only for females with CT, the larger studies had outcomes mostly below the estimated average (Figure 3.1), so that the fixed effect model may have biased symptom prevalence downward. The use of the fixed effect model may also have led to underestimation of the 95% confidence intervals, but that was not an outcome of main interest. Finally, in the definition of symptoms in females, we did not include abdominal pain, which may be associated with late untreated NG or CT infection resulting in pelvic inflammatory disease [Holmes *et al.* 1999]. The combination 'discharge and/or dysuria' therefore underestimates the total spectrum of symptoms that may ultimately lead women to seek care [Costello Daly *et al.* 1998b]. Yet, a meaningful definition should probably be restricted to acute symptoms leading to timely treatment, before complications occur.

In conclusion, our review shows that prevalences of self-reported symptoms among NG- and CT-infected subjects are low across a range of populations, and in spite of variation in rates of STD treatment.

Besides the pathogenicity of the infections and treatment patterns, geographical variation in (subjective) reporting behaviour may be an important determinant of symptom prevalences. For females, non-specific causes of discharge add to this: among NG- and CT-infected females, the occurrence of discharge in fact appears to be largely unrelated to the NG or CT infection. For these reasons, the prevalence of self-reported symptoms alone may not be a good rationale for choosing between NG- and CT- control strategies or for evaluating the success of STD treatment services.

3.6 APPENDIX I

Summary of published data on symptom prevalence in NG- and CIT-infection

Infection, gender	Reference	Setting		Population characeristic	n	Diagnostic test	Symptom	Time of having symptom	Symptom prevalence	Remarks
		Place	Time							
NG in females	[Catterson & Zadoo 1993]	Hawaii USA	1989-1991	active army having routine pap smear	4	culture	discharge	unclear	0%	
							dysuria		0%	
							discharge and/or dysuria		0%	
	[Cave *et al.* 1969]	NewYork USA	no report	ObGy clinic attenders	72	culture	discharge	unclear	36%	
							dysuria		17%	
	[Colvin *et al.* 1998]	rural Hlabisa S.AFRICA	1995	general adult population	8	LCR	discharge	current	0%	
							dysuria		0%	
							discharge and/or dysuria		0%	
	[Mayaud *et al.* 1997b]	refugee camp, Ngara TANZANIA	1994	ANC attenders	3	Gram stain	discharge	unclear	100%	All 3 were coinfected with Tv.
	[Paxton *et al.* 1998b]	rural Rakai UGANDA	1994-95	general population 15-59y	32	LCR	discharge	last 6 months	13%	
							dysuria		22%	
							discharge and/or dysuria		34%	
	[Waters & Roulston 1969]	Winnipeg USA	1964-67	ObGy clinic attenders	86	culture and/or fluorescent antibody	discharge	unclear	16%	Several of those with discharge had Tv.
CT in females	[Bakir *et al.* 1989]	Riyadh S.ARABIA	no report	pregnant ObGy clinic attenders	12	EIA confirmed in culture	discharge	unclear	25%	
	[Catterson & Zadoo 1993]	Hawaii USA	1989-1991	active army having routine pap smear	39	EIA	discharge	unclear	0%	
							dysuria		0%	
							discharge and/or dysuria		0%	

CT in females	[Chokephaibulkit *et al.* 1997]	Knoxville USA	1988- 94	pregnant adolescents aged <19y	67	culture	discharge	unclear	76%	control*: 73%
							dysuria		3%	control: 1.8%. Coinfections with Candida, BV, Tv.
	[Colvin *et al.* 1998]	rural Hlabisa S.AFRICA	1995	general adult population	9	LCR	discharge	current	0%	
							dysuria		0%	
							discharge and/or dysuria		0%	
	[Edwards *et al.* 1985]	Christchurch N. ZEALAND	no report	FP clinic attenders	79	DFA	discharge	unclear	5%	1 had NG and 5 had Tv.
	[Keim *et al.* 1992]	Michigan USA	1987- 89	college womem having routine gynecological exam	140	DFA	discharge	current	16%	control: 14%
							dysuria		3%	control: 0.7%
	[Kovacs *et al.* 1987]	Victoria AUSTRALIA	1985- 86	FP clinic attenders	51	culture	discharge	unclear	28%	control: 28%
	[Lim *et al.* 1989]	Singapore SINGAPORE	1984- 86	contacts of M with NGU	33	culture	discharge	unclear	46%	control:54%
							dysuria		6%	control:14%
	[Oriel *et al.* 1972]	London UK	no report	contacts of M STD clinic attenders	13	culture	discharge	unclear	31%	
							dysuria		8%	
							discharge and/or dysuria		31%	
	[Paxton *et al.* 1998b]	rural Rakai UGANDA	1994-95	general population 15-59y	50	LCR	discharge	last 6 months	12%	
							dysuria		20%	
							discharge and/or dysuria		24%	
	[Saltz *et al.* 1981]	Cincinnati USA	1979-80	adolescent clinic attenders	22	culture	discharge	unclear	55%	control: 37%
							dysuria		9%	control: 17% 36% was coinfected with either Tv, Candida or Streptococcus aureus.
	[Tait *et al.* 1980]	Liverpool UK	no report	contacts of M STD clinic attenders	70	culture	discharge	unclear	31%	10 were coinfected with Tv and 16 with Candida
	[Mayaud *et al.* 1995]	Mwanza TANZANIA	1992-93	ANC attenders	81	culture / Ag.detect	discharge	current	20%	
							dysuria		40%	

NG and/or CT in females	[Paxton et al. 1998b]	rural Rakai UGANDA	1994-95	general population 15-59y	78	LCR	discharge	last 6 months	13%	
							dysuria		21%	
							discharge and/or dysuria		28%	
	[Vuylsteke et al. 1993b]	Kinshasa ZAIRE	1990	pregnant ANC attenders	75	culture / Ag.detect	discharge	current	36%	
							dysuria		7%	
NG in males	[Arya et al. 1973]	rural Teso UGANDA	1971	general population	24	Gram stain & culture	discharge and/or dysuria	current	42%	
	[Jackson et al. 1997b]	Mombasa, KENYA	1994-5	transport workers	15	Gram stain & culture	discharge	unclear	53%	CT and Tv coinfections excluded.
							discharge and/or dysuria		67%	
	[Colvin et al. 1998]	rural Hlabisa S.AFRICA	1995	general adult population	2	LCR	discharge	current	0%	
							dysuria		0%	
							discharge and/or dysuria		0%	
	[Fransen et al. 1985]	Nairobi KENYA	1983	fathers of infants with ophtalmia neonatorum	10	culture	discharge and/or dysuria	unclear	30%	
	[Grosskurth et al. 1996]	rural Mwanza TANZANIA	1991- 92	general population 15-54y	128	Gram stain	discharge	unclear	18%	
	[Handsfield et al. 1974]	Washington, USA	no report	USA army stationed in, or returning from in Vietnam and Saint Louis having routine exam	59	culture	discharge and/or dysuria	unclear	32%	
	[John & Donald 1978]	London UK	1977	contacts of NG cases	50	Gram stain & culture	discharge	unclear	8%	50 NG episodes in 40 patients
							dysuria		20%	
							discharge and/or dysuria		28%	
	[Mayaud et al. 1997b]	Refugee camp, Ngara TANZANIA	1994	outpatient clinic attenders & random subsample of adults	7	Gram stain	discharge	unclear	14%	
							dysuria		14%	
							discharge and/or dysuria		29%	
	[Paxton et al. 1998b]	Rural Rakai UGANDA	1994-95	general population 15-59y	15	LCR	discharge	last 6 months	20%	
							dysuria		40%	
							discharge and/or dysuria		47%	

CT in males	[Rees *et al.* 1977]	Liverpool UK	1973- 76	fathers of infants with conjunctivitis	4	culture	discharge dysuria discharge and/or dysuria	unclear	0% 0% 0%	
	[Colvin *et al.* 1998]	Rural Hlabisa S.AFRICA	1995	general adult population	5	LCR	discharge dysuria discharge and/or dysuria	current	0% 0% 0%	
	[Jackson *et al.* 1997b]	Mombasa, KENYA	1994-5	transport workers	13	EIA	discharge discharge and/or dysuria	unclear	15% 23%	NG and Tv coinfections excluded.
	[Fish *et al.* 1989]	London UK	1985- 86	contacts of F ObGy clinic attenders	7	culture	dysuria	unclear	14%	
	[Grosskurth *et al.* 1996]	rural Mwanza TANZANIA	1991- 2	general population 15-54y	39	Ag.capture	discharge	unclear	8%	
	[Matondo *et al.* 1995]	Hartshill UK	no report	contacts of F STD clinic attenders	15	EIA & DFA	discharge dysuria discharge and/or dysuria	unclear	0% 0% 0%	
	[Paxton *et al.* 1998b]	rural Rakai UGANDA	1994-95	general population 15-59y	36	LCR	discharge dysuria discharge and/or dysuria	last 6 months	6% 8% 8%	
	[Rees *et al.* 1977]	Liverpool UK	1973-76	fathers of infants with conjunctivitis	4	culture	discharge dysuria discharge and/or dysuria	unclear	0% 0% 0%	
NG and/or CT in males	[Grosskurth *et al.* 1996]	rural Mwanza TANZANIA	1991-92	general population 15-54y	158	Gram stain	discharge	unclear	15%	
	[Paxton *et al.* 1998b]	rural Rakai UGANDA	1994-95	general population 15-59y	51	LCR	discharge dysuria discharge and/or dysuria	last 6 months	10% 18% 20%	
	[Watson-Jones *et al.* 2000]	rural Mwanza TANZANIA	no report	general population 15-54y	21	culture/ LCR	Discharge Dysuria	unclear	33% 10%	6 were coinfected with Tv.

*Controls are uninfected subjects from the same base population as the NG- or CT-infected cases. M = Male; F = Female; y = year; incl = included; NG = *Neisseria gonorrhoeae*; CT = *Chlamydia trachomatis*; Tv = *Trichomonas vaginalis*; NGU = non-gonococcal urethritis; ANC = antenatal clinic; ObGy = obstetric & gynecologic; FP = family planning; LCR = ligase chain reaction; EIA = enzyme-linked immunoassay; DFA = direct immunofluorescent antibody; Ag = antigen.

3.7 Appendix II

Studies on the prevalence of discharge and/or dysuria in NG- and CT-infection, patient delay interval among symptomatic patients seeking treatment, and proportion of symptomatic patients seeking effective medical treatment, used for correlation analyses in Figure 3.3.

Sex	Patient delay interval (days)							Symptom prevalence (%)						
	Reference	Place	Time	Infection	Population	n	Mean / median	Reference	Place	Time	Infection	Population	n	Prevalence
F	[Hook III *et al.* 1997]	5 USA cities	1995	NG	STD clinic attenders	16	NG: 5.6[1] NGU: 6.8[1] } 6.6[1]	[Catterson & Zadoo 1993]	Hawaii USA	1989-91	NG and/or CT	active army having routine pap smear	43	0%
	[Darrow 1976]	Sacramento USA	1971	STD	STD clinic attenders	617	10.0[1]	[Cave *et al.* 1969]	New York, USA	no report	NG	ObGy clinic attenders	72	47% (17-53)[2]
	[Faxelid *et al.* 1998]	urban Lusaka, ZAMBIA	1994-95	STD	health center attenders	238	14.0	[Vuylsteke *et al.* 1993a]	Kinshasa, ZAIRE	1990	NG and/or CT	pregnant ANC attenders	75	40% (36-43)[2]
	[Wilkinson *et al.* 1998]	rural Hlabisa, S.AFRICA	1996	STD	primary care clinic attenders and general population	2570	18.0	[Colvin *et al.* 1998]	rural Hlabisa, S.AFRICA	1995	NG and/or CT	general adult population	17	0%
M	[Alani *et al.* 1977]	London, UK	1973-75	NG	STD clinic attenders	82	11.0	[John & Donald 1978]	London, UK	1977	NG	contacts of NG patients	50	28%
	[Judson 1981]	Denver, USA	1979-80	NG	health clinic attenders	890	3.0	[Handsfield *et al.* 1974]	Washington USA	no report	NG	USA army stationed in, or returning from in Vietnam and Saint Louis having routine exam	59	32%
	[Moses *et al.* 1994]	Nairobi, KENYA	1991	STD	health centers attenders	104	7.9[1]	[Fransen *et al.* 1985]	Nairobi, KENYA	1983	NG	fathers of infants with ophtalmia neonatorum	10	30%
	[Wilkinson *et al.* 1998]	rural Hlabisa, S.AFRICA	1996	STD	primary care clinic attenders and general population	2199	10.0	[Colvin *et al.* 1998]	rural Hlabisa, S.AFRICA	1995	NG and/or CT	general adult population	7	0%

Sex	Proportion of patients seeking treatment (%) Reference	Place	Time	Infection	Population	n	Mean / median	Symptom prevalence (%) Reference	Place	Time	Infection	Population	n	Prevalence
F	[Moses *et al.* 1994]	Nairobi KENYA	1991	STD	STD clinic attenders asked about treatment seeking behaviour during previous STD episodes	62	84%	[Vuylsteke *et al.* 1993b]	Kinshasa ZAIRE	1990	NG and/or CT	pregnant ANC attenders	75	40% (36-43)[2]
	[Mosha *et al.* 1993, Newell *et al.* 1993]	urban/ rural Mwanza TANZANIA	1990-91	STD	general population 15-54y	154	55%	[Mayaud *et al.* 1995]	Mwanza TANZANIA	1992-93	NG and/or CT	ANC attenders	81	52% (40-60)[2]
M	[Moses *et al.* 1994]	Nairobi KENYA	1991	STD	STD clinic attenders asked about treatment seeking behaviour during previous STD episodes	52	67%	[Fransen *et al.* 1985]	Nairobi, KENYA	1983	NG	fathers of infants with ophtalmia neonatorum	10	30%
	[Mayaud *et al.* 1997b]	refugee camp Ngara, TANZANIA	1994	STD	general population	289	47%	[Mayaud *et al.* 1997b]	refugee camp, Ngara, TANZANIA	1994	NG	outpatient clinic attenders and random subsample of adults	7	29%
	[Mosha *et al.* 1993, Newell *et al.* 1993]	urban/ rural Mwanza TANZANIA	1990-91	STD	general population 15-54y	563	67%	[Grosskurth *et al.* 1996]	rural Mwanza TANZANIA	1991-92	NG	general population 15-54y	128	18%

[1] The median patient delay interval was estimated from a categorical distribution assuming a homogeneous distribution of cases within each category, and a mean duration of 1.5 times the lower limit for each uppermost category (e.g. 10.5 days for a category of '7 or more days'). [2] Range for the estimated proportion with discharge and/or dysuria, derived from reports of the proportions with either symptom separately. STD=sexually transmitted disease(s); NG=*Neisseria gonorrhoeae*; CT=*Chlamydia trachomatis*; ANC=antenatal clinic; ObGy=obstetric & gynaecologic.

chapter 4

What proportion of episodes of gonorrhoea and chlamydia becomes symptomatic?

Korenromp EL, Sudaryo MK, De Vlas SJ, Gray R, Sewankambo NK, Serwadda D, Wawer MJ, Habbema JDF. What proportion of episodes of gonorrhoea and chlamydia becomes symptomatic? *Int J STD&AIDS*, in press. Reused with permission of the Royal Society of Medicine.

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4.1 Summary

The effectiveness of syndromic treatment as an STD control strategy depends on the proportion of episodes which become symptomatic; few studies have measured this directly.We estimated these proportions for gonorrhoea (NG) and chlamydia (CT), synthesizing data on the point prevalence of self-reported discharge and dysuria among infected cases in rural Uganda, the durations of symptoms, incubation period and asymptomatic episodes, and the effect of treatment on symptom duration.

Estimated proportions of episodes that become symptomatic were 45% for males with NG, 11% for males with CT, 14% for females with NG, and 6% for females with CT; this was on average 1.5-fold higher than symptom prevalence at cross-section among infected cases in this population. Estimates were sensitive to assumptions on the relative durations of asymptomatic and symptomatic episodes, but were invariably inconsistent with previous direct estimates based on a US cohort study.

These results show that the probability of recognizing symptoms in NG and CT episodes varies between settings. In populations with low treatment rates like Uganda, these probabilities can be very low; here, health education should have priority in STD management programmes.

4.2 Introduction

In developing countries, sexually transmitted diseases (STDs) are an important cause of morbidity among adults and STD control has high priority [De Schryver & Meheus 1990]. The choice among STD control strategies depends upon several factors, including the probability that acute symptoms of infection develop [Wilkinson *et al.* 1999, Garnett *et al.* 1999]. If most patients become symptomatic and seek treatment for these symptoms, high quality clinical case management could be an important component of control programmes [Wilkinson *et al.* 1999]. If most patients develop symptoms, but fail to recognize these or do not seek treatment, education on symptom recognition and on the importance of prompt treatment becomes essential. However, if the majority of infections pass without symptoms, syndromic management may be insufficient, and more active interventions, such as screening or mass treatment, may be appropriate in addition.

In cross-sectional surveys among infected cases, the majority of prevalent non-ulcerative infections with *Neisseria gonorrhoeae* (NG) and *Chlamydia trachomatis* (CT) are asymptomatic, especially in females [Adler 1996, McCormack *et al.* 1977, Oates & Csonka 1990, Oriel 1982, Saltz *et al.* 1981]. This does not imply that the probability of developing symptoms at some time during an episode of

these infections is also low [Garnett *et al.* 1999, McCormack 1981]. The duration of symptoms is usually less than the total duration of infection, because symptoms are preceded by an incubation period, and may be followed by a second asymptomatic period before the infection is resolved [Judson 1990b, Thompson & Washington 1983]. Consequently, even if all STD episodes involve symptoms at some point in time, the proportion of infections with symptoms at cross-sectional survey would be less than 100%. The proportion of prevalent cases experiencing current symptoms is further reduced if symptomatic cases seek treatment

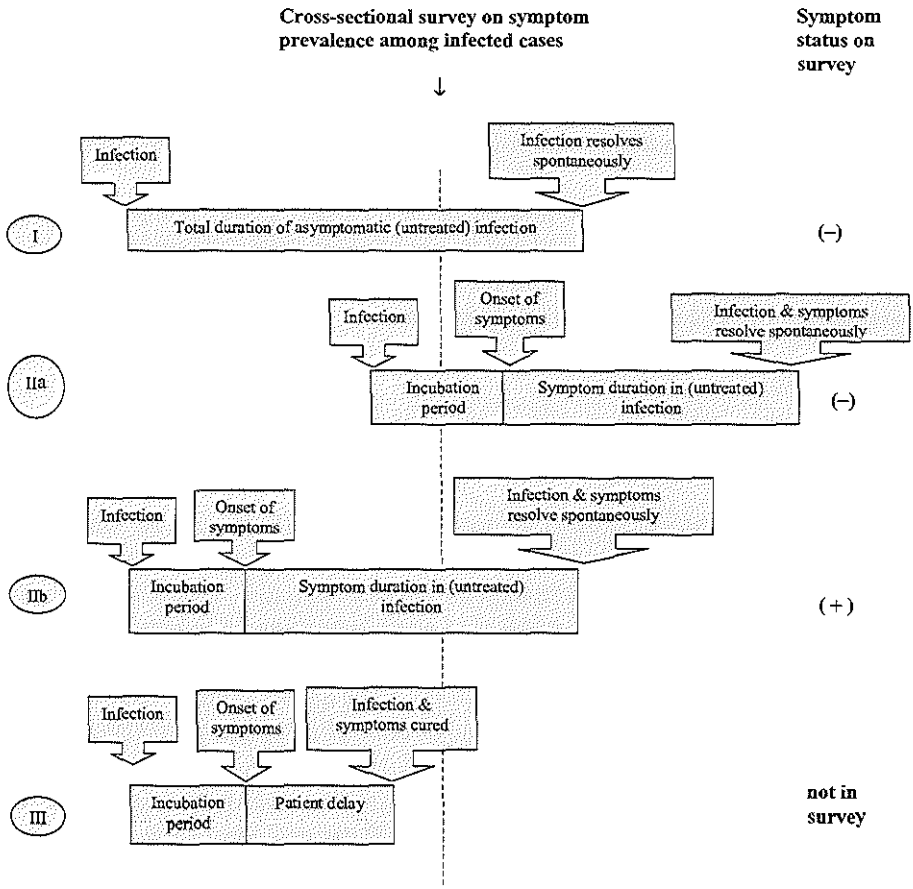

Figure 4.1 **Diagrammatic representation of the alternative courses of an episode of gonorrhoea or chlamydia.** I) without the development of symptoms; II) with symptoms that are not recognized (or acted upon) by the patient; III) with symptoms recognized by the patient, followed by treatment. The vertical line represents a cross-sectional survey on symptom prevalence among infected cases; the negative and positive signs on the right the symptom status as observed in the survey. For discussion of assumptions, see main text.

[Garnett *et al.* 1999, McCormack 1981], because successful medical treatment shortens the duration of symptoms [Garnett & Anderson 1993b, Mayaud *et al.* 1997a]. The influence of these factors on symptom prevalence as observed in cross-sectional surveys is depicted in Figure 4.1.

Thus, the probability of STDs becoming symptomatic is higher than the point prevalence of symptoms as observed at cross-section among infected cases, and might be reasonably high even in population with low symptom prevalences [Garnett *et al.* 1999, McCormack 1981]. This has for example been suggested for underserviced populations in rural Uganda [Serwadda *et al.* 1992, Sewankambo *et al.* 1994, Wawer *et al.* 1999, Paxton *et al.* 1998b, Paxton *et al.* 1998a], for which it is being debated whether symptom incidences are high enough for a syndromic treatment approach to be adequate for STD control. In surveys in this area [Paxton *et al.* 1998b], point prevalences of self-reported current discharge and/or dysuria were 33% ± 9% for NG-infected males, 7% ± 3.6% for CT-infected males, 9% ± 4% for NG-infected females, and 4% ± 2.5% for CT-infected females. (These values are lower than previously published period prevalences, which pertained to symptoms either at the time of survey or in the preceding 6 months [Paxton *et al.* 1998b].) No quantitative estimates are however available on how much higher proportions of episodes that become symptomatic are, and this may vary between populations based on their respective STD treatment patterns.

In this chapter, using the natural history model shown in Figure 4.1, we estimate the probability that NG and CT infection become symptomatic based on data from rural Uganda. We explore how the difference between the probability that symptoms develop and symptom point prevalence varies with alternative treatment patterns, and how it depends on the natural history of the STDs. We discuss the generalizability of the symptom probabilities estimated for Uganda to other settings, and the implications for STD treatment policies in rural Africa.

4.3 Methods

Literature reviews were performed to identify English language articles containing data on the biological determinants of symptom rates among heterosexually infected NG- or CT-patients.

Incubation period

Studies on incubation periods were included if: (i) they were conducted in patients who (all) eventually developed symptoms, and (ii) the estimated date of infection was derived from the sexual history of the patient. This included studies among STD clinic attendees, but not studies among initially asymptomatic preva-

Table 4.1 **Estimation of (total) duration of NG and CT infection from prospective studies on infection dissolution.**

	Reference	n	Symptom status of study subjects at enrolment	Follow-up duration (days)		Proportion (%) infected at follow-up		Estimated mean duration of infection (days)[2]
				range	estimated mean	% testing positive	corrected for culture sensitivity[1]	
NG in males	[Handsfield *et al.* 1974]	28	originally asymptomatic; n = 10 develop symptoms during follow-up	1-165	11	82%	91%	118
	pooled[3]							*118*
CT in males	[Stamm & Cole 1986]	10	asymptomatic	7-28	14	90%	100%	>269[4]
	[Handsfield *et al.* 1976]	10	symptomatic	7-10	9	100%	100%	>175[4]
	[Prentice *et al.* 1976]	13	symptomatic	7 (fixed)	7	69%	77%	26
	[Terho 1978]	13	symptomatic	6-56	18	85%	94%	320
	[Johannisson *et al.* 1979]	52	symptomatic	7-28	18	60%	67%	44
	[Paavonen *et al.* 1980]	21	symptomatic	28 (fixed)	28	76%	84%	166
	[McLean *et al.* 1990]	17	symptomatic	14 (fixed)	14	53%	59%	26
	[Parks *et al.* 1997]	5	62% (of n = 74 M and F combined) symptomatic	4-45	25	40%	44%	31
	pooled[3]							*132*
NG in females	[Mahoney *et al.* 1942]	73	all had clinical signs; no report on perceived symptoms	1-120	72	46%	51%	107
	pooled[3]							*107*

CT in females	[Johannisson *et al.* 1980]	59	symptomatic and asymptomatic	14-45	23	51%	57%	40
	[McCormack *et al.* 1979]	14	symptomatic and asymptomatic	450 – 720	585	50%	56%	995
	[Alexander *et al.* 1977]	15	asymptomatic	42 (fixed)	42	20%	22%	28
	[Rees 1980]	132	symptomatic (with NG)	1-90	36	84%	93%	522
	[Paavonen *et al.* 1980]	15	asymptomatic	28 (fixed)	28	80%	89%	238
	[Rahm *et al.* 1986]	109	asymptomatic	90 (fixed)	90	83%	92%	1112
	[Sorensen *et al.* 1994]	17	asymptomatic	60-720	330	29%	n.a.[5]	267
	[Schachter *et al.* 1975]	33	symptomatic and asymptomatic	14-224	119	76%	84%	704
	[Parks *et al.* 1997]	69	62% (of n = 74 M and F combined) symptomatic	4-45	25	74%	82%	128
	pooled[3]							*499*

[1] Assuming a 90% sensitivity of culture. [2] Under the exponential distribution underlying the calculation of mean durations, the corresponding median values are fixed at ln(2)*mean. E.g. for NG in males, the mean 118 days corresponds to an estimated median of 82 days. [3] Pooled mean over means of individual studies.
[4] Based on the approximation that the proportion still infected was 95% (n = 10 out of 10.5), instead of 100% (n = 10 out of 10), as a finite size correction.
[5] Study used enzyme immuno-assay, rather than culture, for diagnosis; we assumed a 100% sensitivity for immuno-assay.

lent cases identified by screening. We used median incubation periods, but when studies reported only a mean, this was used. For studies reporting only a distribution of cases over intervals of incubation periods, we estimated the median duration assuming a homogeneous distribution of cases within each interval. A weighted average incubation period was calculated by pooling the median or mean incubation periods across studies.

Duration of infection

Ideally, the duration of infection would be estimated from follow-up studies of sexually infected patients followed from infection untill spontaneous resolution (i.e. foregoing treatment). For practical and ethical reasons, such studies have not been done. Some prospective studies are available that report proportions of infected patients who are still infected at follow-up, among untreated asymptomatic cases identified by screening or contact tracing, or symptomatic cases followed for a short period before treatment (Table 4.1). These data do not provide direct estimates of infection duration, because the duration of infection before the first test is unknown (left-censoring), and follow-up is often for a short time relative to the typical duration till resolution of infection, resulting in a high proportion still infected at follow-up and thus precluding a direct measurement of duration till resolution (right-censoring). The average duration of infection can however be estimated, by taking into account the probability that an episode of a given duration is sampled in a cross-sectional study, and the probability that such episodes will have ended by the time of follow-up. Assuming that durations vary between episodes and individuals according to an exponential distribution, the remaining duration of infection from any point in time (here, the moment of detection in a cross-sectional survey) equals the mean total duration, because the rate of resolution under this distribution is constant over time and independent of the past duration. Consequently, the mean duration of infection equals follow-up time divided by the log of the reciprocal of the proportion still infected. So for a typical study where after a follow-up time of 3 months 83% of subjects are still infected [Rahm *et al.* 1986], we would infer a mean duration of infection of 483 days.

In applying this estimation method, some complications had to be considered. First, in the studies included, infection status was mostly measured by culture which has limited sensitivity [Holmes *et al.* 1999], resulting in false-negative test results for subjects still infected and consequent underestimation of the duration. Estimating the average culture sensitivity at 90% [Holmes *et al.* 1999], we adjusted for this bias by dividing proportions testing positive at follow-up in studies which used culture for diagnosis by 0.9. Second, the calculation does not allow for studies in which all subjects are still infected at follow-up. To allow inclusion of such studies, we applied a finite size correction, by adding to the actual

number of observed subjects a hypothetical half non-infected case. For example, in a study where all 10 (or 100%) of subjects were infected at follow-up [Handsfield *et al.* 1976], we replaced this by n=10 out of 10.5 (or 95%). Furthermore, the calculation ignores the fact that positive diagnosis at follow-up may be due to re-infection after spontaneous cure, rather than to unresolved infection. Calculations (Appendix) confirmed that this caused an overestimation of the duration of NG and CT in women, but overall the effect was small; therefore, for simplicity we ignored reinfection in the remainder of the chapter. Finally, most available studies did not distinguish between asymptomatic and symptomatic episodes, or it was unclear whether their outcomes pertain to either or both of these categories. Studies that did report specifically on symptomatic or asymptomatic episodes did not show significant differences in duration between (untreated) asymptomatic and symptomatic episodes (Table 4.1). We therefore assumed, as a baseline scenario, that the total duration of untreated infection is equal for asymptomatic and symptomatic episodes.

Having thus estimated mean infection durations for each study included, we estimated overall means by averaging the durations over studies. We weighed all studies equally, because we suspected the variability in their outcomes to relate to heterogeneity in unknown determinants, and not mainly to chance according to their sample sizes. By substracting the incubation period (see previous subsection) from the estimated total duration of infection, we estimated the duration of symptoms in untreated symptomatic infection.

Treatment and patient delay

Estimates of the proportion of symptomatic cases seeking treatment were derived from survey data collected during the Rakai STD mass treatment trial [Wawer *et al.* 1999, Paxton *et al.* 1998a]. Based on reported treatment seeking behaviour among participants, at most 38% of symptomatic STD patients in rural Uganda receive appropriate treatment for their infection [Paxton *et al.* 1998a]. We used this value as the cure rate for symptomatic NG and CT episodes in both males and females. We assumed that symptomatic cases who seek treatment are all immediately cured after treatment. This is based on observations of very short post-treatment durations of infectiousness for (non-resistant strains of) gonorrhoea [Holmes *et al.* 1967]. Furthermore, we assumed that no asymptomatic cases are treated - which could theoretically occur upon detection by screening or due to non-STD related use of antibiotics. The rationale for this assumption is that access to health services is very limited in this region.

No data were available on patient delay (i.e. the time period between onset of symptoms and receiving treatment) from rural Uganda. We therefore estimated patient delay from reports from a rural South African STD clinic, where the average delay was 10 days in males and 18 days in females [Wilkinson *et al.* 1998]. To

account for the longer patient delay for CT and non-gonococcal urethritis other than NG [Schofield 1982, Boyd *et al.* 1958, Jacobs & Kraus 1975, McCutchan 1984], we specified the patient delay in Uganda as 8 days for gonorrhoea and 12 days for chlamydia in males, and 15 days for gonorrhoea and 21 days for chlamydia in females.

Estimation of the probability of developing symptoms and sensitivity analysis

According to the model (Figure 4.1), the relation between the proportion of infections that are symptomatic at cross-sectional survey (symptom point prevalence) and the probability that episodes become symptomatic at some time, is determined by the relative durations and frequency of asymptomatic and symptomatic stages. Thus, the proportion of infections found symptomatic ($P_{symprev}$) at cross-sectional surveys equals:

$$P_{symprev} = \frac{P_{symprob} \cdot P_{treat} \cdot t_{delay} + P_{symprob}(1-P_{treat}) \cdot t_{symptom}}{P_{symprob} \cdot P_{treat}(t_{incub} + t_{delay}) + P_{symprob} \cdot (1-P_{treat}) \cdot (t_{incub} + t_{symptom}) + (1-P_{symprob}) \cdot t_{asymp\_inf}}$$

where $P_{symprob}$ denotes the probability that episodes become symptomatic at some time, $t_{symptom}$, t_{incub} and t_{asymp_inf} are the duration of symptoms in untreated symptomatic episodes, the incubation period in symptomatic episodes, and the total duration of asymptomatic episodes, respectively; P_{treat} represents the proportion of symptomatic cases seeking treatment and t_{delay} the patient delay interval.

Assuming that symptomatic and asymptomatic episodes have equal durations, this equation simplifies to:

$$P_{symprev} = \frac{P_{symprob} \cdot t_{symptom} - P_{symprob} \cdot P_{treat}(t_{symptom} - t_{delay})}{t_{incub} + t_{symptom} - P_{symprob} \cdot P_{treat}(t_{symptom} - t_{delay})} \qquad \text{(Eq. 1)}$$

This formula does not allow for variation between individuals or episodes in the duration of disease stages, which leads to some underestimation of the probability of developing symptoms (not shown); for simplicity, this small bias is ignored.

In order to assess how robust our estimates of the probability of developing symptoms are, and on which parameters they depend most, we conducted a sensitivity analysis. In univariate sensitivity analysis, each time the estimated value of one single parameter was doubled or halved. In a multivariate sensitivity analysis, we assessed how much estimated symptom probability would change, if multiple parameters were simultaneously doubled or halved in the direction that they either all increased or all decreased the symptom estimate.

Table 4.2 **Estimation of the probability to develop symptoms per episode of gonorrhoea (NG) and chlamydia (CT) in a rural Ugandan population, based on symptom point prevalence among infected cases and its determinants.** For description of methods, see main text.

	Symbol in equation 1 (see Section 4.3)	Male		Female	
		NG	CT	NG	CT
Incubation period for symptomatic episodes	*t.incub*	5 days	11 days	9 days	20 days
Total duration of infection for asymptomatic episodes	*t.asymp_inf*	118 days	132 days	107 days	499 days
Duration of symptoms	*t.symptom*	113 days	121 days	98 days	479 days
Proportion of symptomatic cases treated	P.treat	38%	38%	38%	38%
Patient delay for treated cases	*t.delay*	8 days	12 days	15 days	21 days
Observed symptom prevalence among infected cases	*P.symprev*	33%	7%	9%	4%
Estimated probability of developing symptoms per episode	*P.symprob*	45%[1]	11%	14%	6%
Ratio symptom probability / symptom prevalence		1.4	1.6	1.5	1.6

[1] Example of calculation, for NG in males: $0.33 = x * (0.38*8+(1-0.38)*113) / (x*(0.38*(5+8)+(1-0.38)*(5+113))+(1-x)*118) \rightarrow x=0.45$.

4.4 Results

Stage durations

The median incubation periods pooled over all studies identified were about 5 days for NG in males [Harrison *et al.* 1979, Lodin 1955, Molin 1970, Boyd *et al.* 1958, Schofield 1982, Sherrard & Barlow 1993, 1996, Wallin 1974, Willcox 1976], 11 days for CT in males [Oriel *et al.* 1972, Boyd *et al.* 1958, Johannisson *et al.* 1979, Schofield 1982], and 9 days for NG in females [Molin 1970, Wallin 1974]. For CT in females, no studies were identified. By analogy to the relative difference between NG and CT in males, we inferred an incubation duration for CT in females longer than that for NG, of 20 days.

Table 4.1 shows estimates of infection duration for all studies. The estimated mean durations of infection were around 4.5 months for males with CT and 16 months for females with CT. For males with NG, only one study was identified, from which we estimated the duration at around 4 months. For females with NG, the single study available also gave an estimate of 4 months.

By substracting incubation periods from total durations, mean durations of symptoms in symptomatic episodes were estimated at around 113 days in males with NG, 121 days for males with CT, 98 days for females with NG, and 479 days for females with CT (Table 4.2).

Probabilities of developing symptoms and sensitivity analysis

Based on Equation 1, the observations in rural Uganda were consistent with probabilities of developing recognized symptoms per episode of 45% for NG in males, 11% for CT in males, 14% for NG in females and 6% for CT in females (Table 4.2). These symptom probabilities were on average 50% (a factor 1.5) higher than observed symptom point prevalences.

The results of the sensitivity analysis are plotted in Figure 4.2. The duration of symptoms relative to the duration of asymptomatic episodes, and the fraction of symptomatic cases treated were the most critical determinants of the relation between symptom point prevalence and symptom probability per episode. Patient delay and the incubation period did not markedly affect the estimated symptom probability. If the duration of both symptomatic and asymptomatic episodes were simultaneously doubled or halved, the relationship between symptom prevalence and symptom probability remained almost unchanged. Results were qualitatively similar for both infections and gender categories. In multivariate sensitivity analysis, estimates of symptom probabilities per episode consistent with the symptom point prevalence observed in rural Uganda ranged from 3% (for females with CT) to 83% (for males with NG).

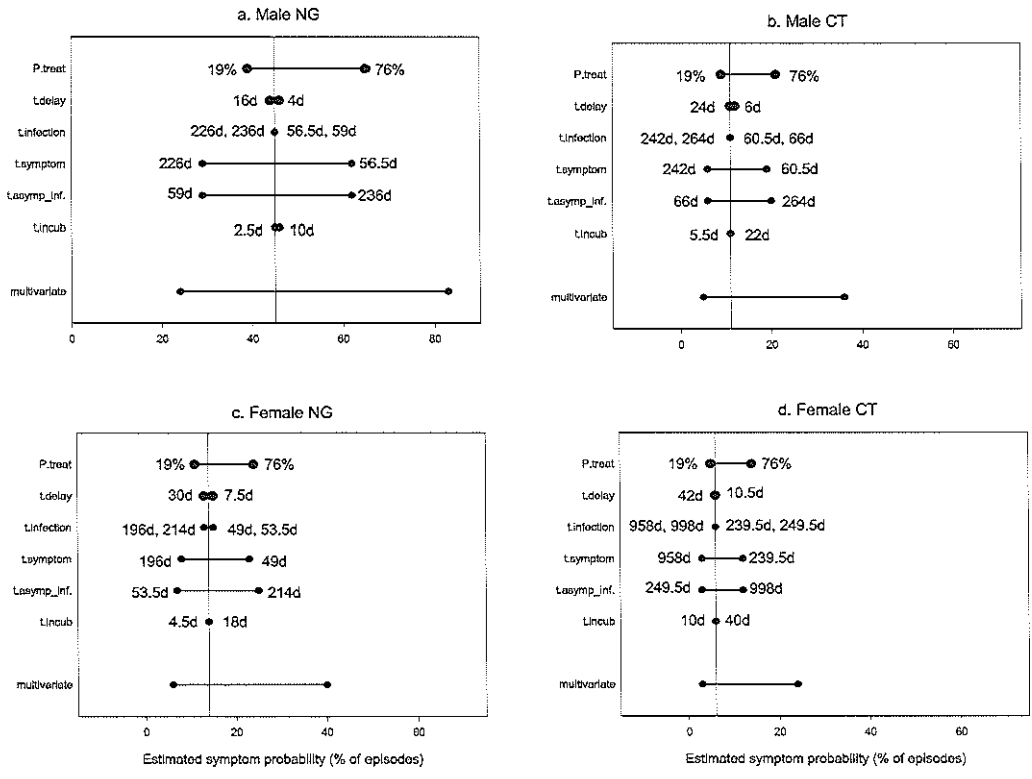

***Figure 4.2* Sensitivity analysis: Ranges of estimated probabilities (%) of developing recognized symptoms in episodes of gonorrhoea (NG) or chlamydia (CT) when doubling or halving values of the determinants of the point prevalence of self-reported symptoms.** The vertical lines represent the baseline estimates shown in Table 4.2. The upper 6 horizontal lines are outcomes of varying 1 parameter at a time. An exception is the line *'t_infection'*, which involves a doubling or halving of the duration of symptoms (*t.symptom*) and of the total duration of asymptomatic infection (*t.asymp_inf*) simultaneously. The lowest line in each graph presents a multivariate sensitivity analysis, in which the incubation period and the proportion of symptomatic cases treated were doubled, while the duration of symptoms without treatment and patient delay were halved (and vice versa). Incubation period (*t.incub*), duration of infection in asymptomatic episodes (*t.asymp_inf*), duration of symptoms without treatment (*t.symptom*), and patient delay interval (*t.delay*) are expressed in days (d); the proportion of symptomatic cases treated (*P.treat*) is expressed as percentage (%). These results indicate that the estimated probability of developing symptoms is most sensitive to the proportion of symptomatic episodes that is treated and to the relative durations of symptoms and of asymptomatic infection.

4.5 Discussion

Considering the biomedical and setting-dependent determinants of symptom prevalence, we estimated the probabilities to develop recognized symptoms per episode of NG and CT infection using data from rural Uganda. Estimated symp-

tom probabilities ranged between 6%, for females with CT, and 45% for males with NG. The probability of symptomatic episodes was higher for gonorrhoea than chlamydia, and higher for males than for females, as reported by others [Schachter *et al.* 1975, McCutchan 1984, Stamm *et al.* 1984, Martin 1990, Holmes *et al.* 1999].

Estimated probabilities to develop symptoms were on average 1.5-fold larger than observed symptom point prevalences among infected cases in a cross-sectional survey in Uganda. This difference between the two measures was so small due to the low treatment rate of symptomatic infections in this population, and the short duration of incubation period relative to symptomatic stages in NG and CT infection. This implies that in populations with treatment rates as low as in rural Uganda, symptom prevalence among NG-or CT-infected cases may in fact be a reasonable indicator of the probability that episodes of these infections become symptomatic.

In order to assess symptom probabilities, we estimated the duration of NG and CT episodes (Table 4.1). These results generally corroborate previous reports based on less systematic approaches. The estimated duration was longest for CT in females (16 months). Previous workers reported the typical duration of CT in females to range between 6 months to 2 years [Rahm *et al.* 1986, Buhaug *et al.* 1989, Parks *et al.* 1997]. The duration of NG in females was previously estimated at 10 weeks to 1 year [Hethcote & Yorke 1984, Wiesner & Thompson 1980], which is consistent with our estimate of 4 months. For males, we estimated CT to last slightly longer than NG (about 4.5 and 4 months, respectively). Previously, NG in males was estimated to last between 3 weeks and 6 months [Holmes 1974, Hethcote & Yorke 1984, Wiesner & Thompson 1980, Garnett & Anderson 1993b]. CT is believed to last longer than NG in males [Holmes *et al.* 1999, Kretzschmar *et al.* 1996], but we could not identify published estimates of the duration of male CT infection. Sensitivity analyses (Figure 4.2) showed that changing the overall duration of infection, by a magnitude likely encompassing the effect of the possible biases discussed above, did not markedly affect estimates of symptom probabilities. This suggests that our estimates of symptom probabilities are robust.

The relative duration of symptomatic as compared to asymptomatic infection was however important (Figure 4.2). Available data (Table 4.1) did not suggest differences between asymptomatic and symptomatic episodes, and on this basis we assumed their durations to be equal. But given the poor definitions of the populations studied with respect to symptomatology, we had limited power to detect possible differences. Based on biomedical insight, symptomatic episodes could last either longer (because they are more severe) or shorter (if they would induce a faster immune response) than asymptomatic episodes. A reason for similar durations may be that, in populations with poor knowledge of STD symptoms as in rural Uganda, symptomatology appears to be determined more by subjec-

tive awareness than by objective disease signs, and would thus be unlikely to correlate with episode duration.

Our specification that, for both untreated and treated symptomatic NG and CT, the infection and its symptoms resolve at the same time also warrants caution. Although post-symptomatic phases of infection have been suggested [Judson 1990b, Thompson & Washington 1983], there is no empirical support for this conjecture. Some studies, on the contrary, suggest that symptoms disappear only after culture has become negative, both for treated [Johannisson *et al.* 1980] and untreated episodes [Mahoney *et al.* 1942, McCutchan 1984]. (In the latter case, our estimation procedure remains valid, since it used the prevalence of symptoms only from cases positive on diagnostic tests.)

Besides uncertainty about the durations of symptomatic and asymptomatic infection, several other limitations must be kept in mind. The assumed proportion receiving treatment was based on treatment seeking rates reported by participants in the comparison arm of an STD mass treatment trial who were referred to clinics for free treatment [Paxton *et al.* 1998a], and these may be higher than in the general population. This may have biased the estimated symptom development probabilities upward. Perhaps most importantly, the prevalence of reported symptoms among infected cases may systematically be higher than the proportion in which the STD under study is the cause of these symptoms. Vaginal discharge in particular, the main acute symptom of NG and CT infection in females, is a very non-specific complaint, which may also occur as a result of trichomoniasis, bacterial vaginosis, candidiasis or pregnancy [Holmes *et al.* 1999]. In the Ugandan study population, the prevalence of (current) discharge was 5% in NG-negative or CT-negative females, which is hardly lower than symptom prevalence among infected females. Therefore, the prevalence of symptoms in NG or CT infected females that is really caused by these infections, may be considerably lower than the values we used. Since estimated symptom probabilities varied almost proportionally with symptom prevalence (Eq. 1), reporting of non-specific symptoms may have biased our probability estimates in females upward.

Finally, we assumed that in the Ugandan surveys on symptom prevalence in NG- and CT-infectees, asymptomatic and symptomatic NG and CT infections were both detected with 100% sensitivity. Gram stain, culture and leucocyte-esterase dipstick (LED), however, have a higher sensitivity in the diagnosis of symptomatic NG than for asymptomatic NG [Judson 1990a, Jackson *et al.* 1997b]. If, by analogy, the sensitivity of the LCR test used in Uganda were also lower for asymptomatic than for symptomatic infection, the survey outcome may have overestimated symptom prevalence, and, hence, we may have overestimated the probability of developing symptoms.

Comparison with previous estimates of symptom probabilities

Few prospective studies directly measured the probability of developing symptoms in untreated NG or CT infection. A study on gonorrhoea in US seamen [Harrison *et al.* 1979] reported a symptom probability of 98%, much higher than the 45% we estimated from the Ugandan data. If we use Equation 1 in the inverse way (estimating symptom prevalence from symptom probability), with the treatment patterns of rural Uganda, a 98% symptom probability would be consistent with a symptom point prevalence of 91% for males with NG, which is much higher than the observed 33% in Ugandan men.

Considering the outcomes of the sensitivity analyses (Figure 4.2a), this discrepancy is unlikely due to imprecision in our methods or the data used. Rather, we may infer that patient delay and treatment rates are not the only setting-specific determinants of symptom prevalence. Notably, a higher degree of underreporting of STD symptoms in Uganda relative to US populations could contribute to this discrepancy. An example of the large influence of reporting behaviour can be found in data from an STD intervention trial in rural Tanzania [Mayaud *et al.* 1997a]. In this study, improved syndromic STD management coupled with information, education and communication (IEC) on symptom recognition and on the benefits of early treatment increased the population prevalence of symptomatic NG and CT. Since the intervention did not alter the overall prevalence of NG and CT [Mayaud *et al.* 1997a], the increase in symptomatic NG and CT probably reflects improved recognition and reporting.

Also variation in the gonococcal serogropus or serovars that prevailed in the respective populations may have influenced their different symptomatology [Ross *et al.* 1994].

The setting-dependency in symptom recognition may as well explain why symptom point *prevalences* in infected populations in Western settings are not always lower than in developing countries, despite higher treatment rates (MK Sudaryo *et al.*, submitted). For example, with the 98% probability of developing recognized symptoms documented for USA male NG patients [Harrison *et al.* 1979], if in this population 95% of symptomatic cases got treated after a mean 2 days of patient delay [Judson 1981], the corresponding symptom point prevalence in the USA would be 50%, i.e. even *higher* than the rural Ugandan value of 33%. Importantly, this example also illustrates that the ratio of the probability of developing symptoms to symptom prevalence increases with the level of treatment: for males with NG, estimated ratios were 1.9 (98% over 50%) for the US population, as compared to 1.4 (45% over 33%) for rural Uganda.

In conclusion, this chapter demonstrated that symptom point prevalence is likely to underestimate the probability of developing symptoms during an episode of infection, by a factor depending largely on STD treatment patterns in the population under study. Given uncertainties about the determinants of this relation,

the obtained symptom probabilities must be considered approximate estimates. These findings nevertheless suggest that in populations with low STD treatment rates as in rural Uganda, the probabilities of developing symptoms in NG and CT episodes may be very low, and not much higher than symptom point prevalence among infected cases. Furthermore, probabilities to develop recognized symptoms vary between populations, and are likely much lower in poorly educated and underserviced populations than in Western settings. The results imply that in underserviced populations, (improved) syndromic treatment alone is unlikely to be a sufficient STD control measure, because it fails to cover the majority of infectees and to curtail transmission. In such populations, population-based education on symptom recognition and treatment seeking is of (at least) paramount importance.

4.6 Appendix

Effect of reinfection on the estimation of STD durations from cohort studies

The proportion of subjects found infected at follow-up in cohort studies of infected patients is the sum of: the proportion who remained infected throughout the follow-up interval; and: the proportion who resolved the infection but got reinfected within the follow-up interval. If we assume that the duration till loss of infection is distributed exponentially with average t_α, then the probability P_α of remaining infected till the end of a follow-up interval τ is: $P_\alpha (t>\tau) = e^{-\tau / t\alpha}$. Assuming in addition that the probability of reinfection for previously infected subjects is constant over time according and the duration till reinfection exponentially distributed with mean t_β, then the probability P_β of resolving the infection and getting reinfected within the follow-up interval τ is: $P_{\alpha+\beta} (t \leq \tau) = 1 - t_\alpha / (t_\alpha - t_\beta) * e^{-\tau / t\alpha} + t_\beta / (t_\alpha - t_\beta) * e^{-\tau / t\beta}$. Using these equations, we can calculate infection durations t_α that take into account the influence of reinfection.

Several studies have measured reinfection rates for NG and CT, and these appear to vary between populations. CT was found to recur at a rate of 5% per year over the first 1.4 years among US male and female soldiers [Barnett & Brundage 2001], and among US females after a median duration of 8-11 months [Burstein *et al.* 2001], in 15% after an average follow-up of 3.4 years [Xu *et al.* 2000], and in 31% over an average interval of 9 months [Richey *et al.* 1999]. For gonorrhoea, one study observed a risk of reinfection within 6 months among US males of 13% [Thomas *et al.* 1996].

When estimating reinfection rates in the studies we used for evaluating durations, we considered that, with a reinfection probability above 30% per year

(i.e. t_β = 2.8 year) the outcomes of four studies listed in Table 4.1 [Parks *et al.* 1997, Mahoney *et al.* 1942, Alexander *et al.* 1977, Sorensen *et al.* 1994] could not be explained, whatever the chosen infection duration. For two studies of chlamydia in females with particularly low observed proportions infected at follow-up (Table 4.1) [Alexander *et al.* 1977, Sorensen *et al.* 1994], observations were inconsistent with any annual infection rate above 10%. We therefore concluded that the actual reinfection rates were for these populations likely lower than these values.

To assess the maximum influence of reinfection, we calculated infection durations assuming a 10% annual reinfection rate for the two studies of chlamydia in females, and a 30% rate for all other studies. Under these assumptions, estimated durations derived from the pool of studies shown in Table 4.1 were 82 days for females with gonorrhoea (as compared to 107 days in the base-case) and 454 days for females with chlamydia (as compared to 499 days in the base case). For males with either infection, estimates remained essentially unchanged. These upperbound estimates suggest that reinfection affected our estimates of infection duration only little.

chapter 5

Comparison of baseline STD prevalences between Mwanza and Rakai populations: the role of selection bias and test diagnostics

Orroth KK, Korenromp EL, White R, Changalucha J, Serwadda D, De Vlas SJ, Hayes RJ, Grosskurth H. Comparison of STD prevalences in the Mwanza and Rakai trial populations: the role of selection bias and diagnostics errors. *Manuscript in preparation.*

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5.1 Summary

Objectives: To assess bias in estimates of STD prevalence in population-based surveys resulting from diagnostic error and selection bias. To evaluate the effects of such biases on STD prevalence estimates from two community-randomised trials of STD treatment in Mwanza, Tanzania and Rakai, Uganda.
Methods: Age- and sex-stratified prevalences of gonorrhoea, chlamydia, syphilis, HSV-2 infection and trichomoniasis observed at baseline in both trials were adjusted for the sensitivity and specificity of the screening and diagnostic techniques, and for sample selection criteria.
Results: After adjustments, gonorrhoea prevalence was higher in men and women in Mwanza (2.7% and 2.8%, respectively) compared to men and women in Rakai (1.0% and 0.9%, resepectively). Prevalence of chlamydia infection was higher in women in Mwanza (9.0%) compared to Rakai (3.3%) but similar in men (2.0% and 2.5%). Prevalence of trichomoniasis was higher in women in Mwanza compared to women in Rakai (39.7% versus 29.5%). HSV-2 seroprevalence was similar in the two populations. Adjustments for syphilis were not required. Prevalence of serological syphilis (TPHA+/RPR+) was similar in the two populations but the prevalence of active, high-titre syphilis (TPHA+/RPR $\geq$ 1:8) in men and women was higher in Mwanza (5.6% and 6.3%) than in Rakai (2.3% and 1.4%).
Conclusions: Baseline STD prevalences were underestimated in Rakai and, especially, in Mwanza, due to diagnostic errors and selection bias. After adjustment, prevalence of curable STD were generally higher in Mwanza than in Rakai. This may partly explain the larger impact of STD treatment on HIV transmission in the Mwanza trial.

5.2 Introduction

Prevalences of sexually transmitted diseases (STD) are often compared between populations in order to gain a better understanding of STD and HIV epidemiology or to determine which control strategy may be most effective in a given epidemiological situation. Two community-randomised trials of STD treatment as an HIV prevention strategy have been conducted in East Africa in Mwanza, Tanzania, and Rakai, Uganda [Grosskurth *et al.* 1995a, Wawer *et al.* 1999]. In the Mwanza trial, improved STD case management was associated with a 38% reduction in HIV incidence [Hayes *et al.* 1995a]. In the Rakai trial, STD mass treatment had no impact on HIV incidence [Wawer *et al.* 1999]. Various hypotheses have been suggested to explain the apparently contrasting results, including that the two trials differed with respect to the baseline prevalence of curable STD [Grosskurth *et al.* 2000]. Based on the reduction in HIV incidence in Mwanza and the association between STD and HIV transmission we would expect a higher prevalence of STD

in Mwanza than Rakai. However, the STD prevalences reported in the two trials cannot be directly compared, as different diagnostic tests and different sampling strategies were used.

STD prevalences observed in surveys such as in Mwanza and Rakai depend upon selection of the sample for measurement, extrapolation of the prevalence measured in this sample to the general population, and the diagnostic technique used. Selection of the population in which the STD is measured may bias observed STD prevalence either upward or downward. The net effect of diagnostic performance depends on the true prevalence level: if prevalence is low, specificity is most important but if prevalence is high sensitivity is critical. Diagnostic errors can lead to either overestimation or underestimation of prevalence.

In this chapter, the measurement errors in STD prevalences due to the selection of the sample in which the STD was measured, screening and test diagnostics were assessed for the Mwanza and Rakai trial surveys. We adjusted the observed baseline prevalences of *Neisseria gonorrhoea* (NG), *Chlamydia trachomatis* (CT), *Trichomonas vaginalis* (TV), syphilis and herpes simplex virus type 2 (HSV-2) infection for these biases, and then compared prevalences between the two populations. We also considered the implications of these comparisons for the interpretation of the discrepant trial outcomes.

5.3 Methods

Framework for adjustments

Observed prevalences were adjusted for the sensitivity and specificity of the diagnostic tests, according to equation 1 [Kelsey *et al.* 1986]:

$$p_{true} = \frac{(p_{observed} + Sp - 1)}{(Se + Sp - 1)} \qquad \text{Eq. 1}$$

where, p_{true} = true prevalence, $p_{observed}$ = observed prevalence, Se = sensitivity, and Sp = specificity.

For outcomes where diagnostics were performed on only a subset of the population based on results of a screening test, prevalences were also adjusted for the screening algorithm. The formula for this combined adjustment is:

$$p_{true} = \frac{p_{observed} - p_{screen}(1 - Sp)}{Se'(Se + Sp - 1)} \qquad \text{Eq. 2}$$

where p_{true} = true prevalence, $p_{observed}$ = observed prevalence (i.e. on the combination of screening test and diagnostic test, under the assumption that those negative on screen are all truly negative), p_{screen} = prevalence of a positive screening

test, Se = sensitivity of the diagnostic test, Sp= specificity of the diagnostic test, and Se'= sensitivity of the screening test. The derivation of Equation 2 is given in the Appendix.

After these adjustments, the overall prevalence of each infection in adults aged 15-54 years was obtained after standardising for age using an average population structure of the two populations based on census data [Bureau of Statistics & Macro-International 1997, Republic of Uganda 1991]. When data were not available for the entire age range 15 to 54, restricted age ranges were used.

Estimates of sensitivity and specificity for diagnostic tests

The sensitivity and specificity of the tests used were estimated based on values documented in the literature for general populations and populations of asymptomatic subjects. When outcomes for these populations could not be found, studies in STD clinic patients were used instead. We averaged test sensitivities and specificities across published studies, and the mean values were used for adjustment of the Mwanza and Rakai observations. This was followed by a sensitivity analysis using the highest documented value for sensitivity from any single study, and the lowest value for specificity from any single study, to estimate a lower limit for the adjusted prevalence range. Similarly, the upper limit for the range was determined by using the lowest sensitivity and highest specificity.

Gonorrhoea and chlamydia – In Rakai, urine ligase chain reaction (LCR, Abbott Laboratories, Abbot Park, Illinois, USA) was used to diagnose NG and CT in men and women. In Mwanza, Gram stain on urethral smears was used to diagnose NG in men. For women, culture and Gram stain from endocervical swabs were used to diagnose NG, and the subject was considered infected if either test was positive. In Mwanza, enzyme immunoassay (EIA, IDEIA Chlamydia; Novo Nordisk Diagnostika, Cambridge, England, UK) from urethral swabs was used to diagnose CT in men, and EIA from endocervical swabs were used for CT in women.

To obtain estimates of sensitivity and specificity, we included only studies using an 'expanded' gold standard, defined as positivity on either cell culture or - if cell culture was negative - on two different non-culture tests such as LCR or PCR. Studies using culture alone as the gold standard were not used, because the imperfect sensitivity of culture would incorrectly suggest a low specificity for the tests under study which have higher sensitivity than culture, such as LCR [Robinson & Ridgway 1996].

In Mwanza, a screening test was used to select the sample of men to be tested for NG and CT, with testing confined to men who either tested positive on urine leucocyte esterase dipstick (LED; Nephur-Test + Leuco, Boehringer-Mannheim, Lewes, England, UK) tests, who complained of discharge during the interview, or who had discharge upon clinical examination. To allow adjustment for the perfor-

mance of the screening test (according to Equation 2), we estimated its sensitivity based on findings in a separate study conducted in 1996 in a rural community in Mwanza region [Watson-Jones *et al.* 2000] (see Results).

Trichomoniasis - The prevalence of *Trichomonas vaginalis* in women was assessed via InPouch TV culture (BioMed Diagnostics, San Jose, California, USA) on self-collected vaginal swabs in Rakai and by wet mount microscopy of vaginal smears in Mwanza. In the reviewed literature, InPouch culture was compared with other culture techniques, PCR, and wet mount microscopy as gold standards. To assess the performance of wet mount microscopy on vaginal specimens, we considered studies comparing this test with InPouch culture, other culture techniques, and PCR.

Syphilis - A non-treponemal test, the toluidine red unheated serum test (TRUST; New Horizons, Columbia, Maryland, USA), was used to screen the Rakai population for syphilis. Those testing positive on the TRUST test were tested using the *Treponema pallidum* hemoagglutination assay (TPHA;TPHA Sera-Tek, Fujirebio, Tokyo, Japan) test [Wawer *et al.* 1998]. In Mwanza, the TPHA test was conducted on all study participants. A non-treponemal rapid plasma reagin (RPR; VD-25 Murex, Dartford, England, UK) test was conducted for those who were TPHA-positive [Grosskurth *et al.* 1995b]. In both populations, we compared the prevalence of serological syphilis (TPHA-positive with any RPR/TRUST titre) and the prevalence of active, high-titre syphilis (TPHA-positive with RPR titre $\geq$ 1:8). The diagnostic performance of the RPR and TRUST tests are similar with 98% sensitivity and 99% specificity [Larsen *et al.* 1995, Hart 1986] and TPHA tests were used in both populations, so no adjustment was needed to validly compare serological or active high-titre syphilis prevalence as measured in Mwanza and Rakai.

HSV-2 seroprevalence - HSV-2 serology for the Rakai trial was conducted at the Centers for Disease Control (CDC) using an immunoblot assay which discriminates between antibodies for HSV-1 and HSV-2 [Wawer *et al.* 1999]. The diagnostic adjustments proposed for the Rakai data are based on comparison with another immunoblot assay as the gold standard [Sanchez-Martinez *et al.* 1991]. Seroprevalence in Mwanza was measured using a monoclonal antibody blocking immunoassay test and the diagnostic adjustment is based on the comparison of this test with Western-blot in a rural African population [Obasi *et al.* 1999].

Estimation of selection bias

If random samples of the population were selected or the entire sample was evaluated, we adjusted STD prevalence for diagnostic test performance only. This was

the case for NG, CT, TV, and syphilis in Rakai and HSV-2 and syphilis in Mwanza [Grosskurth *et al.* 1995b, Obasi *et al.* 1999, Wawer *et al.* 1998]. We restricted comparison of STD prevalences to the gender and age ranges for which data were available from both sites. Thus, comparisons for NG and CT were restricted to women and men aged 15-39 years. Comparisons for TV included women aged 15-49 years (data were not available for TV in men from either site). We compared HSV-2 seroprevalence in 15-29 year-olds and syphilis in 15-54 year-olds.

Where only non-random samples of the populations had been measured, additional adjustments were considered. In women in Mwanza, prevalences for NG, CT, and TV were measured only among antenatal clinic (ANC) attendees. ANC data from Mwanza town have been shown to underestimate HIV prevalence and syphilis prevalence in women in the general population [Kigadye *et al.* 1993, Mosha *et al.* 1993]. Similarly, unpublished analysis on Rakai trial data found age-standardised NG prevalence among 15-39 year-olds to be 0.7% among self-reported pregnant women and 1.6% among women in the general population. For CT in Rakai, the corresponding prevalences were 2.9% and 2.7%, and for TV prevalences were 24% in both groups. These data suggest levels of curable STD are similar or slightly lower in pregnant women compared to the general population in African populations. However, it is unclear whether this can be assumed to apply to women attending antenatal clinics in rural Mwanza. It may be that selection biases associated with antenatal populations differ between urban and rural areas, or that HIV-associated effects on fertility may lead to different biases in rural Mwanza (4% HIV prevalence) and Rakai (16% HIV prevalence). Therefore, the Mwanza data were not adjusted for selection of the ANC sample. Instead, our analyses for Rakai were limited to data from pregnant women (according to self-report), allowing for a valid site comparison.

HSV-2 seroprevalence in Rakai was measured only among individuals reporting they were sexually active. Hence the population adjustment must take into account the prevalence of sexual activity in the different age strata in the sampled group (15-29 year-olds). For this, we assumed that self-report of sexual activity was 50% (half of those truly sexually active reported sexual activity) or 100% sensitive in 15-19 year-olds, 95% or 100% sensitive in 20-24 year-olds, and 100% sensitivity in 25-29 year-olds. After adjusting prevalence of HSV-2 among sexually actives in Rakai for diagnostic biases, the estimated prevalence for this group was multiplied by the estimated proportion sexually active.

5.4 Results

Table 5.1 shows published estimates of the sensitivity and specificity of the diagnostic tests of interest. The average sensitivity and specificity for each test are also given. For Gram stain of urethral smears for NG in men, only one study on diag-

Table 5.1 **Published values for sensitivities and specificities of gonorrhoea and chlamydia diagnostics in women and men and trichomoniasis in women.** LCR = ligase chain reaction; EIA = enzyme-immuno-assay; MOMP = major outer membrane protein; ANC = antenatal clinic; Ob-gyn = obstretical/gynaecology patients; Se = sensitivity; Sp = specificity.

Trial and Test	Gold Standard and Specimen	Se (%)	Sp (%)	Population	Reference
Women					
Chlamydia in Rakai – LCR on urine	Gen-Probe (endocervical) / EIA (endocervical) / LCR (urine)	98.4	100	Ob-gyn	[Lauderdale *et al.* 1999]
	Gen-Probe (endocervical) / LCR (urine)	86.8	100	STD clinic	[Carroll *et al.* 1998]
	LCR (urine) / MOMP-LCR (urine) / culture (endocervical)	95	100	Ob-gyn	[Lee *et al.* 1995]
	LCR (urine) / MOMP-LCR (urine) / culture (endocervical)	92.3	100	STD clinic	[Lee *et al.* 1995]
	LCR (urine) / MOMP-LCR (urine) / culture (endocervical)	78.8	99.4	STD clinic	[Buimer *et al.* 1996]
	LCR (urine) / direct immunofluorescence (urine) or if negative but positive on LCR then MOMP-LCR (urine) / culture (endocervical)	69.6	99.8	STD clinic	[Ridgway *et al.* 1996]
	LCR (urine) / MOMP-LCR (urine) / culture (endocervical)	92.6	100	STD clinic	[van Doornum *et al.* 1995]
Mean		*87.6*	*99.9*		
Chlamydia in Mwanza: EIA on endocervical swab	Gen-Probe (endocervical) / EIA (endocervical) / LCR (urine)	50	100	Ob-gyn	[Lauderdale *et al.* 1999]
	PCR (endocervical) / culture (endocervical) / EIA (endocervical)	61.1	99.9	Hospital	[Skulnick *et al.* 1994]
	PCR (endocervical) / culture (endocervical) / EIA (endocervical)	76.4	97.8	STD clinic	[Wu *et al.* 1992]
Mean		*62.5*	*99.2*		
Gonorrhoea in Rakai: LCR on urine	LCR (urine) / MOMP-LCR (urine) / culture (endocervical)	50	100	STD clinic	[Buimer *et al.* 1996]
	LCR (urine) / Pilin-LCR (urine) / culture (endocervical)	94.7	100	STD clinic	[Stary *et al.* 1997]
	LCR (urine) / LCR (endocervical) / culture (endocervical)	91.7	100	STD clinic	[Carroll *et al.* 1998]
Mean		*78.8*	*100*		
Gonorrhoea in Mwanza: culture	LCR (urine) / MOMP-LCR (urine) / culture (endocervical)	50	100	STD clinic	[Buimer *et al.* 1996]
	LCR (urine) / Pilin-LCR (urine) / culture (endocervical)	84.2	100	STD clinic	[Stary *et al.* 1997]
Mean		*67.1*	*100*		
Trichomoniasis in Rakai: InPouchTV on vaginal swab	InPouch culture (vaginal) / Diamond's culture (vaginal) / wet mount (vaginal)	88.3	100	ANC	[Draper *et al.* 1993]
	PCR (vaginal) / InPouchTV culture (vaginal) / wet mount (vaginal)	69.7	100	Army medical clinic	[Madico *et al.* 1998]
	Diamond's culture (vaginal)	81	100	Adolescent clinic	[Ohlemeyer *et al.* 1998]
Mean		*79.7*	*100*		

Trichomoniasis in Mwanza: wet mount microscopy on vaginal swab	PCR (vaginal) / InPouchTV culture (vaginal) / wet mount (vaginal)	36.4	100	Army medical clinic	[Madico *et al.* 1998]
	InPouch culture (vaginal) / Diamond's culture (vaginal) / wet mount (vaginal)	85.3	99.5	ANC	[Draper *et al.* 1993]
	InPouch culture (vaginal)	15	n.a.	Hospital	[Borchardt *et al.* 1992]
	Diamond's culture (vaginal) / Feinberg-Whittington culture (vaginal)	60	93.2	STD clinic	[Krieger *et al.* 1988]
	Diamond's culture (vaginal) / Feinberg-Whittington culture (vaginal)	50.4	100	STD clinic	[Fouts & Kraus 1980]
Mean		*61.8*	*98.2*		
Men					
Chlamydia in Rakai: LCR on urine	LCR (urine) / MOMP-LCR (urine) / culture (urethral)	77.3	99.4	STD clinic	[Buimer *et al.* 1996]
	LCR (urine) / MOMP-LCR (urine) / culture (urethral)	86.2	100	STD clinic	[van Doornum *et al.* 1995]
	LCR (urethral) / LCR (urine) / Gen-Probe (urethral)	92.5	100	STD clinic	[Carroll *et al.* 1998]
Mean		*85.3*	*99.8*		
Chlamydia in Mwanza: EIA on urethral swab	PCR (urine, urethral) / EIA (urine, urethral) / culture (urethral)	76	99.5	General Population	[Noren *et al.* 1998]
	PCR (urine) / EIA (urethral) / supplemental PCR	60	100	STD clinic	[Palladino *et al.* 1999]
	PCR (urethral) / culture (urethral) /EIA (urethral)	91.7	100	STD clinic	[Wu *et al.* 1992]
Mean		*75.9*	*99.8*		
Gonorrhoea in Rakai: LCR on urine	LCR (urine) / P1 and pilin genes-LCR (urine) / culture (urethral)	88.9	100	STD clinic	[Buimer *et al.* 1996]
	LCR (urine) / LCR (urine) / culture (urethral)	94.7	100	STD clinic	[Carroll *et al.* 1998]
Mean		*91.8*	*100*		
Gonorrhoea in Mwanza: Gram stain	PCR (urine) / culture and/or microscopy (urethral) / supplemental PCR	86.8	100	STD clinic	[Palladino *et al.* 1999]

***Table 5.2* Diagnostic test, screening test and selection bias adjustments for STD measured at baseline in Rakai and Mwanza.** Observed prevalence adjusted according to equation 1 if no screening test used, according to equation 2 when screening test used. For selection bias adjustments see text. M = male; F = female; y = year; NG = gonorrhoea; CT = chlamydia; TV = trichomoniasis; HSV-2 = herpes simplex virus type 2 serology; Se = sensitivity of diagnostic test in Eqs. 1 and 2; Sp = specificity of diagnostic test in Eqs. 1 and 2; Se′ = sensitivity of screening test in Eq. 2; P_{screen} = prevalence of positive screening test in Eq. 2.

	Diagnostic test adjustment		Screening test adjustment		Selection bias adjustment
	Se (range) (%)	Sp (range) (%)	Se′ (%)	P_{screen} (%)	
Rakai					
CT	F: 87.6 (69.6 – 98.4) M: 85.3 (77.3 – 92.5)	F: 99.9 (99.4 – 100) M: 99.8 (99.4 – 100)	n.a.	n.a.	n.a.
NG	F: 78.8 (50 – 94.7) M: 91.8 (88.9 – 94.7)	F: 100 (n.a.) M: 100 (n.a.)	n.a.	n.a.	n.a.
TV	F: 79.7 (69.7 – 88.3)	F: 100 (n.a.)	n.a.	n.a.	n.a.
HSV-2	92 (n.a.)	100 (n.a.)	n.a.	n.a.	Prevalence of sexual activity Females: 15-19y: 0.71 – 0.86 20-24y: 0.99 – 1 25-29y: 1 Males: 15-19y: 0.52 – 0.76 20-24y: 0.94 – 0.97 25-29y: 1
Mwanza					
CT	F: 62.5 (50 – 76.4) M: 75.9 (60 – 91.7)	F: 99.2 (97.8 – 100) M: 99.8 (99.5 – 100)	F: n.a. M: 53.3	F: n.a. M: 15-19y: 0.24 20-24y: 0.26 25-29y: 0.25 30-34y: 0.21 35-39y: 0.26 40-44y: 0.23 45-49y: 0.27 50-54y: 0.27	n.a.

NG	F: 67.1 (50 – 84.2) M: 86.8 (n.a.)	F: 100 (n.a.) M: 100 (n.a.)	F: n.a. M: 87.5	F: n.a. M: 15-19y: 0.24 20-24y: 0.26 25-29y: 0.25 30-34y: 0.21 35-39y: 0.26 40-44y: 0.23 45-49y: 0.27 50-54y: 0.27	n.a.
TV	F: 61.8 (15 – 85.3)	F: 98.2 (93.2 - 100)	n.a.		n.a.
HSV-2	91 (n.a.)	93 (n.a.)	n.a.		n.a.

nostic properties in comparison to an appropriate gold standard was identified, for a STD clinic population [Palladino *et al.* 1999], and so we used data from this study. For the tests used in Mwanza, sensitivity was generally low, mean estimates ranging between 62% and 87%). For the Rakai tests, mean sensitivities ranged between 79% and 92%. Mean specificities were between 98.2% and 100% for Mwanza, and 99.5% and 100% for Rakai.

Table 5.2 lists all adjustments required for the Mwanza-Rakai comparison. For diagnostic tests, these were based on the means and ranges given in Table 5.1. For the screening test used for NG and CT in men in Mwanza, we estimated sensitivity at 53% for CT and 88% for NG; prevalences of positive screening test, needed for the adjustment according to Equation 2, are also given. For selection bias adjustment of the Rakai HSV-2 data, estimated proportions sexually active for each age group are listed according to the assumptions discussed above.

Table 5.3 shows the observed and adjusted prevalence levels for CT, NG, TV and HSV-2 serology. For serological (TPHA+/RPR+) and active high-titre (TPHA+/

Table 5.3 **Observed and adjusted prevalence among women and men for CT, NG, TV, HSV-2 serology, serological syphilis (TPHA+/RPR+) and active syphilis (TPHA+/RPR≥1:8) in Rakai and Mwanza.** Prevalences are age-standardised by five-year age groups according to average age structure of Rakai district and rural Mwanza Region [Republic of Uganda 1991, Bureau of Statistics & Macro-International 1997]. NG = gonorrhoea; CT = chlamydia; TV = trichomoniasis; HSV-2 = herpes simplex virus type 2.

	Observed prevalence (%)		Adjusted prevalence (%) and range	
	Rakai	Mwanza	Rakai	Mwanza
Women				
CT (15-39y)*	2.9	6.4	3.3 (2.5 – 4.2)	9.0 (5.6 – 12.7)
NG (15-39y) *	0.7	1.9	0.9 (0.8 – 1.5)	2.9 (2.3 – 3.0)
TV (15-49y) *	24.0	25.6	29.5 (26.6 - 30)	39.7 (24 – 100)
HSV-2 (15-29y)	41.9	46.8	39.6 – 40.7	47.4
All syphilis (15-54y)	9.9	8.9	–	–
Active syphilis (15-54y)	1.4	6.3	–	–
Men				
CT (15-39y)	2.4	1.0	2.5 (1.9 – 3.1)	2.0 (1.5 – 2.7)
NG (15-39y)	0.9	2.0	1.0 (1.0 – 1.1)	2.7
HSV-2 (15-29y)	23.0	18.2	16.6 – 17.8	13.3
All syphilis (15-54y)	9.6	7.3	–	–
Active syphilis (15-54y)	2.3	5.6	–	–

* for self-reported pregnant (Rakai) and ANC (Mwanza) women.

RPR≥1:8) syphilis for men and women in Mwanza and Rakai, the directy observed prevalences are given. In women, observed prevalence of CT in Mwanza was more than two-fold higher than in Rakai, while after adjustment for diagnostics, it was almost three-fold higher. Similarly the adjustment accentuated the higher prevalence of NG in Mwanza as compared to Rakai. Observed TV prevalence was similar in the two sites, but after adjustment, prevalence was higher in Mwanza compared to Rakai. Observed prevalence of serological syphilis was slightly higher in Rakai than Mwanza but prevalence of active syphilis was higher in Mwanza than Rakai. Also for HSV-2, seroprevalence tended to be higher in Mwanza than in Rakai, even after allowing for possible under-reporting of sexual activity in Rakai. In men, observed CT prevalence was higher in Rakai than Mwanza but after adjustment this difference became smaller. Observed NG prevalence was higher in Mwanza than Rakai and the difference was accentuated after adjustment. Similar to results for women, the observed prevalence of serological syphilis was higher in Rakai than Mwanza, but prevalence of active syphilis was much higher in Mwanza than Rakai. Levels of HSV-2 were slightly higher in Rakai compared to Mwanza.

The sensitivity analyses (last column in Table 5.3) indicate that the outcomes were fairly robust against uncertainty in our estimates of sensitivity and specificity of the diagnostic tests. An exception was TV in females in Mwanza, for which estimated prevalences changed considerably when replacing the mean estimates for sensitivity by values documented from single studies (Table 5.1).

5.5 Discussion

Previously published results from the Mwanza and Rakai trials studies suggested STD prevalences to be comparable in the two sites at baseline [Wawer *et al.* 1998, Grosskurth *et al.* 1995b]. We have shown that, due to measurement error, the levels of curable STD may have been underestimated. This was especially the case in Mwanza, and taking the measruement errors into account, prevalences of curable STD proved to be considerably higher in Mwanza than Rakai for NG, CT (apart from CT in men), TV, and active, high-titre syphilis (for which adjustments were not made). These infections reflect recent sexual behaviour in the populations. On the other hand, the prevalences of HSV-2 and serological syphilis were similar across the sites but these STD reflect the level of sexual risk behaviour over a longer past period. The higher STD prevalences in Mwanza may be due to higher risk behaviour in Mwanza compared to Rakai at the baseline of the trials, which may in turn relate to the more advanced HIV epidemic in Rakai.

Several limitations in our analysis must be highlighted. The adjusted prevalences depend on the effect of selection bias, the performance of screening algorithms,

and the measured sensitivity and specificity of the diagnostic tests. Regarding selection bias, we must consider selection of the ANC sample in Mwanza compared to pregnant women in Rakai when comparing NG, CT and TV prevalences. It is not clear how the data from ANC women in Mwanza may differ from those for all women who know they are pregnant in the population. About 90% of pregnant women in Mwanza attend ANC so we would not expect selective factors such as STD symptoms to bias STD prevalence in the ANC sample [Bureau of Statistics & Macro-International 1997]. The ANC attendees in Mwanza would have been, on average, at later gestation than all pregnant women in the population. Hence, STD prevalence may be underestimated in Mwanza compared to Rakai since women with pregnancies that resulted in spontaneous abortions due to STD infections would not have been in the ANC sample. It seems most likely that ANC sample in Mwanza would have underestimated STD prevalence but there may be other unknown factors which may have biased STD prevalence upwards in the ANC sample.

When comparing NG and CT prevalence in men we have to consider limitations of the performance of the complicated screening algorithm used in Mwanza. We inferred the performance of the screening algorithm (urine LED tests and reporting of symptoms or signs on clinical examination) from its use in a general population survey among men in a rural community of Mwanza region, Misungwi, in 1996 [Watson-Jones *et al.* 2000]. This inference was appropriate because the proportion of men positive for the LED-test, reporting symptoms, or with signs on clinical examination were known to be similar between the Misungwi study and the Mwanza trial. In the trial, the distribution of reasons for positivity on the screening test was: 92% (out of 1451 men) LED-positive only, 4% complaining of discharge or ulcerative symptoms or with signs on clinical exam but LED-negative, and 4% with symptoms or signs and LED-positive [Grosskurth *et al.* 1996]. In the Misungwi study of 438 men, 96% of men who tested positive on the screening algorithm had a positive LED-test only, 2% had signs or symptoms only, and 2% had symptoms or signs and were LED-positive. A further prerequisite for this inference is that the sensitivity of this screening algorithm was similar in both populations. We think this is the case because the determinants of this sensitivity, such as the prevalence of schistosomiasis, are similar in Misungwi and the Mwanza trial communities.

Finally, limitations in the performance of the diagnostic tests used influenced the measured prevalence in the two trials. Due to the earlier date of the Mwanza trial, it was not feasible to use highly sensitive and specific tests which were not available or affordable at that time. This explains why diagnostic biases were larger in Mwanza than Rakai. In this analysis, low sensitivity played a more critical role than low specificity since most adjustments of prevalences were upward (Table 5.3). For NG and CT in men in Mwanza, the effect of low sensitivity of the diagnostic test was enhanced by the low sensitivity of the screening test. The true magnitude of these diagnostic biases are however not certain, since we used

estimates of test sensitivity and specificity mostly from laboratory evaluations in Western settings (Table 5.1), where sensitivity and/or specificity may be better than under the conditions in the rural African sites. In addition, the majority of estimates for sensitivity and specificity of diagnostic tests came from STD clinic populations. We might expect the sensitivity of the tests to be worse for asymptomatic individuals compared to symptomatic individuals, and this would underestimate STD prevalence in both Mwanza and Rakai. Finally, the gold standards used to measure sensitivity and specificity may be imperfect, which would harm our ability to estimate true absolute preavlence. However, where possible the same gold standards were used for Mwanza and Rakai, so our site comparison of the relative prevalences in the two populations should be valid even if the absolute prevalences remain unknown due to an imperfect gold standard.

This illustration of the importance of sample selection and diagnostic techniques in biasing observed STD prevalences has implications for the conduct and interpretation of randomised trials and other surveys with STD prevalence outcomes. The complexity of the adjustments made for the screening algorithm in Mwanza indicates it is preferable to use random sub-samples of the general population to monitor STD prevalence.

With respect to diagnostic biases, in intervention trials, not only their effects on baseline prevalence but also the observed impact of the intervention on prevalence must be considered. Limitations in accuracy of diagnostic tests will in general result in dilution of observed impact on prevalence (i.e., differences between arms at follow-up, or reductions over time within one arm). If specificity is limited, prevalence in any sample will be overestimated, and the relative difference in prevalence between arms or timepoints underestimated. As an example, assume the *observed* impact of an intervention on CT was to reduce prevalence from 4% to 2% (relative risk=0.5). With 100% sensitivity and 99% specificity, the true prevalence - after adjustment for imperfect specificity - would be 3% in the comparison arm and 1% in the intervention arm, consistent with a relative risk of 0.33. If sensitivity is limited but specificity is 100%, the relative difference in the true prevalence between arms or timepoints is the same as the relative difference in observed prevalence.

In conclusion, the biases demonstrated in STD prevalences in the general population cohorts of the Mwanza and Rakai trials illustrate the critical attention which should be paid to selecting the population in which the STD is to be measured and the diagnostic technique to be used when conducting a research study with STD prevalence outcomes. Notably, besides the properties of diagnostic tests, the sensitivity of screening tests must not be neglected. In intervention trials, high specificity is critical to avoid dilution of impact measures. We have shown that, after taking into account the biases, the prevalences of curable STD were higher in Mwanza than Rakai at the baseline of the trials. Based on this, we would expect

STD treatment to have a larger impact on HIV incidence in Mwanza than Rakai. This finding would, in part, explain why STD treatment resulted in reduced HIV incidence in Mwanza but not in Rakai.

5.6 Appendix

Derivation of adjustment for diagnostics and screening, Equation 2

Test 1: Screening test

	True Status		
Test	Positive	Negative	Total
Positive	a	b	c
Negative	c	d	f
Total	g	h	N

Test 2: Diagnostic test

	True Status		
Test	Positive	Negative	Total
Positive	k	l	i
Negative	m	n	j
Total	a	b	e

Let:

Se = sensitivity of diagnostic test = $\frac{k}{k+m}$

Sp = specificity of diagnostic test = $\frac{n}{l+n}$

Se' = sensitivity of screening test = $\frac{a}{a+c}$

Sp' = specificity of screening test = $\frac{d}{b+d}$

$$P_{observed} = \frac{i}{N}$$

$$P_{screen} = \frac{e}{N} = p_{true}Se' + (1-Sp')(1-p_{true})$$

$$i = aSe + (1-Sp)b$$
$$i = gSe'Se + (1-Sp)(1-Sp')h$$

$$\begin{aligned} P_{observed} &= p_{true}Se'Se + (1-Sp)(1-Sp')(1-p_{true}) \\ &= p_{true}Se'Se + (1-Sp)(p_{screen} - p_{true}Se') \\ &= p_{true}(Se'Se - Se' + SpSe') + p_{screen}(1-Sp) \end{aligned}$$

Equation 2 in Section 5.3: $p_{true} = \frac{p_{observed} - p_{screen}(1-Sp)}{Se'(Se + Sp - 1)}$

chapter 6

HIV spread and partnership reduction for different patterns of sexual behaviour – a study with the microsimulation model *STDSIM*

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6.1 Summary

We studied how sexual behaviour affects population HIV spread simulating stylized risk profiles: 1) prostitution, no short relationships (resembling settings in South-East Asia); 2) prostitution, concurrent short relationships (resembling South-America and urban sub-Saharan Africa); 3) no prostitution, concurrent short relationships (resembling rural sub-Saharan Africa); 4) prostitution, serial short relationships (a generic low-risk setting).

We explored the impact on HIV prevalence of prevention programs accomplishing postponement of sexual debut, reduction in partner change rate and in prostitution. We described the representation of sexual behaviour in the microsimulation model *STDSIM*, comparing it to non-individual-based models.

The profiles generate markedly different time courses of HIV spread. Concentration of risk causes a rapid initial spread (Profiles 1 and 2), whereas the final prevalence depends more on the overall extent of risk behaviour in the general population (highest for Profiles 2 and 3). Effects of partnership reduction are strongly context-dependent. Small decreases in numbers of partners reduce HIV spread considerably if they reflect decreases in the contacts of highest risk in that setting. In settings with risk behaviour dispersed over a large part of the population (Profiles 2 and 3), indirect effects can cause the impact on HIV to be disproportionately large compared to the magnitude of behaviour change.

6.2 Introduction

In the continuing absence of cure or vaccines for HIV, avoidance of exposure remains the primary mode of HIV control. In the developing world, over 90% of HIV infections occur through heterosexual transmission [Over & Piot 1992]. Yet, little systematic research has been performed into the effects of different forms of behavioural risk reduction on HIV spread in the general population [Choi & Coates 1994, Peterman & Aral 1993, Oakley *et al.* 1995].

Sexual behaviour varies widely between countries, as has been shown in surveys performed throughout the world [Caraël 1995, WHO/UNAIDS 1998]. Large differences in sexual practices also exist within populations. Mathematical models have shown that the extent of heterogeneity in sexual promiscuity within a population [Anderson & May 1991] and of concurrency in relationships [Morris & Kretzschmar 1995, 1997, Garnett & Johnson 1997] have a large impact on the spread of HIV. Much less studied is how these variables affect the outcomes of behavioural interventions. Obviously, the impact of reducing certain types of risk, such as prostitution or overlap in relationships, varies with their relative occurrence in a population. Moreover, behavioural patterns may affect the effectiveness of interventions via the time course in HIV spread they gener-

ate. The same intervention may work out differently in settings where HIV has already spread into the general population, compared to settings where the infection is still confined to core groups and about to spread wider.

Mathematical modelling can help studying the complex interactions determining the spread of sexually transmitted diseases (STD) and their control. Different types of models can be used. On the one hand, there are relatively simple, deterministic models describing general mechanisms operating in the spread of infectious diseases on a population level [Gupta *et al.* 1989, Garnett & Anderson 1996a]. The other extreme are stochastic, comprehensive models simulating the dynamics of disease spread at the level of individuals and their interactions [Mode *et al.* 1989, Auvert *et al.* 1990, Leslie & Brunham 1990, Kretzschmar *et al.* 1993, Morris & Kretzschmar 1995, Boily & Anderson 1996, Ghani *et al.* 1997]. The latter type of models is particularly suitable for application in specific epidemiological settings. One such microsimulation model, under development as a tool in decision support in developing countries, is *STDSIM* [Van der Ploeg *et al.* 1998].

In this chapter, we present how the spread and control of HIV is simulated in *STDSIM*. To illustrate how *STDSIM* can be adapted to specific settings, we projected the effectiveness of behavioural interventions for four hypothetical settings, differing in the pattern of sexual behaviour: 1) prostitution is the only type of risk behaviour; 2) prostitution and short, possibly concurrent relationships put men of all ages and young women at risk; 3) both males and females have multiple short, often concurrent relationships throughout life, but there is no prostitution; and 4) serial monogamy and limited prostitution. The first three 'profiles' could be thought of as simplistic descriptions of behavioural patterns encoun-

***Table 6.1* Schematic description of model profiles of sexual behaviour.** Indicated is which risk behaviours are allowed in each profile, depending on individuals' present engagement in steady relationship(s) ('unmarried' vs. 'married').

Profile	Males				Females		Real-world setting approximated
	prostitute visiting		short relationships		short relationships		
	unmarried	married	unmarried	married	unmarried	married	
1	+	+	-	-	-	-	South-East Asia
2	+	+	+	+	+	-	South-America, urban sub-Saharan Africa
3	-	-	+	+	+	+	rural sub-Saharan Africa
4	+	-	+[1]	-	+[1]	-	generic low-risk

[1] Serial monogamy. Source: Worldbank, 1997.

tered in, respectively, 1) South-East Asia [Caraël *et al.* 1995, WHO/UNAIDS 1998], 2) South-America and urban sub-Saharan Africa [D'Costa *et al.* 1985, Buvé *et al.* 1995] and 3) rural sub-Saharan Africa [Caraël *et al.* 1995, Morris *et al.* 1995]. The fourth profile is a generic low risk profile, included for contrast with the other three profiles. The profiles are schematically described in Table 6.1. In earlier work, we have analyzed the effectiveness of condom use in different risk groups in preventing HIV using the above profiles [Worldbank 1997, Van Vliet *et al.* 1998]. Here, we focus on interventions accomplishing reductions in the number of partners: less prostitution, lower relationship formation rates, and postponement of sexual debut. We compare our results to insights into the mechanisms of STD spread gained with simpler models. We discuss the relevance of the projections for policy making in HIV control. Finally, we pay attention to the advantages and disadvantages of using microsimulation in modelling STD control, with special reference to the representation of sexual behaviour in the *STDSIM* model.

6.3 The *STDSIM* model

Projections were made with the microsimulation model *STDSIM* [Van der Ploeg *et al.* 1998]. In a microsimulation model, the life histories of hypothetical individuals are simulated over time in a computer program. Each individual is represented by a number of characteristics, of which some remain constant during simulated life (e.g. sex and date of birth), whereas others change (e.g. number of sexual partners). Changes in personal characteristics result from events such as the start and end of sexual relationships. These events are stochastic: if and when an event occurs is determined by Monte-Carlo sampling from probability distributions. To generate model outcomes for a simulated population, the characteristics of the simulated individuals are aggregated.

STDSIM simulates the transmission, natural history and health consequences of HIV and four classical sexually transmitted diseases (cSTDs), and possibilities for their control. The model is event-driven: all events are listed and performed in chronological order. At the occurrence of an event, the characteristics of the individual(s) and/or relationship(s) to which the event pertains are updated. In addition, events can generate new events, which occur either immediately - for example, the death of an individual terminates all relationships of this individual - or later in the simulation - for example, at birth, the moment is determined when the person will first become sexually active.

Aspects affecting the transmission of STDs are grouped into six modules. The modules demography, transmission, natural history, health care and interventions were described by Van der Ploeg *et al.* [Van der Ploeg *et al.* 1998], and are only summarized below. In order to explain the profiles of sexual behaviour used in

this analysis, we describe the module sexual behaviour in detail in the next section.

Model assumptions on demography, the transmission and natural course of HIV/STDs, and the general level of health care refer to a 'typical' third world country. Input quantifications for this chapter are based on data from surveys and scientific studies performed mainly in Africa, as documented earlier [Van Vliet *et al.* 1998]. We use age-specific fertility rates corresponding to an average total fertility rate of 3.6 [Unicef 1995]. Mortality rates are specified according to a standard, Coale-Demeney (West) life table, with a mean life expectancy of 62.5 for females and the corresponding life expectancy for males [Coale & Demeneny 1966]. Migration is not taken into account.

Assumptions on the transmission, natural course and treatment of curable STDs are specified for each STD separately on the basis of the scientific literature. We assumed HIV disease to last for 8 years on average, after which the patient dies [Morgan *et al.* 1997b, Nagelkerke *et al.* 1990]. We model HIV transmission efficiency as a bath-tub pattern [Anderson & May 1988, Jacquez *et al.* 1994, De Vincenzi 1994]. Transmission probabilities are 0.2% per contact from male to female and 0.1% per contact from female to male during the long asymptomatic phase (average duration 7 years), 20 times as high during the first 10 weeks of infection, and 5 times as high during the last, symptomatic year. Stage-specific HIV transmission risks are increased by the presence of a cSTD in either partner of an HIV-discordant sexual couple by a factor 5 for chlamydia or gonorrhoea, and by a factor 25 for (infectious) syphilis or chancroid [Cameron *et al.* 1989, Laga *et al.* 1993, Kreiss *et al.* 1994, Hayes *et al.* 1995c].

HIV is introduced into the model population randomly in 1 prostitute or, in scenarios without prostitution, in 10 sexually active males and 10 sexually active females. In addition, each year some STD infections are attributed to persons in the model population randomly. These represent infections acquired through sexual contacts with persons living outside the model population. For HIV, this annual incidence was set at a constant 0.01% for the population aged 16 and over, from the time of HIV introduction onwards.

Model projections and analyses

Projections were made for a time period of 33 years after introduction of HIV in the population in year 0. Prevention strategies were specified to start in year 15 after introduction of HIV and to lead to sustained behaviour changes until the end of the simulation period. In order to reduce stochastic fluctuations in simulation outcomes, for each profile and intervention scenario we averaged the results of 150 runs. Population size was chosen at approximately 20,000 individuals at start of the intervention; this may reflect the size of an average community, within which the majority of sexual partners of inhabitants live. We assessed

the effectiveness of interventions by comparing HIV prevalences in the general adult population between 15 and 49 years between simulations with and without interventions.

6.4 Modelling sexual behaviour

In *STDSIM*, sexual contacts and relationships constitute a dynamic network through which STDs can be transmitted. For example, when a simulated person contracts an STD, his/her uninfected partner(s) become(s) at risk for infection. We consider three types of (exclusively hetero-)sexual contact: (i) steady relationships ('marriages'); (ii) short relationships; (iii) prostitution (contacts between female prostitutes and male clients). Formation of relationships occur in a process-like way, using the concepts of availability for (supply) and search (demand) of new partners [Le Pont & Blower 1991, Morris 1991]. Figure 6.1 illustrates this process. New relationships are formed between available men and available women. People become available for relationships for the first time at sexual debut (t1 in Figure 6.1). At each subsequent change in the number of current partners, a new duration till availability is determined. This duration (e.g. the interval between t_5 to t_7 in Figure 6.1) may be shorter than the duration of an ongoing relationship (t_5 to the end of the end of the horizon in Figure 6.1), thus allowing for concurrent relationships (t_8 to t_9). Availability ends when a new relationship is formed. This happens either when someone is selected by a new partner (t_5 in Figure 6.1), or when a full 'period of availability' (t_1 to t_2) has elapsed and the

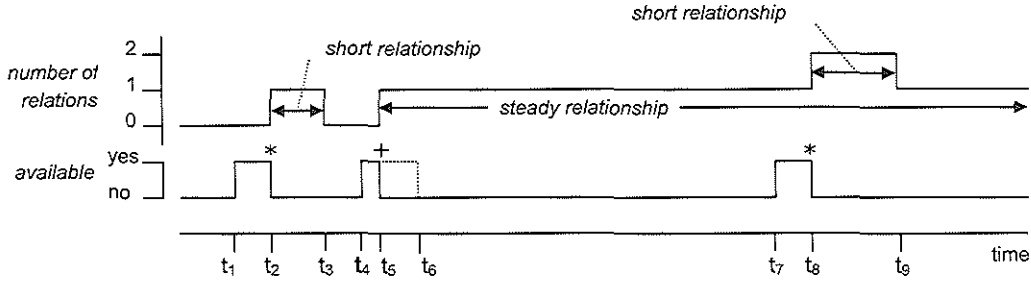

***Figure 6.1* Example of the sexual life history of a typical young male in Profile 3.** The male becomes first available at t_1 (sexual debut). As he is not found during his 'period of availability' between t_1 and t_2, he selects a partner himself (*) and starts a short relationship at t_2. This relationship ends at t_3. After a delay, he becomes available again at t_4 for a period until t_6. At t_5 he is however selected (+) by a partner for a steady relationship, which terminates his remaining time of availability (the remainder is indicated with a dashed line). During this relationship, the man becomes available again at t_7. After his period of availability, at t_8, he selects (*) a partner for a concurrent short relationship which ends at t_9.

person selects a partner from the pool of available people of the opposite sex in a preferred age group (at t_2).

The mechanisms of availability and partner selection do not reflect actual (psychological, behavioural or social) processes, but allow us to steer the representation of behaviour from both the male and the female population. The mathematical framework of the behavioural module and the input parameter operationalization for this chapter are described in detail below.

Sexual debut

Sexual debut is defined as the start of a first period of availability for sexual relationships. In this exercise, for both males and females, the *timepoint of first availability* is drawn from a uniform probability distribution with a minimum of 12 and a maximum of 20 years. This distribution ensures adequate fit of data from sub-Saharan Africa, including that virtually all persons eventually become sexually active [Feyisetan & Pebley 1989, Caraël *et al.* 1991, Bertrand *et al.* 1991, Hogsborg & Aaby 1992, Munguti *et al.* 1997, Konings *et al.* 1994].

Relationships: availability and partner selection

The *time till availability* for a new relationship is determined by an exponential probability function. At each change in an individual's number of current partners, a new time till availability is drawn, according to:

$$f(t) = \frac{1}{\mu} \cdot e^{-t/\mu} \qquad \text{Eq. (1)}$$

where μ is the mean time till availability for one specific individual at a given point in his simulated life:

$$\mu = \tau_{s,r} / (r_{s,a} \cdot p) \qquad \text{Eq. (2)}$$

with $\tau_{s,r}$ = the time interval that depends on the person's sex (s) and relationship status (r) (currently in a steady, short or no relationship); $r_{s,a}$ = sex (s) and age (a) group specific promiscuity factor; p = personal promiscuity level. The values for $\tau_{s,r}$ and $r_{s,a}$ are listed in Tables 6.2 and 6.3. Where applicable, a distinction is made between the 4 behavioural profiles used in this chapter.

The personal promiscuity level p, which reflects the heterogeneity in promiscuity within the population, is determined by a gamma distribution:

$$f(p) = \frac{1}{\beta^{\alpha} \cdot \Gamma(\alpha)} \cdot p^{\alpha-1} \cdot e^{-p/\beta} \qquad \text{Eq. (3)}$$

Table 6.2 **Values of the mean time till availability, depending on current relationship status, denoted $\tau_{s,r}$ in Eq. 2.**
∞ = infinite, i.e. these persons will not become available anymore, so that concurrency is not possible for persons in this relationship status. M = male; F = female.

relationship status	Profile 1		Profile 2		Profile 3		Profile 4	
	M	F	M	F	M	F	M	F
married	∞	∞	10	∞	5	5	∞	∞
only short relationship(s)	1	1	1	1	1	1	∞	∞
no relationship	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Table 6.3 **Sex and age specific promiscuity indices $r_{s,a}$.** M = male; F = female.

age (years)	Profile 1		Profile 2		Profile 3		Profile 4	
	M	F	M	F	M	F	M	F
< 25	0.001	0.001	4	4	4	4	20	20
25 - 29	0.5	1	1	1	1	1	1	1
30 - 89	1	1	1	1	1	1	1	1

The average personal promiscuity level p_m is 1.0, because p_m is used merely to specify heterogeneity in promiscuity in the population, and not its level. In this chapter, we chose the shape parameter α equal to 2.5 (β equals p_m/α).

While being available for new relationships, an individual can be selected by someone who has ended his/her period of availability. If the person has not been selected by the end of his period of availability, he himself then selects a partner from the pool of available people of the opposite sex. The *period of availability* (e.g. t_1 to t_2 in Figure 6.1) is given by an exponential probability distribution:

$$f(t) = \frac{1}{\kappa} \cdot e^{-t/\kappa} \qquad \text{Eq. (4)}$$

where the mean duration of availability κ is given by:

$$\kappa = \frac{\delta}{r_{s,a} \cdot p} \qquad \text{Eq. (5)}$$

with δ=0.5 yr in this chapter; see Table 6.3 for $r_{s,a}$ and Eq. 3 for p.

Relationships: partner preferences

Partnership formation is guided by age preference matrices (one for each sex, Table 6.4) specifying the probability to prefer a partner from a certain age class. In case no potential partner is available in the preferred age class, a partner is sought in another age class, by immediate renewed sampling among the remaining age classes for which the preference was larger than zero (e.g. in Table 6.4a, for males aged 15-19 years: the 3 female classes in the range 15-29 years, but not the older age classes). If no partner is available in any of the preferred age classes, the person remains available for another availability period, according to Eq. 4. This cycle repeats until the person has a new partner.

We used age preferences matrices estimated to realize reported age differences between sexual partners [Hogsborg & Aaby 1992, Konings *et al.* 1994, Munguti *et al.* 1997]. In case of imbalances between the availability of and demand for partners in certain age/sex classes (e.g. strong preferences for female partners in

Table 6.4 **Age preference matrices for selecting a new partner of a) males (male age groups in rows, female age groups in columns) and b) females (female age groups in rows, male age groups in columns).** Males prefer somewhat younger partners, e.g. 75% of males between 25 and 30 choose females under age 25, whereas females prefer somewhat older partners. If no value is indicated, partners in this age category are not allowed.

a.	female age (y)								
male age (y)	12-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-89
12-14	0.8	0.2	-	-	-	-	-	-	-
15-19	0.6	0.3	0.1	-	-	-	-	-	-
20-24	0.3	0.4	0.2	0.1	-	-	-	-	-
25-29	0.1	0.25	0.4	0.2	0.05	-	-	-	-
30-34	-	0.1	0.25	0.4	0.2	0.05	-	-	-
35-39	-	-	0.1	0.25	0.4	0.2	0.05	-	-
40-44	-	-	-	0.1	0.25	0.4	0.2	0.05	-
45-49	-	-	-	-	0.1	0.25	0.4	0.2	0.05
50-89	-	-	-	-	-	0.1	0.25	0.4	0.25
b.	male age (y)								
female age (y)	12-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-89
12-14	0.4	0.3	0.2	0.1	-	-	-	-	-
15-19	0.15	0.25	0.3	0.2	0.1	-	-	-	-
20-24	-	0.1	0.2	0.35	0.25	0.1	-	-	-
25-29	-	-	0.1	0.2	0.35	0.25	0.1	-	-
30-34	-	-	-	0.1	0.2	0.35	0.25	0.1	-
35-39	-	-	-	-	0.1	0.2	0.35	0.25	0.1
40-44	-	-	-	-	-	0.1	0.3	0.35	0.25
45-49	-	-	-	-	-	-	0.1	0.2	0.7
50-89	-	-	-	-	-	-	-	0.2	0.8

age group 15-19, but few females of this age available), however, the realized age mixing does not match the pre-specified age preferences. This is apparently the case in the simulations of this chapter: whereas the age preference matrices specify males selecting on average 5 years younger females (Table 6.4a) and females on average 5 years older males (Table 6.4b), realized age differences (Table 6.7) are less than those in the input age matrices, indicating a relative shortage of young females. Another reason for smaller age differences realized as compared to the input age matrices is that model output on realized age differences pertains to relationships ongoing at 1 time point (as do empirical data pertaining to *ongoing* relationships), rather than to all relationships ever formed. In such cross-sections, shorter relationships are underrepresented, whereas these relatively often include relationships between very old men and young women that end comparatively early due to the male's death. Apart from assortativeness by age, no other preferences apply; for example, promiscuous individuals have no explicit preference for other promiscuous partners.

Relationships: steady or short

The probability that a new relationship is steady depends on whether or not at least one of the partners is already engaged in a steady relationship, and on the age of the male partner. Table 6.5 lists these probabilities. At the start of a new steady relationship, its duration is drawn from an exponential distribution with a mean of 100 years. This quantification was chosen to make most steady relationships lifelong while allowing some divorces to occur (e.g. 18% of steady relationships last less than 20 years). The duration of short relationships is drawn from a gamma distribution with a mean of 0.2 years and shape parameter 0.5.

In the model, the frequency of intercourse in relationships varies with the age of the male partner, but it is identical for steady and short relationships, and independent of the number of current relationships. In this chapter, the frequency

Table 6.5 **Probability that a new relationship is steady, by age of the male partner and marital status of both partners.**

age male (years)	Profile 1		Profile 2		Profile 3		Profile 4	
	both unmarried	one/both married	both unmarried	one/both married	both unmarried	one/both married	both unmarried	one/both married
<19	1	0	0	0	0	0	0	0
20 – 24	1	0	0.5	0	0.5	0	0.5	0
25 – 29	1	0	0.8	0	0.8	0	0.8	0
30 – 90	1	0	1.0	0.1	1.0	0.1	1.0	0

was 1.5 times per week per relationship [Bertrand *et al.* 1991, Hogsborg & Aaby 1992, Borgdorff 1994, Konings *et al.* 1994].

Prostitution

Males' frequency of prostitute visits is determined by defining a number of frequency classes (in this chapter 0, 1, and 6 visits per year), and subsequently specifying the proportions of the married and unmarried male population (up to a maximum age, in this chapter 60 years) in each class (Table 6.6). A personal prostitute visiting inclination, assigned to each male at birth, determines which individual males are assigned to which frequency classes, for both married and unmarried (part of) life. The assignment is made such that no males move to a higher frequency class at marriage, or to a lower frequency class than before marriage at divorce. For Profile 1, this means that all single males visiting prostitutes once a year (i.e. 50%) quit this practice upon marriage, while of the 50% with 6 visits per year, 10% stop visiting prostitutes, 20% reduce the frequency to once a year, and 20% continue with 6 visits per year.

At each prostitute visit as well as at sexual debut, the time till a male's next prostitute visit is determined according to the exponential distribution:

$$f(t) = \frac{1}{\phi} \cdot e^{-t/\phi} \qquad \text{Eq. (6)}$$

where $1/\varphi$ is the personal frequency of prostitute visiting.

Prostitutes are recruited according to the male demand from sexually active females within a user-specified age range. In this study the minimum age of prostitutes ranged from 15-25 years, the maximum age was 30 years, the minimum career duration was 1 year. We chose an average number of visits per week per prostitute of 10, which - in the absence of adequate data of wholly representative samples - we believe is a reasonable order of magnitude [Kreiss *et al.* 1986,

Table 6.6 **Distribution (in %) of males over different frequency classes of prostitute visiting, according to marital status.**

Number of prostitute visits per year	Profile 1		Profile 2		Profile 3		Profile 4	
	unmarried	married	unmarried	married	unmarried	married	unmarried	married
0	0	60	60	60	100	100	60	100
1	50	20	20	20	-	-	20	-
6	50	20	20	20	-	-	20	-

Simonsen *et al.* 1990,Asamoah-Adu *et al.* 1994]. Client contacts are divided over the pool of prostitutes in time order.The number of prostitutes is checked and - if necessary - adapted every year to match the user-specified frequency number of client contacts per prostitute as closely as possible, given the number of prostitute visits by males. If the number of prostitutes is too small, additional prostitutes are recruited. If the number of prostitutes is too large, a randomly selected prostitute terminates her career before the indicated date. In addition, every time a woman in the appropriate starting age range becomes widowed, the model also checks whether there is a shortage of prostitutes, and if so, the woman is recruited.

Condom use

In this study, 5% of the males use condoms consistently in all their non-marital contacts, i.e. prostitute visits and short relationships [Lindan *et al.* 1992, Mills *et al.* 1997, Ng'weshemi *et al.* 1996]. Also, 20% of the prostitutes use condoms during all client contacts [Hanenberg *et al.* 1994, Ng'weshemi *et al.* 1996]. As a result, condoms are used in 24% of all prostitution contacts (100%-(100%-20%)*(100%-5%)).A user-specified proportion (95% in this chapter) of contacts in which a condom is used is adequately protected from HIV and STD transmission, the remainder representing failure due to breakage or incorrect use.

Behavioural profiles

In the construction of the behavioural profiles used in this chapter (Table 6.1), the values and distribution functions of the following parameters were identical in all profiles:

- age of sexual debut (see above);
- durations of relationships (see above);
- age preference matrices for relationship formation (Table 6.4);
- prostitute age range and duration of career (see above);
- prostitute frequency of client contacts (see above),

whereas the following parameters effectuated the differences between the profiles:

- probability that a new relationship is steady, depending on the marital status of both partners and the age of the male (Table 6.5);
- duration till availability (Table 6.2 and Eq. 1 and 2) and period of availability (Table 6.3 and Eq. 4 and 5), depending on age, sex and relationship status;
- prostitute visiting frequency of males, depending on their marital status (Table 6.6 and Eq. 6).

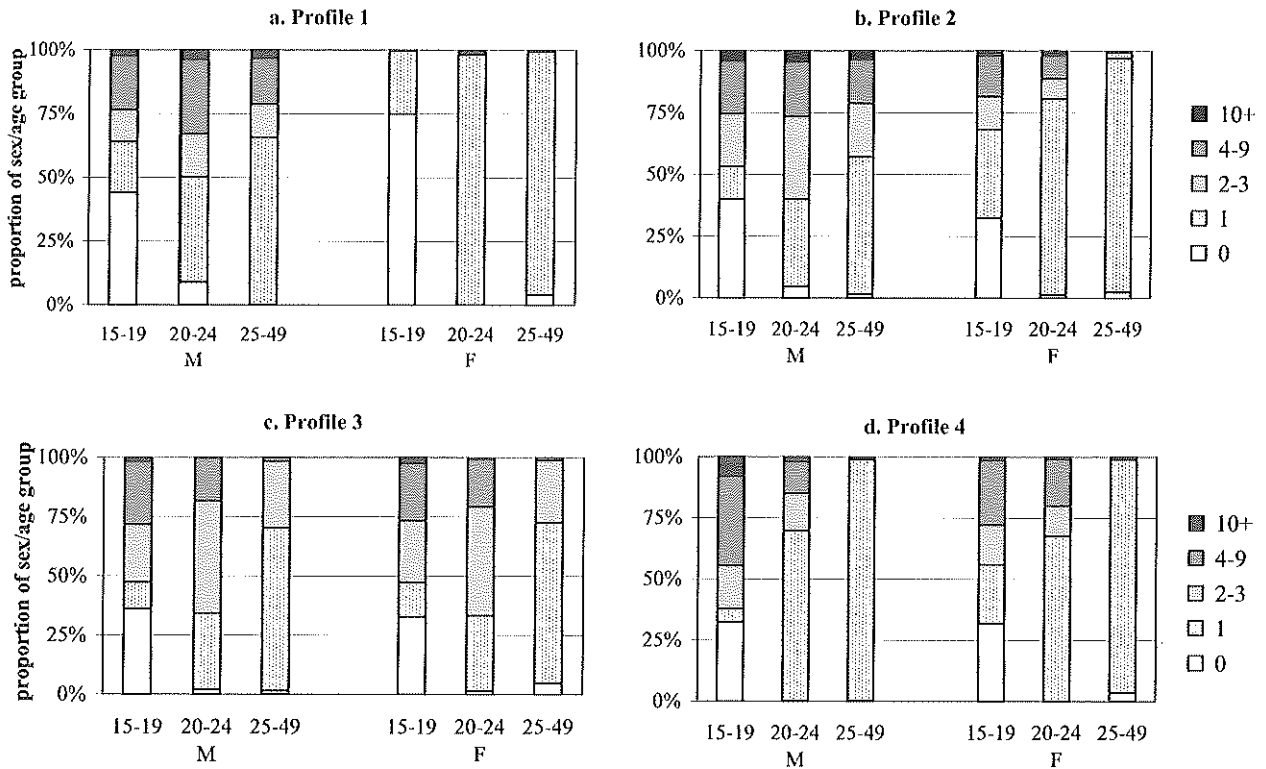

***Figure 6.2 STDSIM* projections of proportions (%) of the general adult population (15-49 years) having had 0, 1, 2-3, 4-9 or 10 or more partners during one year, by sex and age group, for each profile.** 'Partner' refers to either a relationship or a prostitution contact. Results are for the situation 2 years before introduction of HIV in the population, and are averaged over 150 simulated populations of on average 20,000. M = male; F = female.

For the latter set of parameters, we chose extreme values so as to create contrasts between the profiles. These parameter values - in contrast to the former - do therefore not necessarily correspond to actual situations.

The resulting differences in partnership dynamics between the profiles can be grasped from the respective age and sex distributions in the number of partners during 1 year, an outcome also commonly used in behavioural surveys. In the model output, each prostitute contact counts as a new partner for both the client and the prostitute. Figure 6.2 shows the number of partners during 1 year predicted for each profile, for a timepoint just before introduction of HIV in the population. In all profiles, the epidemic will ultimately change the level and distribution of risk behaviour, due to selective HIV-related deaths among persons at high risk. Table 6.7 gives the corresponding proportions in current steady and short relationships, proportions with multiple partners over 3 months and 5 years, realized age differences between spouses, and proportion of prostitutes for each profile.

In Profile 1 (prostitution), numbers of partners are strongly asymmetric between males and females. With the exception of prostitutes, women have sexual intercourse only within steady relationships. This is reflected in a majority of females having 0 or 1 recent partner. All single males engage in prostitution, resulting in high numbers of recent partners for males aged 20-24 years, who have all initiated sexual activity but are mostly not yet in a steady relationship. Since 40% of married males also visit prostitutes, the proportion with more than 1 recent partner remains high for age group 25-49 years. In Profile 2 (prostitution + concurrent relationships), both men and women who are not in a steady relationship engage in - possibly overlapping - short relationships. Concurrency in relationships and high rates of partner change imply large numbers of partners for the young. At older ages, females end up in monogamous steady relationships, as evidenced by a majority having only 1 recent partner. In contrast, married males continue to engage in short relationships with single - mostly younger - females, and 40% visit prostitutes; this results in continued high numbers of partners. In Profile 3 (concurrent relationships), behaviour is relatively symmetric between the sexes: both women and men have multiple, concurrent relationships, also after marriage. Full symmetry in numbers of partners is not accomplished, because in relationships women are usually younger than men (Tables 6.4 and 6.7). Despite the absence of prostitution, the number of persons with more than 1 partner in the last year is high, due to overlap in relationships. In Profile 4 (serial monogamy), all persons behave monogamously, apart from - mainly young - males who may visit prostitutes while unmarried, but engaged in a short relationship. Among adolescents, high promiscuity causes new relationships to be initiated almost immediately after termination of previous ones. Consequently, the number of recent partners is high for the youngest age group (15-19 years). In comparison to Profile 3, numbers of partners in this age group are low for females, because Profile 4 does not allow concurrent relationships, but high for

***Table 6.7* Basic behavioural model output for each profile (means over 150 simulated populations).** Results are for the situation 2 years before introduction of HIV. In view of the average durations of STD episodes and of the highly infectious primary HIV stage (see Section 6.3), the proportion with ≥2 partners during the last 3 months is an approximation of the proportion with concurrent partnerships including prostitute contacts [Ghani *et al.* 1997].

Outcome	age group (years)	Profile 1		Profile 2		Profile 3		Profile 4	
		M	F	M	F	M	F	M	F
Proportion (%) currently in steady relationship	15-19	17	25	0	40	0	33	0	27
	20-24	52	61	77	83	77	79	88	74
	25-49	98	95	97	93	96	91	99	94
	15-49	**76**	**76**	**76**	**82**	**75**	**78**	**79**	**78**
Proportion (%) currently in short relationship	15-19	n.a.[1]		21	16	32	26	48	34
	20-24	n.a.[1]		10	8	21	22	9	21
	25-49	n.a.[1]		2	1	15	12	0	0
	15-49	**n.a.[1]**		**6**	**5**	**12**	**11**	**10**	**10**
Proportion (%) with ≥2 partner (incl. prostitute contacts) in past 3 months	15-19	15	0.2	22	16	26	30	37	23
	20-24	22	1.1	30	8	30	34	9	14
	25-49	20	0.2	27	0.7	18	16	0.2	0.1
	15-49	**20**	**0.3**	**26**	**5**	**21**	**22**	**9**	**7**
Proportion (%) with ≥2 partner (incl. prostitute contacts) in past 5 years	15-19	52	0.3	57	58	61	64	65	62
	20-24	84	1.6	95	59	98	97	99	73
	25-49	49	4.6	67	13	69	67	9	11
	15-49	**55**	**3**	**71**	**29**	**72**	**72**	**34**	**31**
Average age difference with steady partner (own age – age partner, in years)	15-19	-1.6	-3.9	n.a.[1]	-6.0	n.a.[1]	-5.3	n.a.[1]	-4.8
	20-24	-0.6	-2.7	2.2	-4.4	1.8	-3.8	0.5	-2.7
	25-49	1.0	-1.4	2.8	-3.2	2.1	-2.8	1.0	-1.3
	15-49	**0.7**	**-1.6**	**2.7**	**-3.6**	**2.1**	**-3.0**	**0.9**	**-1.7**
Proportion (%) of adult female population active as a prostitute			0.36		0.28		n.a.		0.05

[1] No partnerships possible in this category. M = male, F = female.

males, due to prostitution in Profile 4. Since only unmarried males visit prostitutes, persons of older age, who are often married, mostly have only one recent partner.

Although these theoretical profiles of sexual behaviour cannot be equalled to specific countries, the qualitative resemblances to the geographical regions mentioned in the Introduction (Table 6.1) are parallelled by similarities in numbers and age/sex patterns in having non-regular partners, as can be seen by comparison with general population behavioural and health surveys [Caraël *et al.* 1991, Cleland *et al.* 1992, WHO/UNAIDS 1998].

Prevention strategies

We considered the effects on the spread of HIV of the following three ways of reducing numbers of partners:

1. a 2-year delay in the age of sexual debut. This intervention was implemented as a shift of the whole probability distribution function, i.e. a shift of the minimum from 12 to 14, the mean from 16 to 18, and the maximum from 20 to 22 years;
2. a halving of relationship formation rates. This intervention was implemented as a 50% reduction in the average personal promiscuity level, which doubles the mean duration till availability and the mean period of availability till selecting a partner. Note that reducing relationship formation rates was not compensated by prolongation of the duration of ongoing relationships;
3. a 50% reduction in prostitution, implemented as a halving of the proportion of males in the frequency categories of 1 and 6 prostitute visits per year (Table 6.6).

These magnitudes of behaviour change were based on risk reductions observed in sub-Saharan African and South-East Asian countries: 1) [Asiimwe-Okiror *et al.* 1997], 2) [Ng'weshemi *et al.* 1996, Konde-Lule *et al.* 1997] and 3) [Ng'weshemi *et al.* 1996, Jackson *et al.* 1997c, Mills *et al.* 1997, Asiimwe-Okiror *et al.* 1997].

6.5 The epidemiology of HIV in the four profiles

Figure 6.3 shows the prevalence of HIV in the general adult population resulting from uncontrolled spread of the virus over time, as a mean over 150 simulation runs for each profile. Figure 6.4 gives the relationship between risk behaviour, indicated as individuals' numbers of partners over the past year, and HIV prevalence for the years 3, 13 and 33 after introduction of the virus into the population.

In Profile 1, the epidemic evolves rapidly, starting with prostitutes and males visiting prostitutes (Figures 6.3 and 6.4a,b). Only after some time, prevalence in females in the general population (most of whom have 1 partner) starts to increase. The more rapid rise of prevalence among females with 2 or 3 partners represents monogamous women widowed and remarried after their husband's death from HIV. Around the 10th year of the epidemic, population prevalence slightly falls again and stabilizes at about 10%. This fall is due to selective HIV mortality in the high risk group of males visiting prostitutes. While selective mortality reduces the level of prostitution in the surviving population, it does not change the prevalence *within* each risk group because HIV status is mainly determined by persons' own (male) or husbands (female) behaviour, and hardly by the extent of prostitution in the rest of the population. Around year 20, an equilibrium is reached: the inflow of new HIV cases counterbalances the outflow of infected persons by HIV-related death. Comparison of prevalences among males and females with 4 or more partners (Figure 6.4a+b) shows that being a prostitute is more risky than being a prostitute visitor. This results from the respective frequencies of contacts - 1 or 6 times per year for male clients, 10 times per week for prostitutes - and the higher efficiency of transmission from male to female, as compared to female to male. The pace of HIV spread in Profile 2 and 1 is comparable for the first few years. In contrast to Profile 1, however, HIV prevalence

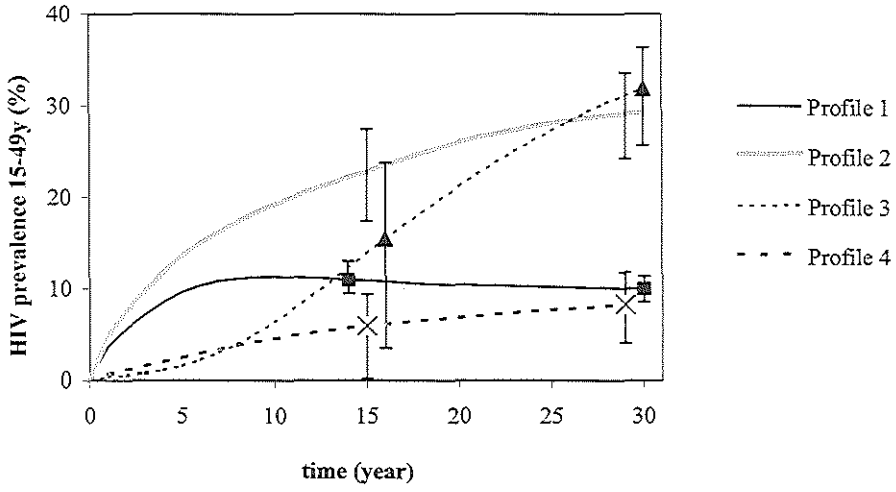

***Figure 6.3* Projections of HIV prevalence (average over 150 runs) in the adult population (15-49y) for the four behavioural profiles.** Time is indicated in years since the introduction of HIV in the population. The vertical bars indicate 10th and 90th percentiles over 150 runs for years 15 and 30; these have been slightly shifted horizontally to prevent overlap.

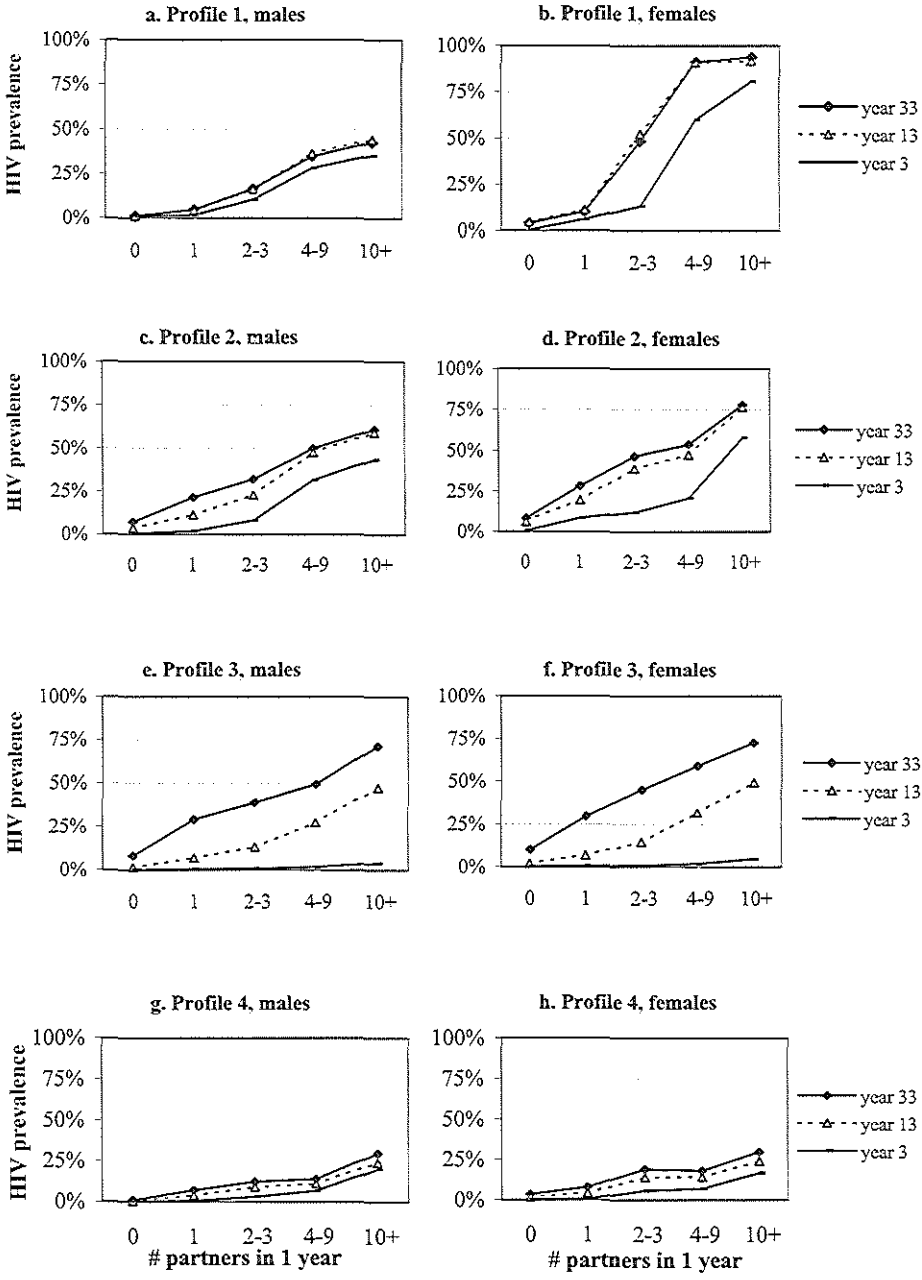

***Figure 6.4* Predicted HIV prevalence (%) stratified by numbers of partners over the last year in the adult population (15-49y), for each profile in different years in the epidemic.** Time is indicated in years since the introduction of HIV in the population. M = male; F = female. The size of each partner group can be seen in Figure 6.2.

in Profile 2 continues to rise to a much higher level of 30% in year 30 (Figure 6.3). In the beginning of the epidemic (before year 13 in Fig. 6.4c), most infections result from prostitution contacts, as can be seen in the increase of HIV prevalence for males having 4 or more partners (Fig. 6.4c), and females having 10 or more recent partners (Figure 6.4d). Between year 13 and 33 (Fig. 6.4c,d), the virus invades the general population through the partners of prostitute clients and short relationships, and the slope of the curve of HIV prevalence by numbers of partners flattens. In Profile 3, the epidemic starts at the lowest pace of all profiles, since there is no high-risk group of prostitutes and their clients to fuel the epidemic. However, by year 10 prevalence is growing faster than in any other profile, and is still increasing when it reaches 32% in year 33 (Figure 6.3). This continued rise is due to the occurrence of concurrent relationships in all age/sex groups in the general population. By year 33, HIV prevalence exceeds 25% even for individuals with only one partner per year (Figure 6.4e,f). The latter group consists of those who got infected through risk behaviour at younger age, and those put at risk by their partners. In Profile 4, the HIV epidemic starts slowly, but the prevalence continues to rise until after year 30 (Figure 6.3). The absence of overlap in relationships in Profile 4 precludes an eventually wide spread of the epidemic, prevalence reaching only 8% in year 30.

Whereas overall HIV prevalence at the end of the evaluation horizon is comparable between Profiles 1 and 4, the link between HIV prevalence and an individual's recent number of partners is much stronger in Profile 1 than in Profile 4 (Figure 6.4a,b and 4g,h: year 33). This reflects the specification that risk status - the own or the husband's inclination to visit prostitutes - is fairly constant throughout life in Profile 1 (apart from changes in marital status), whereas it changes with age in Profile 4 - most youth engage in risk behaviour, while few older persons do. In other words, in Profile 1 the number of partners during the last year is a better indicator of the lifetime risk of infection than in Profile 4.

Comparing Profiles 2 and 3, the association between HIV prevalence by number of partners is similar for year 33 - by which time absolute prevalence levels in the general population are also similar. For earlier years however, the association is stronger in Profile 2, where the prevalence reaches its maximum level in the groups with 4 or more partners already by year 13 (Fig. 6.4c,d).

In profile 3, in contrast, HIV prevalence continues to rise further between year 13 and 33 in all groups including those with 4 or more partners (Fig. 6.4e,f). The rapidity of saturation in high risk groups in Profile 2, as compared to Profile 3, thus corresponds with the faster spread of HIV into the general population in Profile 2.

Summarizing, the more concentrated risk behaviour in part of the population (Profiles 1 and 2), the faster the initial spread of HIV, since an increase in the number of infected persons in the high-risk group immediately increases the risk of exposure for other high-risk group members. If the rest of the population does

not engage in risk behaviour (Profile 1), saturation of infection and selective mortality in the high-risk groups later in the epidemic cause HIV prevalence to stabilize or even decline after an initial outbreak. If risk behaviour is more dispersed over the population (Profile 3), there is no initial fuel in the form of a high-risk group, but the number of people who are at some risk due to their behaviour is eventually much larger, so that the infection spreads slower but finally reaches a much higher prevalence level. These results are consistent with general conclusions drawn on the basis of earlier models [Gupta *et al.* 1989, Garnett & Anderson 1993a, 1996a]. The comparison between profiles makes clear that an initially steep rise in prevalence is not necessarily indicative of the most devastating epidemic. Countries with still low prevalence levels should therefore remain alert, rather than optimistically hope the epidemic will pass by their country. The marked differences in time courses of (uncontrolled) epidemics also illustrate that caution is needed when evaluating the impact of interventions by simply monitoring prevalence trends.

Comparing the projected HIV prevalences to the real-world settings they are intended to represent (Table 6.1), the effective condom programme implemented in an early phase of the epidemic in Thailand [Hanenberg *et al.* 1994, Nelson *et al.* 1996] prohibits a comparison between Profile 1 and Thailands hypothetical 'uncontrolled' HIV epidemic. Profiles 2 and 3 reasonably project the prevalences attained in Uganda and other sub-Saharan African countries in the early years of - but before major intervention in - the epidemic [Carswell 1987, Serwadda *et al.* 1992].

HIV spread varied considerably between individual simulation runs (see confidence intervals in Figure 6.3). Outliers occurred on the lower side of the distribution - no epidemic at all, or only after a delay - and reflect a large variability in the onset of spread of the virus after its introduction in the population. For simulating the impact of interventions in ongoing HIV epidemics, we therefore excluded runs with an HIV prevalence in the adult population under 0.5% in the starting year of interventions from the analyses below. This criterion resulted in exclusion of 1 out of 150 runs for Profiles 1 and 3, and 24 runs for Profile 4.

6.6 IMPACT OF BEHAVIOURAL INTERVENTIONS

Effects on numbers of partners

To understand how the simulated behaviour changes affect HIV spread, we first show their effects on recent numbers of partners of adults, over the 3rd year after start of the intervention (Figure 6.5).

In Profile 1, a delay of sexual debut or halving of relationship formation rates has little effect on the number of partners for males (Fig. 6.5a). The reason is that

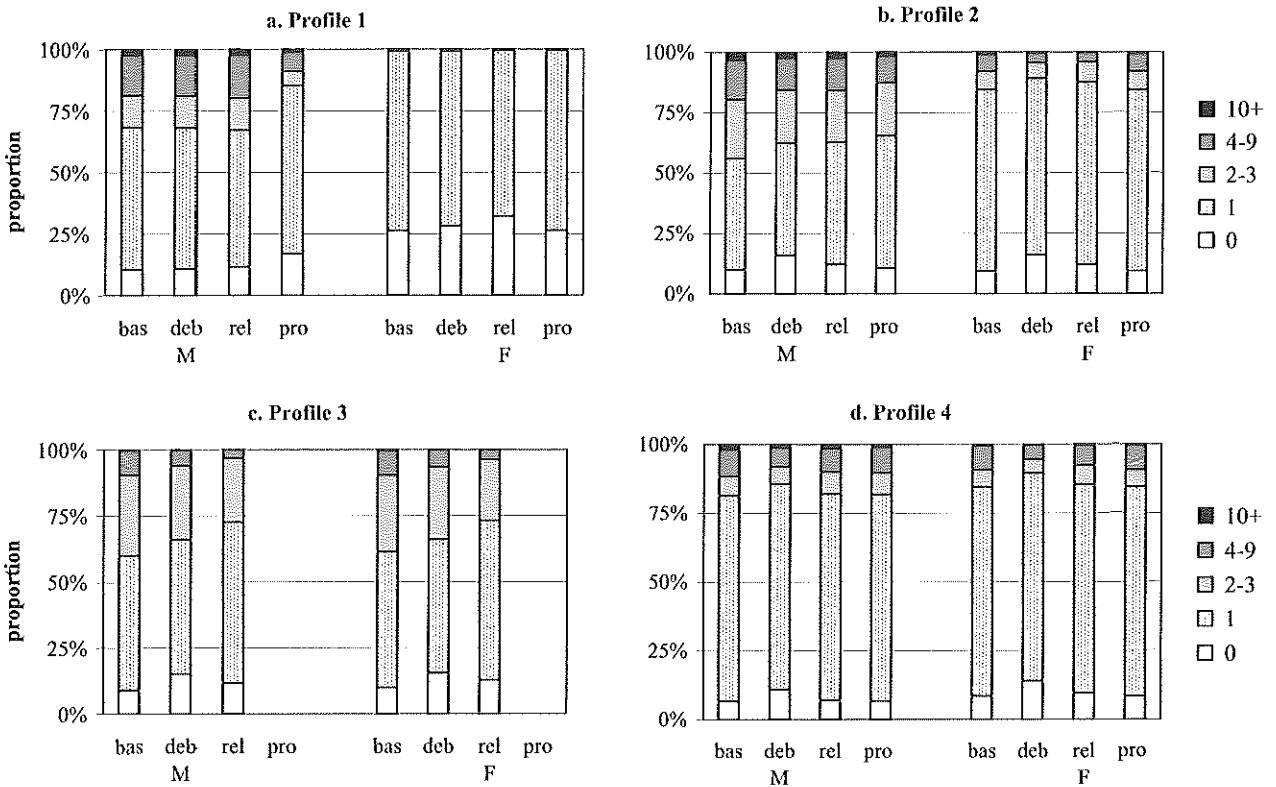

Figure 6.5 **Predicted effect of behavioural interventions on the numbers of sexual partners during the last year of adults males and females (15-49y) in the model, for the 3rd year after start of the interventions (year 18).** bas = baseline; deb = delay of sexual debut; rel = reduction in relationship formation rates; pro = reduction of prostitution; M = male; F = female.

in Profile 1 the number of partners is almost exlusively determined by prostitute visits, which occur throughout life at a constant frequency (apart from changes associated with marital status). For females, both interventions slightly increase the proportion single, especially in the youngest age group (15-24 years), reflecting a delay of marriage. This effect is largest for reducing relationship formation rates. In contrast to the former interventions, halving the proportion of males visiting prostitutes markedly reduces the number of partners of males, in all age groups. This intervention does, however, not affect the number of partners of females, except for halving the number of prostitutes. In Profile 2, delay of sexual debut for both sexes increases the proportion singles while decreasing the proportion with multiple recent partners (Fig. 6.5b). Whereas the change is moderate on an aggregate level, it is considerable in the younger age groups (15-24 years). Halving relationship formation rates decreases the proportion with multiple partners as well, but in all age groups equally, and this is compensated by an increase in the proportion with one, rather than zero, recent partners. A reduction in prostitution increases the proportion of males with 1 partner at the expense of the proportion with multiple partners. As in Profile 1, it has little effect on the number of partners of females. In Profile 3, a delay of sexual debut reduces numbers of partners markedly, but less than halving relationship formation rates (Fig. 6.5c), because concurrent relationships can be started at all ages. As in Profile 2, postponing sexual debut increases the proportion with zero partners, whereas reducing relationship formation rates mainly increases the proportion with 1 partner. These shifts are similar for males and females, as can be expected from the symmetry in numbers of partners in the situation without intervention. In Profile 4, delaying sexual debut reduces the proportion with multiple partners considerably for both sexes, and even more than a reduction in relationship formation rates or in prostitution (Fig. 6.5d). This follows from the restriction of risky to unmarried youth, and the fact that both types of risk behaviour (short serial relationships and prostitution) are reduced by postponement of sexual debut.

In all profiles, the shortening of the premarital period with high partner change rates by a delay in sexual debut is partially - but not fully - compensated by a consequent delay in first marriage (not shown). In Profiles 1, 2 and 4, for males, decreasing prostitution causes the largest reduction in numbers of partners, whereas for females, larger reductions result from decrease in relationship formation rates or delay of sexual debut.

Effects on HIV spread

The projected impact of the interventions on HIV prevalence in the different profiles is depicted in Figure 6.6. Figure 6.7 shows prevalences of HIV by number of partners in the past year for the different interventions, in year 33 of the simu-

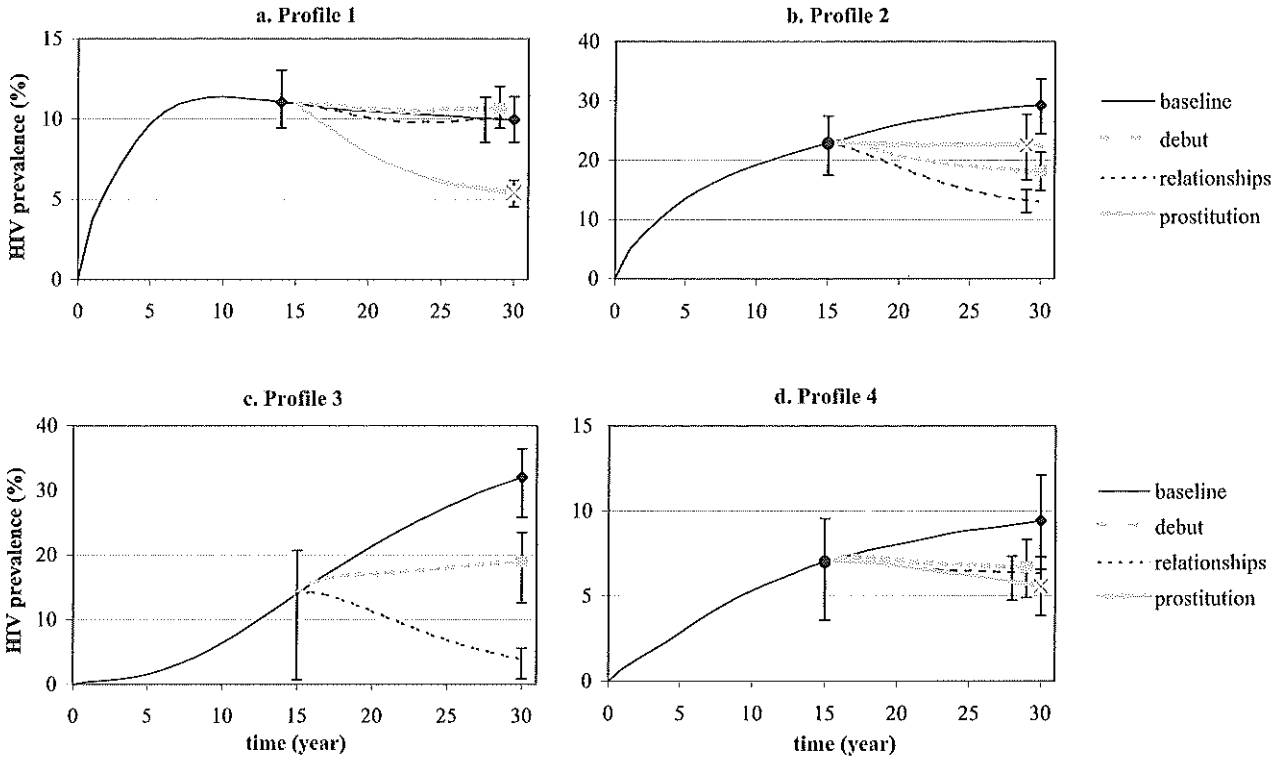

***Figure 6.6* Projected impact of behaviour interventions on HIV prevalence (average, 10th and 90th percentiles) in the general adult population (15-49y) for each profile.** Interventions start in year 15. Confidence intervals around intervention projections for year 30 have been shifted horizontally to prevent overlap.

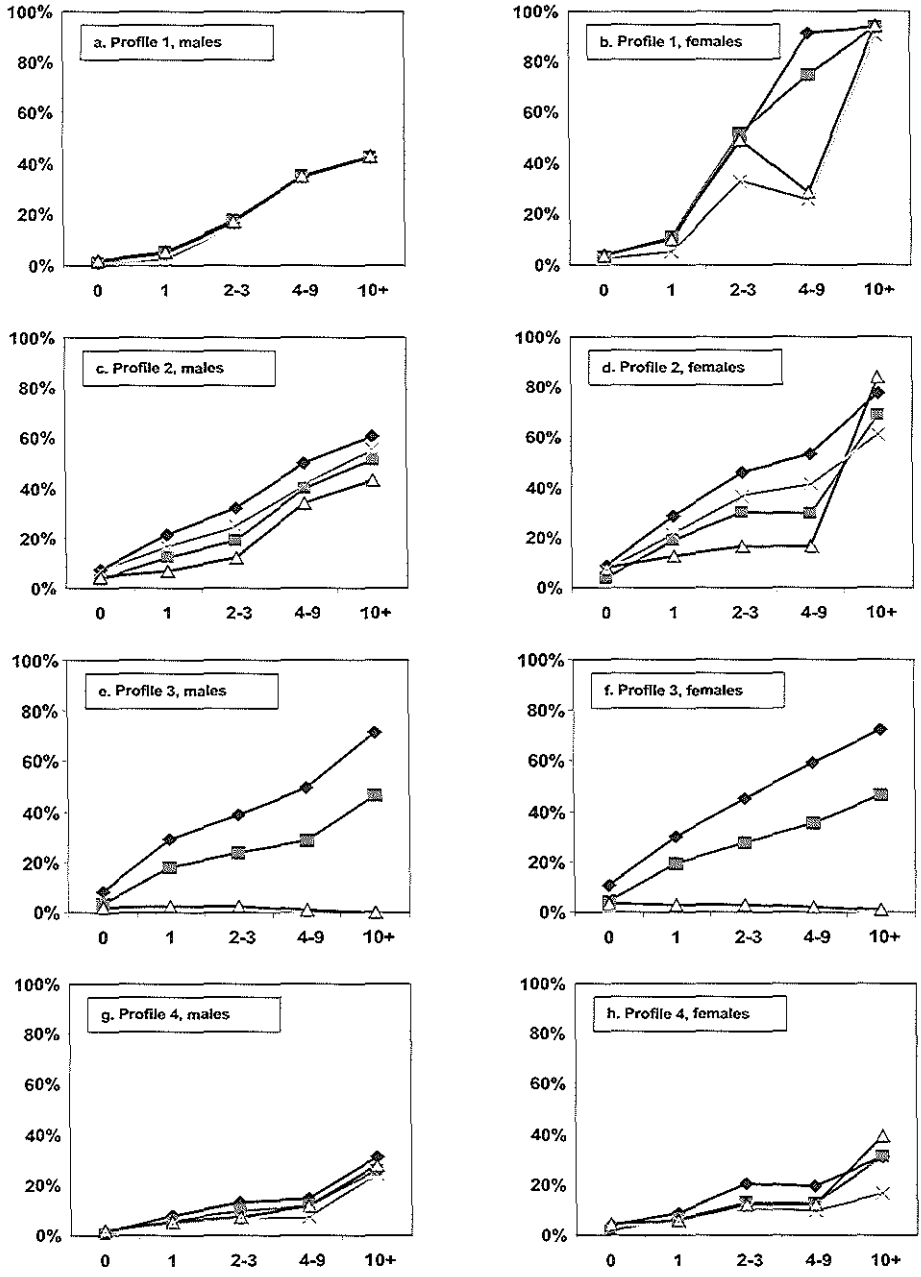

***Figure 6.7* Predicted HIV prevalence (%) stratified by numbers of partners over the past year in the adult population (15-49y), 33 years after the introduction of HIV (i.e. 18 years after start of the simulated interventions).** Symbol key: ◆ no intervention, ▩ delay of sexual debut, △ reduction in partnership formation rate, ✕ reduced prostitution. The size of each partner group can be seen in Figure 6.5.

lated intervention.

In Profile 1, halving the number of males visiting prostitutes markedly reduces HIV prevalence in the general population (Figure 6.6a). In spite of the reduction in the number of males with multiple partners (Fig. 6.5a), the intervention hardly reduces in prevalence *within* each male risk group (Fig. 6.7a). In monogamous women (those with 1 partner in Fig. 6.7b), HIV prevalence is somewhat reduced indirectly, thanks to husbands quitting prostitution. A similar lowering of HIV prevalence is seen for females with 2-9 partners, which is however a very small group (Fig. 6.5a). Since this dynamic effect is limited to monogamous women, the magnitude of impact on HIV in the general population (a halving of the equilibrium prevalence from 10% to 5%) is proportional to the halving in the number of males visiting prostitutes. The marginal effect of the other two interventions is in line with their negligible effects on numbers of partners (Figure 6.5a,b).

In contrast to Profile 1, all interventions in Profile 2 are effective in reducing HIV. Halving relationship formation rates, by decreasing numbers of partners in both sexes, has a much larger impact than reducing prostitution, which predominantly reduces numbers of partners of males. Notably, if the interventions in Profile 2 were performed earlier in the epidemic, e.g. in year 3, reducing prostitution would initially be the most effective intervention (not shown). Delay of sexual debut has an intermediate effect. In contrast to Profile 1, effective interventions reduce HIV not only in the total population, but also to some extent within each partner group (Fig. 6.7c+d), indicating an additional effect on top of the decrease in the number of individuals with multiple partners. This explains why halving relationship formation rates reduces the equilibrium prevalence more than half (from over 30% to under 15%) even though this intervention does not reduce prostitution.

In Profile 3, halving relationship formation rates brings HIV prevalence down to a very low level, the equilibrium prevalence falling from over 33% to below 5%. This disproportionally large effect results from an - indirect - reduction in HIV prevalence *within* each risk group, on top of the reduction in the *number* of persons with multiple partners (Fig. 6.7e+f). Counterintuitively, at the end of this intervention, HIV prevalence is lowest in those with multiple partners. This group consists of young persons who have not yet become infected, while those with fewer partners are older and have become infected by risk behaviour at a younger age. The total effect of halving relationship formation rates is much larger in Profile 3 than in Profile 2, because in Profile 3 concurrent relationships are the only type of risk behaviour, in contrast to in Profile 2. Delay of sexual debut decreases HIV less than halving relationship formation rates, in agreement with their respective effect on numbers of partners. Relative to the small age band reached with this intervention - only the first 2 years out of a prolonged period of continued promiscuity (see Table 6.3 and Fig. 6.2) - however, the magnitude of effect on HIV prevalence is still considerable. As demonstrated by reductions in prevalence within each partner group (Fig. 6.7e+f), this disproportional

impact is also due to additional indirect effects.

In Profile 4, reducing prostitution does slightly better than the other interventions, even though postponement of sexual debut reduces the numbers of partners most (Fig. 6.5d). Apparently, avoidance of specifically a prostitute contact reduces HIV spread more than avoidance of an average partnership among youths, which can be either a prostitution contact or a serial relationship. This is understandable since for relationships to become risky, one partner must first have become infected; for monogamous adolescents not visiting prostitutes, this may take several years. In line with this, limiting prostitution reduces HIV prevalence within each partner group more than the other two interventions (Fig. 6.7g+h). In other words, limiting prostitution has larger indirect effects in Profile 4 than postponing sexual debut or halving relationship formation rates.

6.7 Discussion

Microsimulation: the level of individuals

The results of this study were obtained by using the microsimulation technique. The advantages of the microsimulation approach in infectious disease modelling are: *(i) intuitive representation:* microsimulation describes characteristics and events at the level of the individual, as they may be considered to be in real-world situations - e.g. individuals' present status and history of sexual partnerships and STD infections, or starting to use condoms with a certain partner; *(ii) dynamic interactions and network effects:* changes at the macro-level automatically follow from processes defined at the individual level. For example, selective HIV attributable mortality of high risk groups automatically results from simulation of underlying risk behaviour of individuals and their interactions; *(iii) applicability to specific settings:* it is easy to define and simulate specific settings with respect to demography, behaviour, epidemiology and the type of interventions being considered or executed, for instance, a rise in condom use from 20% to 60% of casual contacts for young males in Nairobi; *(iv) flexibility in output:* it is easy to produce the type of output matching available data, or to mimic the outcomes of epidemiological studies including their possible biases, e.g. the odds ratio for HIV infection of having had an STD during the last year as an approximation of the STD cofactor effect. Our ultimate goal with *STDSIM* is its application in the evaluation of HIV and STD control options in various developing settings. Since these differ in behaviour, epidemiology etc., and in the type of data available, the above mentioned advantages of microsimulation are of critical importance.

A problem in applying microsimulation models to the spread of infectious disease is to fit parameter values to available data. The representation of especially

sexual behaviour as individual events requires parameters which do no necessarily have a straightforward relation to data. Even with sophisticated types of data as collected in local network studies [Morris 1997], input parameters must often be determined by iterative fitting of model *output* against these data under varying *input* assumptions. An example in *STDSIM* are the mean durations till availability and of availability for new relationships, which we fit by comparing current and recent numbers of partners to the data from behavioural surveys. Adequate fit of model outcomes to data does not guarantee the uniqueness of the chosen set of parameter values. Especially if few data are available, as is often the case, different combinations of parameter values may each be compatible with the same set of data. Lacking comprehensive data sets in current application areas of the model, this difficulty is partly solved by using expert opinion, in addition to data from different sources, to fix part of the parameters, improving the chances to find a unique fit of the remaining ones [Van der Ploeg *et al.* 1998, Korenromp *et al.* 2000d].

Microsimulation: stochasticity

A vital characteristic of *STDSIM* is stochasticity in outcomes. In the present simulations, stochastic variation over runs in HIV prevalence over time was considerable, largely due to outlier runs in which the epidemic emerged much later or not at all. This feature, which has been observed in other microsimulation models [Morris & Kretzschmar 1995], could reflect true stochasticity in disease spread for populations of a given size, and extent of isolation/mobility. Large differences in the timing of HIV emergence and spread have been observed between regions which lie isolated from one another, but have similar risk patterns [Buvé *et al.* 1995]. Handling of this variability in model predictions can be difficult. Clearly, it makes no sense to calculate the impact of interventions on non-existing epidemics; therefore, in this theoretical exercise, we have excluded zero-runs from such analyses. Less evident is whether - and to what extent - outlier runs should be excluded when trying to fit the model to a real-world epidemic of known magnitude at a certain timepoint, which probably has resulted from many (sub-)local, differently timed epidemics.

Context dependency of intervention impact

Our projections demonstrated that the impact of different forms of partnership reduction on HIV spread depends to a large extent on the type(s) and extent of prevailing risk behaviour. Obviously, the impact of a delay of sexual debut is considerable in settings where risk behaviour is concentrated in youth (Profiles 2, 3, and especially 4). The extent of this effect, however, depends critically on

the assumption that a delay of sexual debut is not accompanied by a parallel shift in the age window of high-risk behaviour (e.g. by postponement of marriage). Comparison of Profiles 2 and 3 with Profiles 1 and 4 showed that lowering the rate of partner change is more effective in reducing risk in case of concurrent relationships as compared to monogamous populations. This supports earlier suggestions [Morris & Kretzschmar 1997] that messages promoting one partner at a time may be as important as messages promoting fewer partners. The context dependence of the impact of interventions also implies that programmes proven highly effective in some settings, e.g. 100% condom use in prostitution in Thailand, are not necessarily equally effective in other settings.

Dynamics of intervention effects

The simulations showed disproportionately large effects on HIV spread of partnership reductions in some profiles. In Profile 3, halving relationship formation rates reduced the average number of partners during one year from 1.7 to 1.3, but in the longer term almost eradicated HIV. This dynamic effect, which was illustrated with reductions of prevalence within groups of a certain number of partners (Fig. 7e+f), results from two mechanisms. First, a reduction in numbers of partners reduces the risk of HIV acquisition for an individual both directly - because of fewer (concurrent) partners - and indirectly - because those partners also have fewer partners themselves, and are less often HIV-infected. Second, this effect is multiplied with a concurrent, disproportionate lowering of STD cofactor prevalences in individuals and their partners, as this mechanism applies also to the other STDs.

The projections for Profile 3 illustrate that promiscuity needs not to be abolished completely for a large and decisive epidemiological impact. This conclusion matches insights gained earlier using the concept of (basic) reproductive numbers (R_0): a reduction moving the reproductive number in the group most determining population prevalence below 1 suffices [Hethcote & Yorke 1984, Garnett & Anderson 1995]. Practically, the potential for large dynamic effects of behaviour change implies that apparently small shifts in numbers of partners, as sometimes detected in behavioural surveys e.g. in Uganda [Asiimwe-Okiror *et al.* 1997], are potentially significant contributors to halting HIV spread. In Profile 1, in contrast, halving the proportion of males engaging in prostitution lowered the equilibrium HIV prevalence only proportionally, corresponding with the absence of HIV reductions *within* groups stratified by numbers of partners (Figure 6.7a+b). While this intervention halves the size of the group at risk (prostitutes, clients and their spouses), it does not affect the spread of HIV beyond this risk group, lacking a bridge type of contacts to the rest of the population (e.g. non-prostitution casual partnerships between high-risk and low-risk members; cf. [Morris *et al.* 1996]).

In summary, the extent to which a reduction in a single dominant type of risk behaviour succeeds in lowering HIV depends not only on the magnitude of impact in the target group, but also on the sexual network in the whole population. Indirect effects are largest in dense sexual networks including concurrent relationships eventually covering a large part of population (Profiles 2 and 3), and smallest in looser networks that lack bridging between the high-risk (prostitution) setting to the rest of the (monogamous) population (Profile 1).

Comparison of model outputs on reductions in numbers of partners (Fig. 6.5), changes in HIV prevalence stratified by number of partners (Fig. 6.7), and impact on overall HIV prevalence (Fig. 6.6), showed that shifts in numbers of partners alone cannot fully explain the magnitude of impact on HIV spread. To predict long-term epidemiological effects on a population level, changes in multiple attributes must be analyzed simultaneously - e.g. numbers of partners and HIV prevalence by number of partners.

For increased condom use as an alternative preventive measure, comparable dynamic effects on HIV spread as for partnership reduction would apply, since condoms also reduce both HIV and STD incidence directly, and HIV incidence also indirectly through STD prevalence reduction. In earlier *STDSIM* projections, halving the proportion of males or of prostitutes not using condoms consistently in casual partnerships [Van Vliet *et al.* 1998] was indeed almost as effective as halving of partnership formation rates (this chapter). Comparing partnership reduction and condom use to STD treatment, however, the STD treatment likely has much less dynamic effects, since it reduces HIV incidence exclusively indirectly by lowering STD prevalences. Therefore, halving the number of casual partners likely has a larger potential for HIV prevention than doubling the proportion of STD episodes treated.

Validity and usefulness of intervention projections

Uncertainty about what would have been the course of an epidemic without an observed behaviour change hampers valid comparisons between observational studies and model outcomes. In Uganda, reductions in casual partnerships and in prostitution have been credited for the stabilization and subsequent drop in HIV prevalence as observed in different sentinel surveillance groups since the early 1990s [Mulder *et al.* 1995, Konde-Lule & Sebina 1993, Konde-Lule *et al.* 1997, Asiimwe-Okiror *et al.* 1997]. Others [Wawer *et al.* 1997, Brody 1996] have explained this decline from saturation effects, as evident from AIDS-mortality outweighing HIV incidence in cohort studies in rural Uganda. Our baseline simulations of Profiles 2 and 3, which in behavioural patterns and HIV epidemiology come closest to Uganda (before large-scale prevention efforts), suggest that declines in HIV prevalence as large as observed in Uganda are unlikely to be explained by saturation effects alone. The simulations also showed that behav-

iour changes as noted in Uganda - a 2 year delay in sexual debut [Asiimwe-Okiror *et al.* 1997] and a 20-50% reduction in the proportion of adolescents having non-regular sex [Konde-Lule *et al.* 1997] - can indeed contribute disproportionally to lowering HIV prevalence.

No studies have yet been published that quantitatively and in a controlled way investigated the effects of behaviour change on HIV or STD incidence in developing countries. Therefore, our results can best be regarded as qualitative and in the right order of magnitude, rather than as exact quantitative estimates. One source of uncertainty in the model predictions lies in the assumptions on STD/HIV interactions. Since the projected impacts of partnership reductions were in part accomplished via STD cofactors, the magnitude of the predicted impact on HIV depends on the assumed cofactor magnitudes, which are as yet unknown. The larger STD cofactors, the larger the predicted impact of partnership reduction will be. Uncertainty also pertains to the assumptions on intervention coverage. The magnitudes of risk reduction in intervention studies on which these were based [Jackson *et al.* 1997c, Mills *et al.* 1997] need not be indicative of what can be achieved in other, non-research, settings. Feasibility may also differ between settings, whereas we applied the risk reductions observed in certain countries to all model profiles. Moreover, behavioural responses are often not sustainable after the end of the intervention, especially if resulting from vertically implemented, small-scale prevention programs (e.g. [Stall *et al.* 1990, Asamoah-Adu *et al.* 1994]). This could cause the assumed reductions in numbers of partners - which were based on short-term intervention studies and programme evaluations - to be unrealistic for the 15 years of the simulated interventions. On the side of intervention efficacy, the simulated interventions could in reality have additional effects ignored by the model. For example, delay of sexual debut could have a larger impact on HIV spread if risk factors associated with young age of females, such as cervical ectopy and trauma during intercourse [UN 1993, Mayer & Anderson 1995, Sullivan *et al.* 1997, Mostad 1998], would increase susceptibility to and/or infectivity of STD infection. Finally, even if all relevant effects of interventions were included in the model, projected effectiveness at realistic coverage could not be the only criterion when prioritizing between HIV control options. Costs must also be considered. For programmes achieving certain behavioural changes in developing countries, costs can as yet only be guessed and they will probably vary considerably between settings. Still, the large indirect effects of even small behaviour changes, as demonstrated in this chapter, make such intervention effects a valuable aim striving for.

chapter 7

Model-based evaluation of single-round STD mass treatment for HIV control in Mwanza

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7.1 Summary

Objectives: To compare the impact of single-round mass treatment of sexually transmitted diseases (STD), sustained syndromic treatment and their combination on the incidence of HIV in rural Africa.
Methods: We studied the effects of STD interventions by stochastic simulation using the model *STDSIM*. Parameters were fitted using data from a trial of improved STD treatment services in Mwanza, Tanzania. Effectiveness was assessed by comparing the prevalences of gonorrhoea, chlamydia, syphilis and chancroid, and the incidence of HIV, in the general adult population in simulations with and without intervention.
Results: Single-round mass treatment was projected to achieve an immediate, substantial reduction in STD prevalences, which would return to baseline levels over 5-10 years. The effect on syphilis was somewhat larger if participants cured of latent syphilis were not immediately susceptible to re-infection. At 80% coverage, the model projected a reduction in cumulative HIV incidence over 2 years of 36%. A similar impact was achieved if treatment of syphilis was excluded from the intervention or confined to those in the infectious stages. In comparison with sustained syndromic treatment, single-round mass treatment had a greater short-term impact on HIV (36 versus 30% over 2 years), but a smaller long-term impact (24 versus 62% over 10 years). Mass treatment combined with improved treatment services led to a rapid and sustained fall in HIV incidence (57% over 2 years; 70% over 10 years).
Conclusions: In populations in which STD control can reduce HIV incidence, mass treatment may, in the short run, have an impact comparable to sustained syndromic treatment. Mass treatment combined with sustained syndromic treatment may be particularly effective.

7.2 Introduction

HIV/AIDS continues to spread rapidly in many developing countries. For example, HIV prevalence in the general adult population exceeds 30% in parts of southern Africa, and high incidence rates have been reported from parts of south-east Asia [UNAIDS 1997]. In most of these countries, neither vaccination nor affordable and effective treatments are likely to be available for many years, leaving preventive measures as the only realistic option for control.

The results of epidemiological studies strongly suggest that other sexually transmitted diseases (STDs) enhance the sexual transmission of HIV [Cameron *et al.* 1989, Plummer *et al.* 1991, Laga *et al.* 1993], by increasing both the susceptibility of HIV-uninfected and the infectiousness of HIV-infected individuals [Mertens *et al.* 1990]. Increased shedding of HIV in the genital tract in STD-

infected HIV patients seems to be one of the biological mechanisms underlying this cofactor effect [Mostad *et al.* 1997, Cohen *et al.* 1997]. Whilst STDs represent a major public health problem in their own right [Worldbank 1993], it has been suggested that STD control should also reduce HIV transmission [Pepin *et al.* 1989]. The World Health Organization has promoted syndromic case management of STDs in areas lacking reliable diagnostic services [WHO 1994]. In a community-randomized trial in the rural population of Mwanza region, Tanzania (with an HIV prevalence of 4% in mid-1992), improved STD services using this approach reduced HIV incidence by 38% (95% confidence interval (CI): 15 - 55) over 2 years [Grosskurth *et al.* 1995a, Hayes *et al.* 1995a].

Syndromic treatment of STDs relies critically on the occurrence and recognition of symptoms, and on appropriate treatment-seeking behaviour and therapy compliance [Alary *et al.* 1996, Wilkinson 1997, Dallabetta *et al.* 1998]. Unfortunately, a considerable proportion of STDs are asymptomatic, and symptomatic patients often fail to recognise their condition or resort to ineffective sources of care. Furthermore, partner treatment rates are generally low in developing countries [Buvé *et al.* 1993, Hayes *et al.* 1997, Winfield & Latif 1985]. To overcome these limitations, STD mass treatment has been suggested as an alternative or complementary approach for the control of STDs and HIV [Adler *et al.* 1996, Wawer *et al.* 1998]. Mass treatment has been applied successfully in eradication programmes for yaws and endemic syphilis [WHO 1965, Antal & Causse 1985]. As a test of concept, the effectiveness of repeated mass treatment of STDs has recently been investigated in a community-randomized trial in rural Rakai district, Uganda, with a high HIV prevalence (16%). After two rounds of mass treatment at 10-month intervals, the investigators observed significant reductions in the prevalence of syphilis and trichomoniasis and non-significant reductions in gonorrhoea, chlamydia and bacterial vaginosis, but surprisingly no reduction in HIV incidence, the adjusted incidence rate ratio of HIV (intervention/comparison arm) over the first 20 months being 0.97 (95% CI, 0.81-1.16) [Wawer *et al.* 1999].

Despite these disappointing results, STD mass treatment, possibly in combination with other interventions, may represent an effective strategy for STD and HIV control in some populations. It is therefore important to understand the mechanisms influencing the dynamics of STD and HIV transmission under conditions of mass treatment. Computer models that are sufficiently sophisticated to simulate the transmission dynamics of STD infections within human populations, are increasingly used to analyze complex problems of this kind [Anderson & May 1988, Anderson 1989, Garnett & Anderson 1996a, Robinson *et al.* 1997]. Various models have been used to study the impact of alternative strategies to prevent the spread of HIV in Sub-Saharan Africa [Rowley & Anderson 1994, Garnett & Anderson 1995, Kault 1995, Low-Beer & Stoneburner 1997, Bernstein *et al.* 1998]. So far, simulations exploring the impact of STD control on HIV spread [Robinson *et al.* 1997, Bernstein *et al.* 1998, Auvert *et al.* 1990, Stover & O'Way 1995, Robin-

son *et al.* 1995] distuinguished at maximum two types of STDs (ulcerative and inflammatory) acting as cofactors for HIV transmission. However, the transmission dynamics, and hence the response to control measures, of STDs of different aetiologic origin within these types can be very different [Brunham & Plummer 1990, Stigum *et al.* 1994, Kretzschmar *et al.* 1996]. To predict the impact of STD control on HIV transmission, it is important, therefore, to distinguish between STDs. The stochastic microsimulation model *STDSIM* was specifically designed for this purpose.

This chapter describes the application of the *STDSIM* model to predict the short- and long-term effects of a single round of STD mass treatment on STDs and HIV in a rural African population. We discuss a number of biomedical determinants of the effectiveness of this intervention, and examine the predicted impact of mass treatment in comparison with, or in combination with, the continuous provision of syndromic treatment services. The model was quantified using data from the Mwanza trial population, in order to assess the likely impact of mass treatment in a setting at a comparatively early stage of the HIV epidemic (as evidenced by a relatively low prevalence and a high incidence/prevalence ratio) compared to rural areas in Uganda [Wawer *et al.* 1999, Nunn *et al.* 1995]. We considered a single-round rather than a multi-round treatment strategy to better illustrate the short-term and long-term effects of mass treatment, and because a single-round approach is likely to be more feasible in resource poor settings.

7.3 Methods

Microsimulation model *STDSIM*

The model has been described in detail elsewhere [Van der Ploeg *et al.* 1998, Korenromp *et al.* 2000c]. *STDSIM* simulates the natural history and transmission of HIV infection and four bacterial STDs (gonorrhoea, chlamydia, syphilis and chancroid) in a population defined by a detailed set of parameters. The model population consists of individuals with assigned characteristics that change over time. The formation and dissolution of sexual partnerships between individuals, and transmission of STDs during contacts between sexual partners, are modelled as stochastic events. The explicit representation of individuals, partnerships, instances of STD transmission and STD episodes is considered a valid approach to simulate STD transmission dynamics [Robinson *et al.* 1997, Auvert *et al.* 1990, Robinson *et al.* 1995, Kretzschmar *et al.* 1996, Mode *et al.* 1989, Leslie & Brunham 1990, Ghani *et al.* 1997, Morris & Kretzschmar 1997]. For example, it allows for concurrent partnerships, an important determinant of STD spread [Morris & Kretzschmar 1997, Watts & May 1992]. Moreover, the microsimulation approach makes *STDSIM* flexible in the specification of interactions between different

STDs and HIV at the level of single sexual contacts between uninfected and infected partners. *STDSIM* allows us to simulate a variety of (combinations of) interventions, and to study their impact on various epidemiological outcome measures over time.

Model quantification

Demographic, behavioural and biomedical model parameters were quantified using data from the rural population of Mwanza region, Tanzania, documented through a series of studies conducted in the context of the trial of improved (syndromic) STD treatment services [Grosskurth *et al.* 1995a, Grosskurth *et al.* 1995b, Grosskurth *et al.* 1996, Hayes *et al.* 1995a, Mayaud *et al.* 1995, Mayaud *et al.* 1997a, Munguti *et al.* 1997, Todd *et al.* 1997]. Baseline prevalences of HIV, syphilis, gonorrhoea and chlamydia were fitted to those measured at the start of the trial in 1992, whereas HIV incidence (in the absence of intervention) was fitted to that observed in the comparison arm of the trial during follow-up from 1992 to 1994. In the model, HIV was assumed to enter the population in 1983.

Demography

The model structure and the set of parameter values used in this study with respect to Demography and Sexual behaviour are described in detail in the Appendix. In brief, age-specific fertility rates per woman per year were specified using data from the 1996 Demographic Health Survey of rural Tanzania [Bureau of Statistics & Macro-International 1997]. Mortality rates in HIV-uninfected individuals were quantified using data from the Mwanza trial cohort [Todd *et al.* 1997]. Migration was ignored. Simulated populations averaged 19,080 individuals in mid-1992. This population size, of which about half was in the age range of 15-54 years, was estimated to be roughly the average size of communities in the Mwanza trial [Grosskurth *et al.* 1995b]. The age/sex distribution and growth rate of the model population corresponded to that in rural Tanzania in 1996 [Bureau of Statistics & Macro-International 1997].

Sexual behaviour

The model allows for three categories of (hetero-)sexual partnerships: steady relationships (e.g. marriages), short relationships, and 'one-off' sexual contacts between a small group of women, who may or may not define themselves as prostitutes, and a larger group of men. Formation of relationships is simulated using the concepts of availability for (supply) and selection of (demand) new partners [Le Pont & Blower 1991]. Relationship formation follows age preference matrices guiding the search for new partners from the same or adjacent age groups.

Heterogeneity within the population in sexual behaviour, which has an important influence on STD transmission dynamics [Garnett & Anderson 1996a, Ghani

et al. 1997, Morris 1991, Garnett & Anderson 1993a], is incorporated in three ways in *STDSIM*. First, the simulated population is heterogeneous in the number, type and overlap of sexual relations, which vary according to age, sex and an individual promiscuity level. Second, the frequency of having one-off contacts with female 'prostitutes' varies between males. This personal frequency can change with marital status, but is otherwise constant throughout a man's sexual life. Third, the age of sexual debut varies between individuals and between the sexes. For this study, parameter values were based as far as possible on data on reported sexual behaviour collected from a random sub-sample of the Mwanza trial cohort [Munguti *et al.* 1997]. Age of sexual debut in the model was assumed to average 15 years for males and 15.5 years for females, and was distributed between individuals uniformly over the age range 12-18 years for males and 12.5-18.5 years for females.

The values of parameters determining partnership formation and dissolution and the frequency of one-off contacts were determined by simultaneous fitting of the following types of data [Munguti *et al.* 1997]: (i) the proportion currently married and the number of spouses, by age group and sex; (ii) the numbers of partners over the past year reported by males, by age group; (iii) the age pattern in the number of partners over the past year reported by females. In the absence of cross-sectional data on the occurrence of overlap in partnerships, we consider that fitting the model simultaneously to these static (i) and dynamic (ii, iii) measures of sexual activity should provide an adequate representation of partnership dynamics, including concurrency, in the Mwanza population.

In the resulting quantification, 55% of single and 25% of married sexually active males aged 15-49 years engaged in one-off sexual contacts, at an average frequency of once yearly. A further 5% of males in this age range had one-off contacts on average 6 times per year, irrespective of their marital status. This male demand for one-off contacts was fulfilled by a mean 0.5% of the female sexually active population, who each had on average 1 such contact per week. This quantification provided a good fit to the proportion married and numbers of recent partners of males in different age groups (Figure 7.1). For females, the model fitted the observed age pattern in numbers of partners, but the predicted number of partners was higher than reported. This is defensible because of likely underreporting of non-marital partners by females and underrepresentation of high-risk females in the sub-cohort [Munguti *et al.* 1997].

The frequency of intercourse was assumed to be 1.5 times per week in relationships where the male partner was younger than 35 years of age and once per week for older males, consistent with data on factory workers in Mwanza town [Borgdorff *et al.* 1994]. These frequencies applied to both steady and short relationships, and were constant over the course of relationships. The prevalence of condom use during follow-up of the Mwanza trial was very low: only 2.4% of men and 2.3% of women reported ever using condoms with partners other than their spouse, and only three individuals (out of 1117) reported regular use

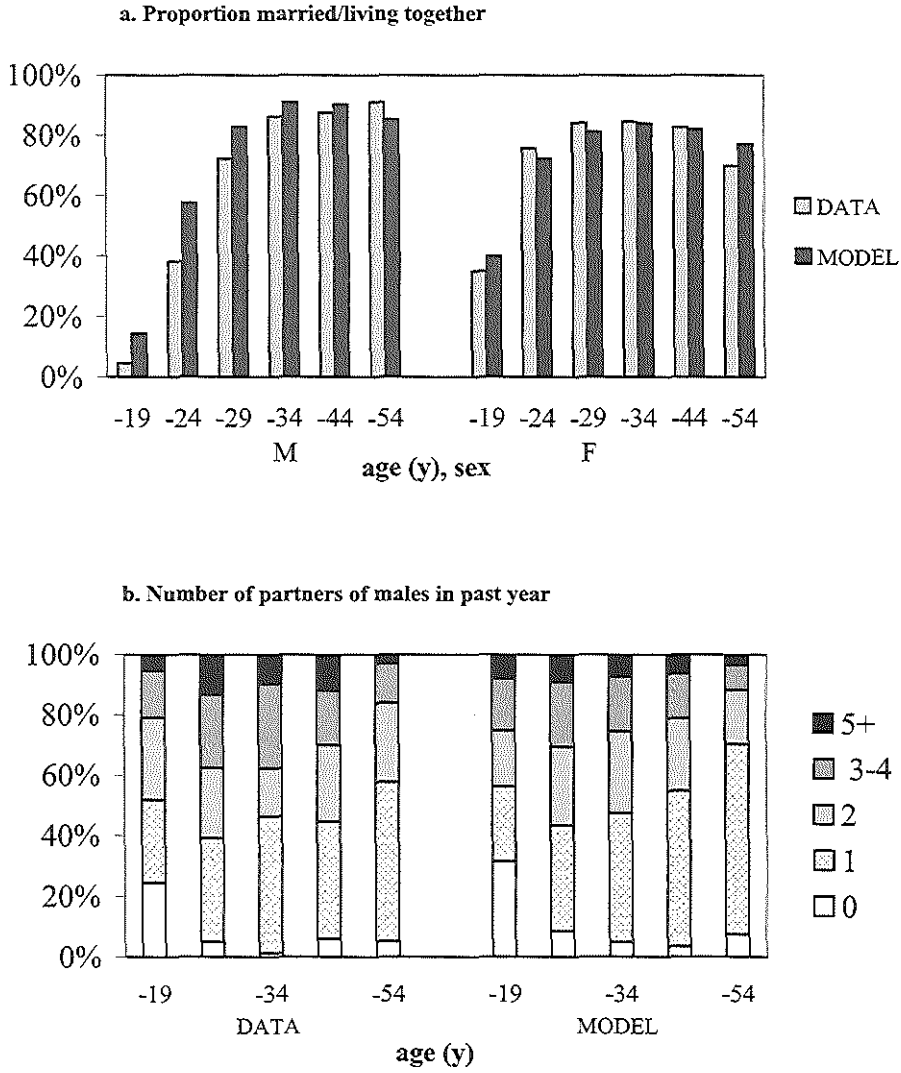

Figure 7.1 **Fit of the *STDSIM* quantification against data from a subcohort of the Mwanza trial population at start of the intervention in mid-1992 [Munguti *et al.* 1997].** a) proportion married and/or in a steady relationship, by sex and age group (youngest age group: 15-19 years); b) number of sexual partners during the past year of males, by age group. Mean of 130 simulated populations.

[Grosskurth *et al.* 1995a].Therefore, condom use was ignored in the model.

To model the effects of sexual contacts with individuals outside the study population (e.g. with visitors or during travel), additional risks of infection for HIV and each STD were assumed for each individual aged 15-44 years.These corresponded to an average of 0.40 and 0.15 extra sexual contact per person per year,

for males and females respectively. Lacking corresponding data from Mwanza, these numbers were based on the proportion of study participants reporting outside partners during the last year in rural Rakai (12% for males, 7% for females [Wawer *et al.* 1998], multiplied by an assumed number of contacts per outside partner of 3 for males and 2 for females.

Biomedical parameters

Assumptions regarding the natural history and transmission of HIV and other STDs (Table 7.1) were derived mostly from the literature. Since we focus on outcomes for adults, and since heterosexual transmission accounts for the great majority of adult infections in this region [Over & Piot 1992], other modes of transmission were not taken into account.

Durations of (stages of) STD infections were assumed exponentially distributed with means given in Table 7.1. As a convenient simplification, syphilis was assumed to consist of two consecutive stages. The 'infectious' stage corresponds roughly to primary and secondary syphilis, and this accounts for the relatively long duration assumed for this stage. In the absence of effective treatment, patients progress to a non-infectious 'latent' stage. HIV infection was represented as two consecutive stages, pre-AIDS (mean duration 7 years) and AIDS (mean duration 9 months), each following a Weibull distribution with shape parameter 2.

Of all biomedical parameters, per-contact transmission probabilities and STD cofactor effects are probably the most uncertain. Transmission probabilities were within plausible ranges adjusted to provide a good fit to HIV and STD prevalences in Mwanza. For chancroid, there is only one published empirical estimate of the per-contact transmission probability (43%, for male-to-female transmission) [Plummer *et al.* 1983]. We adjusted this point estimate downwards to obtain a predicted chancroid prevalence consistent with the limited data from Mwanza. We estimated an approximate population prevalence of 1%, based on 1.3% of males reporting genital ulcers in rural Mwanza in 1990/1 [De Vincenzi 1994], assuming some under-reporting of ulcers, and given (unpublished) data from an STD clinic in Mwanza town showing that 20%-55% of ulcers were attributable to chancroid.

Transmission probabilities and cofactor effects of STDs were assumed identical for symptomatic and asymptomatic episodes. For syphilis, the cofactor effect applied only during the infectious stage. In case of multiple cofactors (one partner in an HIV-discordant couple carrying multiple STDs simultaneously, or both partners carrying one or more STDs), the maximum cofactor for any single STD applied. We assessed the robustness of results to variations in these uncertain parameters by sensitivity analyses (see below).

Following cure of STD infections (either spontaneous or due to treatment), individuals were assumed immediately susceptible to re-infection, in line with clinical experience [Holmes *et al.* 1970]. For syphilis, however, it is unclear

Table 7.1 STDSIM parameter values concerning transmission and natural history of STD infections, cofactor effects and performance of treatment, used to reflect the situation in rural Mwanza, Tanzania.

Parameter		HIV	Gonorrhoea	Chlamydia	Syphilis	Chancroid	Reference
Transmission probability per contact	M→F	0.003	0.22	0.20	0.30[b]	0.15	[Plummer *et al.* 1983, De Vincenzi 1994, Holmes *et al.* 1970, Hooper *et al.* 1978, Katz 1992, Lycke *et al.* 1980, McCutchan 1984, Csonka & Oates 1990]
	F→M	0.0008	0.15	0.12[a]	0.20[b]	0.10	
Relative increase in per-contact HIV-transmission probability due to STD	susceptibility		10	10	100[b]	100	[Cameron *et al.* 1989, Laga *et al.* 1993, Robinson *et al.* 1997, Laga *et al.* 1991, Hayes *et al.* 1995c]
	infectiousness		10	10	100[b]	100	
Annual risk of infection by contacts from outside study population[c] (x 10^{-3})	M	0.043	2.1	2.4	0.72	0.48	[Wawer *et al.* 1998], E
	F	0.061	1.2	1.5	0.41	0.27	
Probability that infection becomes symptomatic	M	1.0	0.50	0.30	0.95	0.95	[Grosskurth *et al.* 1996, Holmes *et al.* 1999], E
	F	1.0	0.20	0.15	0.50	0.70	
Mean duration of infectious stage if not treated (weeks)	M	400	9	12	26	16	[Todd *et al.* 1997, Holmes *et al.* 1999, Mwijarubi *et al.* 1993, Over & Piot 1992, Morgan *et al.* 1997b]
	F	400	13	16	26	16	
Mean duration of infectious stage if treated (weeks)	M	NA	2	3	2	2	[Holmes *et al.* 1999]
	F	NA	8	10	2	2	
Mean duration of latent (non-infectious) stage (weeks)	M				520		[Holmes *et al.* 1999, Magnuson *et al.* 1956, Sparling 1990, Garnett *et al.* 1997], E
	F				520		
Fraction of symptomatic STD episodes cured by unimproved services	M		0.05	0.05	0.05	0.05	[Mosha *et al.* 1993]
	F		0.05	0.05	0.05	0.05	
Fraction of symptomatic STD episodes cured by improved services	M		0.5	0.5	0.5	0.5	[Mosha *et al.* 1993], E based on unpublished data from intervention clinics in Mwanza
	F		0.5	0.5	0.5	0.5	
Fraction of steady partners of STD patients notified and cured under improved services[d]	M		0.28	0.28	0.28	0.28	E based on unpublished data from intervention clinics in Mwanza
	F		0.28	0.28	0.28	0.28	

Fraction of STDs cured by mass treatment	M		0.95	0.95	0.95	0.95	E
	F		0.95	0.95	0.95	0.95	

[a] In contrast to certain empirical observations [Lycke *et al.* 1980], in the model the transmission probability of chlamydia was chosen not much lower than that of gonorrhoea, to adjust for the low sensitivity of culture of chlamydia relative to gonorrhoea. [b] Refers to infectious stages only. [c] Product of transmission probability, prevalence in outside partners (assumed similar to that within the study population), proportion reporting outside partner(s) over the past year (12% for males and 7% for females in the age range 15-44 years [Wawer *et al.* 1998], and an assumed number of contacts per outside partner of three for males and two for females. [d] Product of fraction of steady partners of patients treated (35%) and estimated efficacy of treatment (80%). M = male, F = female, NA = not applicable under conditions prevailing in rural Mwanza, E = authors' estimate.

whether this assumption is valid [Hooper *et al.* 1978, Katz 1992], and cure may be followed by a period of reduced susceptibility, particularly if treatment is given at a late stage of infection. Projections were therefore made not only for immediate susceptibility (default scenario), but also for alternative scenarios varying in the duration of non-susceptibility after mass treatment in the latent stage (means of 1 and 5 years).

Coverage and effectiveness of STD treatment

Assumptions regarding the coverage and effectiveness of (improved) syndromic services were based on observations from Mwanza. For each STD, a fixed proportion of symptomatic patients was assumed to be treated and cured clinically. The trial intervention was assumed to increase this proportion from 5% to 50%. STD episodes cured were assumed to have a shorter duration than untreated episodes (Table 7.1). Only the symptomatic STD for which the patient sought treatment was cured; concurrent asymptomatic infections were not. Partner referral in the intervention arm of the trial was represented as the simultaneous cure of the STD for which a patient sought treatment in 28% of steady partners infected with that STD. This level was based on estimates from Mwanza intervention clinics.

STD mass treatment was assumed to cover 80% of the population, in line with the coverage achieved in the Rakai trial [Wawer *et al.* 1999]. Mass treatment was in the model delivered at a single point in time, and instantaneously cured 95% of infected individuals, irrespective of the STD and stage of infection. We also examined the effects of alternative mass treatment regimens, in which syphilis treatment either was excluded or covered the infectious stage only.

Simulation design

Projections of HIV and STD prevalence and incidence were made for four scenarios: (a) no intervention; (b) sustained syndromic STD treatment services commencing in mid-1992; (c) a single round of mass treatment in mid-1992; (d) a combination of single-round mass treatment in mid-1992 followed by sustained syndromic treatment. This timing corresponded to the Mwanza trial, in which the intervention was introduced between December 1991 and December 1992.

In order to reduce stochastic fluctuations in the projections, 500 simulation runs were conducted to generate 500 populations. This set of 500 simulated populations was used for fitting parameter values. Thereafter, populations with a HIV prevalence among adults (15-54 years) of <2 or >6% at start of the interventions were excluded, since they were inconsistent with the observed baseline prevalence in Mwanza of 4%. Applying these criteria, 130 out of the simulated populations were included. The full set of 500 populations and the selected 130 populations were very comparable in mean STD and HIV prevalences and incidences over time, age/sex patterns in numbers of partners, and age/sex pat-

terns in HIV prevalence and incidence in mid-1992 (not shown). The selection reduced the variability around the mean for HIV prevalence and incidence, but not for STD prevalences. For instance, in mid-1992 HIV prevalence was 3.7 (2.2 - 5.6; mean, 10th and 90th percentiles) for the 130 included populations, as compared to 3.7 (0.12 - 9.7) for all populations. In the remainder of the chapter, we focus on average outcomes for the subset of simulated populations.

Simulations with and without interventions were run for each included population. The impact of an intervention on HIV was calculated as the cumulative reduction in the number of new HIV infections in adults (15-54 years) for each population separately (matched comparison), for different evaluation periods. Impact was expressed as the mean ± the standard error of the mean (SE) over the 130 populations.

Sensitivity analyses

Simulations were repeated for alternative quantifications varying in the values of uncertain biomedical parameters. For each alternative scenario, the HIV transmission probability was re-adjusted to fit the prevalence measured at the start of the Mwanza trial (4%). Thereafter, populations fitting Mwanza with respect to HIV prevalence in mid-1992 were selected, interventions simulated and their impact calculated as described in the previous section.

7.4 Results

Simulations in the absence of intervention and fit against Mwanza baseline data

Model predictions for the prevalence of STDs and HIV and the incidence of HIV and syphilis in the absence of intervention are shown in Figures 7.2 and 7.3. Syphilis was the most prevalent STD (Figure 7.2c), with a prevalence of around 7% in mid-1992. Most individuals with syphilis were in the latent stage, and the prevalence of infectious syphilis was about 0.5% (Figure 7.4). Prevalences of chlamydia, gonorrhoea and chancroid in mid-1992 were around 5%, 3% and 1% respectively; after the introduction of HIV, these showed a spontaneous decline over time (Figure 7.2a,b,d), resulting from HIV-related mortality. Since having multiple sexual partners puts individuals at risk of both HIV and STDs, STDs are more prevalent among HIV-infected subjects, so that deaths of HIV-positives reduce the number of STD-infected individuals. In the absence of intervention, syphilis incidence remained almost constant (Figure 7.3a). In contrast, HIV incidence increased from around 1% in 1992 to over 2% by 2005 (Figure 7.3b), while

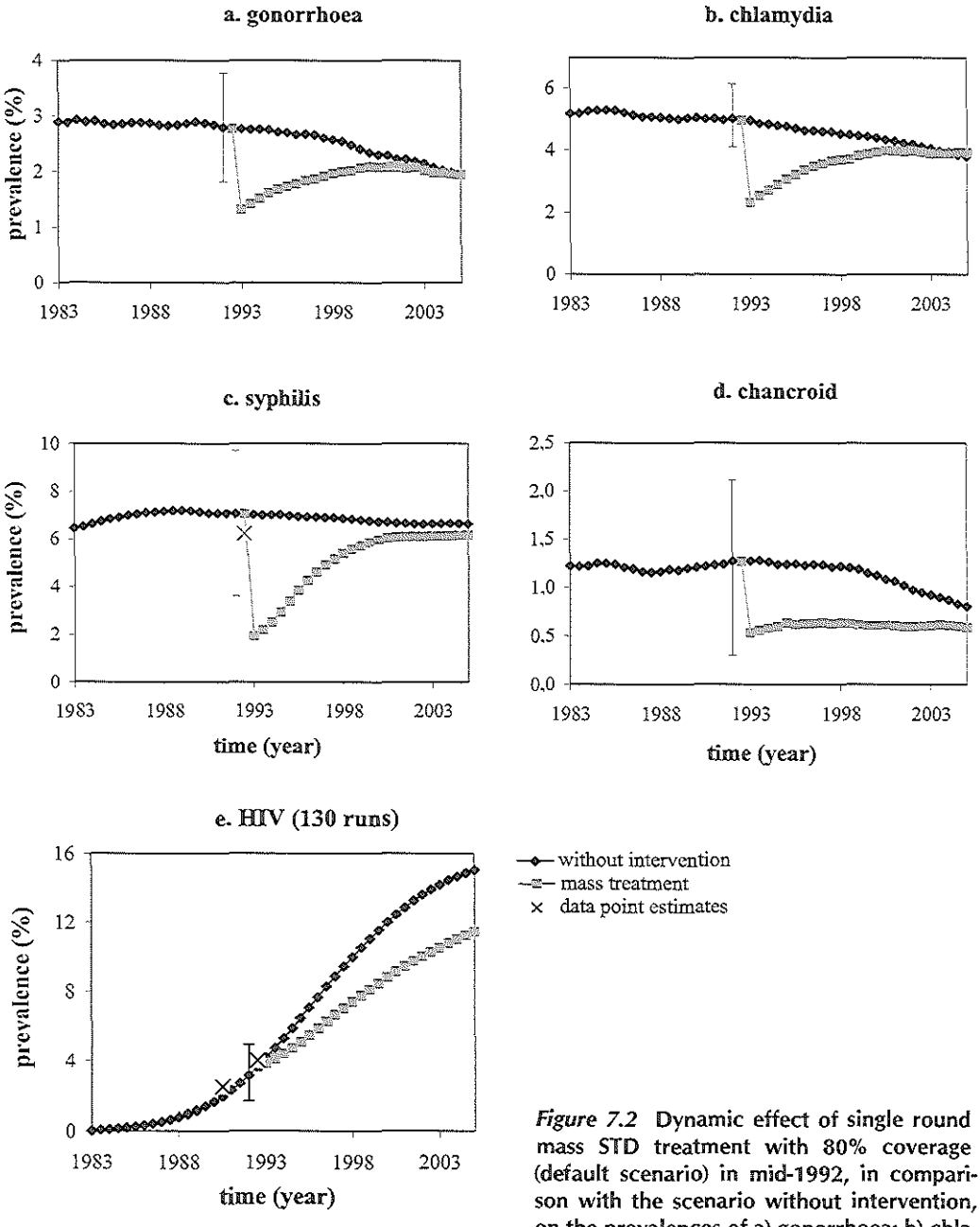

Figure 7.2 **Dynamic effect of single round mass STD treatment with 80% coverage (default scenario) in mid-1992, in comparison with the scenario without intervention, on the prevalences of a) gonorrhoea; b) chlamydia; c) syphilis; d) chancroid and e) HIV in the general adult population (15-54 years).** Mean of 130 simulated populations. 10th and 90th percentiles for mid-1992 are plotted, but for clarity slightly shifted to the left. Empirical point estimates of prevalences of syphilis and HIV from the trial baseline survey and of HIV in mid-1990 [Barongo *et al.* 1992] are indicated as x. This default scenario of mass treatment assumed immediate susceptibility to syphilis reinfection after treatment of all forms of syphilis. Numbers on the x-axis reflect the beginning of each calendar year.

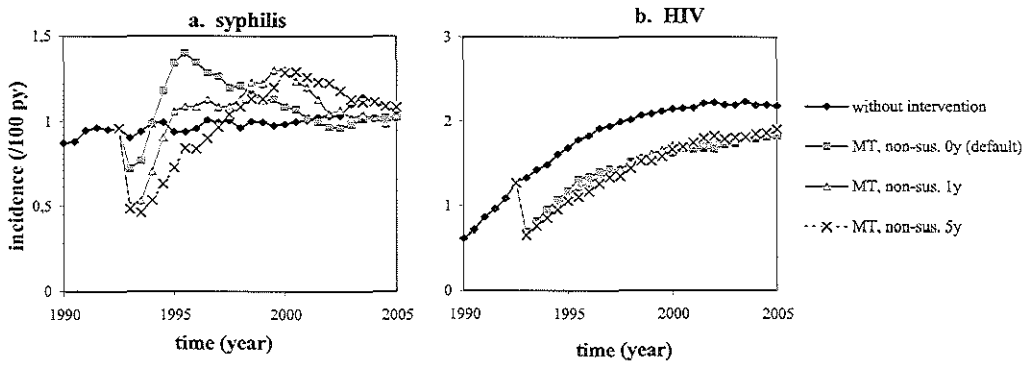

***Figure 7.3* Impact of single round mass treatment on a) syphilis incidence and b) HIV incidence in the general adult population (15-54 years), for varying durations of non-susceptibility to reinfection after cure of latent syphilis.** The curves with 0 years of non-susceptibility constitute the default scenario, corresponding to the results shown in Figures 7.2 and 7.4. Mean of 130 simulated populations.

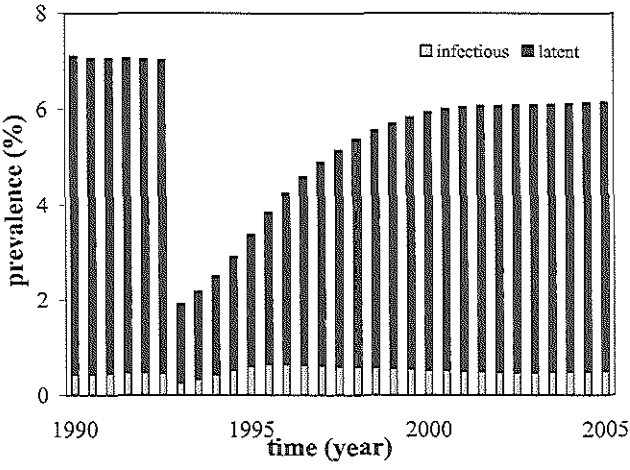

***Figure 7.4* Dynamic effects of single-round mass treatment (default scenario) on the prevalence of syphilis in the general adult population (15-54 years), differentiated by disease stage.** Mean of 130 simulated populations.

HIV prevalence increased from 4% in 1992 to 15% in 2005 (Figure 7.2e).

Where reliable population-based data were available, projections for 1992 were in good agreement with results from the comparison arm of the Mwanza trial (Fig. 7.2c and 7.2e) [Grosskurth *et al.* 1995a, Grosskurth *et al.* 1995b, Mayaud *et al.* 1997a]. Also, the projected prevalence of HIV in mid-1990 (2%) was in line with a point-estimate of 2.5% in mid-1990 in rural villages in Mwanza comparable to the trial communities (Fig. 7.2e) [Barongo *et al.* 1992]. For outcomes measured in the trial by sex and age (HIV incidence, HIV prevalence and syphilis prevalence), age and sex patterns in model outcomes were consistent with the data.

Simulations of syndromic treatment and fit against Mwanza trial data

The improvement of syndromic treatment services was projected to increase the average number of STD episodes cured over 2 years (the duration of the trial) from 121 to 1074, for a model population of around 19,080 individuals. In comparison, during the Mwanza trial, an estimated 1,551 STD episodes were treated per 19,080 individuals in the intervention arm [Gilson *et al.* 1997]. Assuming that about 70% of these patients were cured (unpublished observations from the trial), this corresponds to 1036 STD episodes cured per 19,080 adults, with which the model predictions agree well.

After the onset of this intervention, HIV incidence was predicted to decrease markedly over time (Figure 7.5;Table 7.2).The reduction was steepest during the first few years, but still continued 10 years later. Over two years of intervention, a cumulative reduction in HIV incidence of 30% was projected; over 10 years, the reduction amounted to over 60%.The predicted reduction in HIV incidence over two years was lower than that observed in the trial over 2 years of follow-up (30% versus 38%), but fell well within the limits of the 95% CI (15-55%) obtained from the empirical data [Hayes *et al.* 1995a].

For the STDs included, the model predicted that the introduction of improved syndromic management was followed by substantial reductions in prevalence.

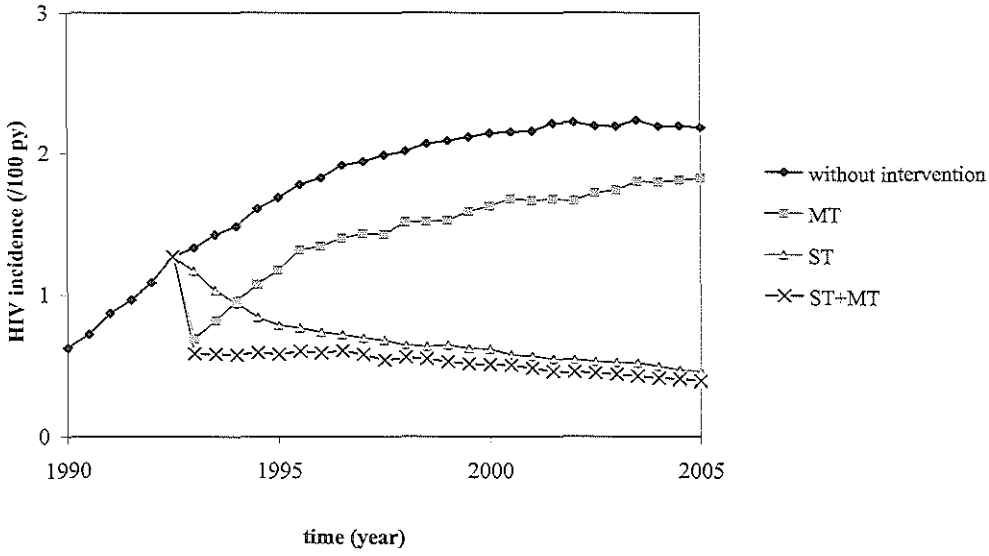

Figure 7.5 **Impact of different STD treatment strategies on HIV incidence in the general adult population (15-54 years).** MT: single round mass treatment (default); ST: sustained syndromic treatment; ST+MT: combination of single-round mass treatment (default) with sustained syndromic treatment. Interventions were implemented in mid-1992. Mean of 130 simulated populations.

These predictions are difficult to compare with data from Mwanza. After 2 years, the prevalence of infectious syphilis in the model was reduced by 59% and that of all stages of syphilis by 13%. The empirical data showed a significant reduction in the prevalence of syphilis in the intervention compared with the comparison arm [Mayaud *et al.* 1997a]. The reduction in active syphilis (*Treponema pallidum* haemagglutination assay (TPHA)+, rapid plasma reagin (RPR) >=1:8) was 29% (95% CI, 7-46), but this was observed after treatment of all RPR+ cohort members for syphilis at baseline of the trial for ethical reasons. The observed reduction in new cases of active syphilis, which are more likely to represent cases of infectious syphilis [Sparling 1990], was 38% (95% CI, -2 to 62). These observations seem broadly consistent with the predicted prevalence reduction. The prevalences of chlamydia and gonorrhoea were in the model reduced by 20% and 43% after 2 years. In comparison, among a subset of men in the trial, the prevalence of gonorrhoea and/or chlamydia was reduced by only 4% (95% CI, -85 to 50), but the prevalence of symptomatic urethritis was reduced by 49% (95% CI, -3 to 75) [Mayaud *et al.* 1997a]. Among female antenatal clinic attenders, the reduction in the prevalence of gonorrhoea and/or chlamydia was 7% (95% CI, -75 to 51). These data were, however, based on small numbers, available for only subsets of the trial population, and there were limitations in the sensitivity and specificity of the diagnostic tests. The model predicted an 81% reduction in the prevalence of chancroid; in the trial it was not possible to determine the prevalence of chancroid.

Simulations of single-round mass treatment

The projected single-round mass treatment cured 1,119 STD episodes in the total population of 19,080. By reducing STD incidence, the intervention reduced the number of symptomatic episodes cured by clinical treatment in the years thereafter, for example, over the first two years from 121 to 67.

Mass treatment resulted in an immediate and steep reduction in all STDs, and prevalences 1 year later were 50-80% lower than without intervention (Figure 7.2). Thereafter, without further intervention, prevalences increased over time and approached the levels observed in the absence of intervention within 5 to 10 years. The recurrence was comparatively slow for chancroid.

The reduction in the prevalence of syphilis was due mainly to a marked decrease in latent syphilis (Figure 7.4). The prevalence of infectious syphilis showed a much smaller reduction, and returned to and exceeded its previous level within a short time. The incidence of syphilis also showed an initial reduction, but thereafter increased rapidly, exceeding initial levels by around 50% within 3 years (Figure 7.3a). The size of these effects depended critically on the assumed period of non-susceptibility to re-infection following cure. The longer the period of non-susceptibility, the greater was the initial fall in incidence, and

the slower and less marked the subsequent increase above baseline levels. However, a 'rebound' effect was observed even when assuming a 5-year period of non-susceptibility, albeit delayed.

Mass treatment reduced HIV incidence by up to 50% for the first 6 months after the intervention (Figure 7.3b; Table 7.2). Thereafter incidence increased over time, but 10 years later it was still lower than without intervention. The short-term effect of mass treatment on HIV incidence was slightly greater assuming a period of non-susceptibility following cure of latent syphilis (Figure 7.3b). When alternative regimens of mass treatment were considered, the reduction in HIV incidence was in the longer term comparable if treatment for syphilis was excluded or if infectious syphilis cases were treated while latent cases were not (Table 7.2).

Simulations of mass treatment combined with improved STD treatment services

The projected combined intervention achieved cure of 1,119 STD infections by mass treatment in mid-1992; the sustained improvement of syndromic treatment resulted in a further 513 episodes cured over the first 2 years, as compared to 121 effective clinical treatments for the scenario without intervention.

Under this combined intervention, HIV incidence was reduced steeply within the first year and continued to decrease thereafter (Figure 7.5; Table 7.2). The reduction in cumulative HIV incidence over 2 years (57%) was much larger than the impact of either mass treatment (36%) or syndromic treatment (30%) in isolation. In the long run, incidence levels achieved under either the combined intervention or syndromic treatment alone converged. However, the cumulative reduction in HIV incidence over 10 years achieved with the combined intervention (70%) was larger than that of syndromic treatment alone (62%), because of a greater number of infections prevented over the first few years.

Sensitivity analyses for STD parameter assumptions

As an indication of the robustness of the results, we assessed the sensitivity of the predicted impact of treatment strategies to variations in STD parameter assumptions (Table 7.1), some of which were based on limited data. Table 7.3 shows prevalences of HIV and STDs by mid-1992 and the impact of the treatment strategies on HIV incidence over the first 2 years, for several alternative scenarios. Decreasing all cofactor magnitudes in the same direction markedly decreased the projected impact on HIV of all interventions in comparison with the default scenario. At cofactor values above the default, however, impact hardly increased, indicating a saturation effect. These variations did not affect the ranking of impact

between the three treatment strategies.

The impact of mass treatment was insensitive to the relative cofactor strengths of gonorrhoea and chlamydia (inflammatory STDs) as compared to syphilis and chancroid (ulcerative STDs). The impact of syndromic treatment, in contrast, would be larger (40% reduction over 2 years) if the cofactor effect of inflammatory STDs was decreased (from 10 to 2.5 times) while the cofactor effect of ulcerative STDs was at the same time increased (from 100 to 250 times). If inflammatory and ulcerative STDs had equal cofactor effects (25 times), the impact of syndromic treatment was much less (14% over 2 years) than in the default scenario.

Increasing or decreasing STD transmission probabilities caused an increase or decrease in the prevalence of the respective STD of a much larger magnitude, reflecting the non-linearity in STD transmission dynamics [Garnett & Anderson 1995, Koopman & Longini 1994]. The resulting prevalence levels of gonorrhoea, chlamydia and syphilis, differed markedly from those observed in Mwanza. For chlamydia, the higher the transmission probability and, consequently, its prevalence, the more favourable the impact on HIV incidence of mass treatment would be as compared to syndromic treatment. In contrast, for chancroid, the higher the transmission probability and prevalence, the less favourable the impact of mass treatment would be relative to syndromic treatment. These opposite effects reflect the low proportion of chlamydia episodes that are symptomatic (Table 7.1) and, hence susceptible to syndromic treatment, and the high proportion symptomatic for chancroid. For gonorrhoea, the relative impact on HIV incidence of the different STD interventions was insensitive to variations in the transmission probability and prevalence. Assuming a higher transmission probability for syphilis, the impact of mass treatment was markedly less than in the default scenario, and less than of syndromic treatment even in the first year of intervention. This reflects the critical influence of the rate of re-infection with syphilis on the impact of STD mass treatment.

The relative impact over time of the different treatment strategies on HIV was independent of whether HIV infectivity was assumed to be constant (the default scenario) or to vary over the course of infection, with peaks during primary infection and AIDS (Table 7.3).

In all scenarios except those varying the transmission probability of syphilis and the relative cofactor effects of inflammatory and ulcerative STD, single-round mass treatment reduced cumulative HIV incidence over the first 2 years as much as or slightly more than sustained syndromic treatment. In all scenarios, the combined intervention had about twice the impact of syndromic treatment alone over this period. Time patterns in HIV incidence under the respective interventions were comparable between all scenarios. In all scenarios except that equalling the cofactor effects of inflammatory and ulcerative STD, the instantaneous HIV incidence rate under conditions of syndromic treatment fell below that for mass treatment within 2 years (results not shown).

***Table 7.3* Sensitivity analyses for STD assumptions.** Results refer to the subset of simulated populations with an HIV prevalence among adults (15-54 years) in mid-1992 between 2 and 6% (varying between 105 and 263 out of 500 populations). Impact of interventions is expressed as the proportion reduction in cumulative HIV incidence over 2 years (mean ± SE, in %).

			(adjusted) HIV transmission probability		Projected STD prevalences in mid-1992 (%)					Proportional reduction in HIV incidence over 2 years (%)		
Scenario / parameter change			M→F	F→M	HIV	gonorrhoea	chlamydia	syphilis	chancroid	ST	MT	ST+MT
default	(see Table 7.1)		0.003	0.0008	3.7	2.8	5.0	7.0	1.3	30 ± 1.2	36 ± 2.1	57 ± 1.3
STD cofactors	*cofactor values:*											
	gonorrhoea/chlamydia	2.5x	0.01	0.003	3.6	2.8	5.0	7.3	1.3	24 ± 1.6	28 ± 1.7	44 ± 1.3
	syphilis/chancroid	25x										
	gonorrhoea/chlamydia	25x	0.0012	0.00035	3.8	2.8	5.0	7.0	1.2	29 ± 1.5	38 ± 1.8	61 ± 1.2
	syphilis/chancroid	250x										
	gonorrhoea/chlamydia	2.5x	0.0017	0.00045	4.0	2.8	4.9	6.5	1.1	40 ± 1.9	36 ± 2.7	62 ± 2.2
	syphilis/chancroid	250x										
	gonorrhoea/chlamydia	25x	0.0041	0.0011	3.7	3.0	5.0	6.9	1.1	14 ± 0.9	37 ± 0.8	48 ± 0.7
	syphilis/chancroid	25x										
STD transmission probabilities	gonorrhoea	↑	0.0028	0.00075	3.9	*12*	4.9	6.8	1.1	23 ± 1.1	30 ± 1.5	49 ± 1.1
		↓	0.0032	0.00085	3.7	*0.2*	5.0	7.1	1.2	30 ± 1.6	37 ± 1.9	57 ± 1.5
	chlamydia	↑	0.0028	0.00075	3.8	2.8	*15*	6.8	1.2	21 ± 1.3	32 ± 1.4	48 ± 1.2
		↓	0.0034	0.0009	3.9	2.8	*0.4*	7.0	1.2	34 ± 1.3	34 ± 2.4	59 ± 1.2
	syphilis	↑	0.0029	0.008	3.8	2.9	5.0	*13*	1.0	25 ± 1.5	11 ± 2.4	41 ± 1.9
		↓	0.0032	0.00085	3.9	2.9	5.1	*2.5*	1.6	32 ± 1.2	43 ± 1.4	61 ± 0.9
	chancroid	↑	0.0009	0.00025	3.8	2.9	5.1	6.7	*12*	35 ± 0.6	34 ± 0.7	65 ± 0.4
		↓	0.0056	0.0015	3.9	2.8	5.0	7.2	*0.1*	16 ± 1.3	26 ± 1.9	41 ± 1.6

HIV infectivity over the course of infection ('bathtub' pattern)	stage of infection:										
	- first 10 weeks	0.026	0.007	4.0	2.8	4.9	7.0	1.1	33 ± 1.9	40 ± 2.6	61 ± 1.5
	- asymptomatic (350 weeks)	0.0013	0.00035								
	- AIDS (40 weeks)	0.0065	0.00175								

↑ = transmission probability x 1.5; ↓ = transmission probability x 0.67. Bold italic text indicates the projected prevalence of the STD for which parameters were changed in that scenario. ST = syndromic treatment; MT = mass treatment; ST+MT = combined intervention; M = male; F = female.

7.5 Discussion

The projections indicate that single-round mass treatment may substantially reduce the prevalence of gonorrhoea, chlamydia and chancroid. Lacking regular repetition, however, the impact of mass treatment on the transmission dynamics of STDs is only temporary, so that prevalences will finally return to their equilibrium levels. The rate at which this occurs depends on the case reproduction rate of each STD, the coverage achieved, and the rate of re-introduction of STDs due to sexual contact with infected individuals from outside the study population. In these projections, chancroid, the STD with the lowest assumed transmission probability, re-emerged slowest.

The model showed that effects on syphilis are complex. In a population with poor treatment services, most prevalent cases have a latent infection and are therefore immune to new episodes of syphilitic ulceration [Sparling 1990, Jekel 1968]. Relatively few have ulcers or are in the infectious secondary stage, but mass treatment reaches both the infectious and the latent cases. As cured patients become susceptible again and are re-infected, syphilis incidence increases steeply, resulting in rates higher than before intervention. This effect is enhanced by heterogeneity in sexual behaviour. For example, in the simulation, the baseline syphilis prevalence in women engaging in one-off contacts was 38% compared with 7% in all women. Thus, although the overall pool of susceptible individuals increased only marginally as a result of mass treatment (from 93 to 98%), the number of susceptibles among persons at high risk, and consequently of potential new source infections, increased substantially.

The extent and timing of any increase in syphilis incidence depends on the duration of non-susceptibility to re-infection following cure (Figure 7.3a). Unfortunately empirical data on the duration and extent of non-susceptibility are sparse [Magnuson *et al.* 1956, Garnett *et al.* 1997], and both may depend on the stage of infection when treatment is given. Epidemiological evidence for or against resurgence of syphilis at a population level following mass treatment is also scarce. Mass treatment campaigns against endemic syphilis and yaws were generally successful, although in some cases resurgence was noted [Antal & Causse 1985, Grin & Guthe 1973, Willcox 1985, Meheus & Antal 1992]. However, the majority of these campaigns were uncontrolled, accompanied by general improvements of health services and living conditions, which may themselves have led to reductions in endemicity, and followed by regular re-treatment rounds. Furthermore, comparability with STD mass treatment is limited by differences between the endemic treponematoses and venereal syphilis in their mode of transmission (and consequently in the role of population heterogeneity in sexual behaviour), and in baseline prevalences. Prospective studies involving long-term follow-up of patients treated for venereal syphilis at different stages are needed to address this question.

Model simulations were based on cofactor effects by which STDs enhance the transmission of HIV. The results of cohort studies and intervention trials strongly argue for the existence of these effects [Cameron *et al.* 1989, Plummer *et al.* 1991, Laga *et al.* 1993, Grosskurth *et al.* 1995a, Laga *et al.* 1994], and biological studies have provided evidence for underlying mechanisms [Mostad *et al.* 1997, Cohen *et al.* 1997, Laga *et al.* 1991]. However, the magnitudes of these cofactor effects are not yet known. Odds ratios from observational studies are likely to considerably underestimate them, since they usually refer to extended periods of exposure during only some of which an STD would have been present [Boily & Anderson 1996]. Data from cohort studies in Nairobi [Cameron *et al.* 1989, Plummer *et al.* 1991] have been estimated to be consistent with a 10- to 50-fold increase in the probability of male-to-female HIV transmission per single sexual exposure, and a 50- to 300-fold increase for female-to-male transmission, in the presence of genital ulcers [Hayes *et al.* 1995c]. In simulations of a rural population cohort in Uganda, the assumption most consistent with empirical data was that the probability of HIV transmission per sexual contact was enhanced 100-fold during episodes of ulcerative STDs, and 5-fold during episodes of non-ulcerative STDs [Robinson *et al.* 1997]. Assuming similar cofactor effects in our study, we obtained a satisfactory fit to HIV prevalence and incidence rates observed in the comparison arm of the Mwanza trial cohort, and to the impact of syndromic treatment. Assuming weaker or stronger cofactor effects, the predicted impact of both mass treatment and syndromic treatment would be smaller or larger, respectively (Table 7.3). Some conditions with potentially sizeable cofactor effects, such as *Herpes simplex virus* type-2 (HSV-2) infection and bacterial vaginosis [Sewankambo *et al.* 1997, Spiegel 1991], cannot be effectively treated. At present such infections are not included in *STDSIM*. If incurable STDs are prevalent and their cofactor effects are substantial, we may have overestimated the cofactor magnitudes for curable STDs and, consequently, the impact on HIV incidence of any STD treatment strategy.

The projected impact of mass treatment on HIV incidence was determined by the beneficial effect of comparatively long-lasting decreases in the prevalence of gonorrhoea, chlamydia and chancroid, and the adverse effect on the incidence and prevalence of infectious syphilis occurring soon after mass treatment. In these simulations, including the scenario assuming immediate susceptibility to re-infection after treatment in the latent phase (Figure 7.3b;Table 7.2), the net effect was positive. Yet this may differ according to epidemiological conditions, depending for example on the relative prevalences of syphilis and other curable STDs in a population.

In the investigation of alternative regimens of mass treatment of syphilis, the model predicted a similar long-term impact on HIV incidence if syphilis treatment was excluded from the mass treatment regimen altogether, or if infectious stages of syphilis were covered but latent syphilis remained untreated (Table 7.2).

The first of these scenarios might be achieved if mass treatment consisted of a combination of single-dose oral antibiotics including azithromycin and ciprofloxacin, which would cover all four target STDs except syphilis. Azithromycin may have some effect on active infections with *Treponema pallidum*, but is unlikely to be curative unless given over a longer period [Verdon *et al.* 1994]. The second scenario would be achieved if single-dose benzathine penicillin injections were given only to individuals presenting with the symptoms or signs of a genital ulcer or condylomata lata (a common and highly infectious form of secondary syphilis). This regimen would combine features of mass treatment and syndromic treatment. Its disadvantages would be that genital examination would be required to detect unrecognised ulcers, which is unlikely to be feasible in mass treatment campaigns, and that patients with non-syphilitic ulcers would be treated unnecessarily, including some with latent syphilis. It is of note that the treatment strategy most effective in reducing HIV incidence may not be the best strategy for reducing the disease burden of syphilis at the individual level. Untreated latent syphilis may lead to serious late complications, and in women to perinatal infection and adverse birth outcomes. The design of STD interventions clearly needs to take such ethical considerations into account.

In our projections for the Mwanza population, the impact of a single round of mass treatment on HIV incidence was in the long run much smaller than that of sustained syndromic treatment (Figure 7.5, Table 7.2). However, mass treatment achieved a much steeper initial decline in HIV incidence. From an epidemiological perspective, the effectiveness of mass treatment relative to syndromic treatment depends on the relative contribution to HIV transmission of commonly asymptomatic curable STD, like gonorrhoea and chlamydia, as compared to commonly symptomatic curable STD, like chancroid. This in turn depends on the relative prevalences of these infections and on their cofactor effects (Table 7.3). Other influential factors are the frequency of occurrence and the relative cofactor effects of a symptomatic relative to an asymptomatic course of an episode with a certain STD. Cofactor effects may be stronger for symptomatic than for asymptomatic STD, as suggested by a study of HIV-infected men with urethritis in which viral shedding correlated with the degree of inflammation [Cohen *et al.* 1997]. In our model, identical cofactor effects were assumed for symptomatic and asymptomatic episodes. Thus our projections may underestimate the impact of syndromic treatment, provided that a significant proportion of symptomatic patients would recognize their symptoms and act upon them. This latter effect could however not be explored with the present *STDSIM*, in which the cofactor effect of each STD is assumed to be the same regardless of symptomatology. If both treatment strategies were combined, the short-term decrease in HIV incidence resulting from mass treatment was sustained over time, because individuals experiencing new STD infections could thereafter access syndromic treatment services. This advantage would be particularly strong if syphilis incidence were to increase following mass treatment, as our projections suggest.

A number of comparisons were made between model projections and trial outcomes. The reduction in HIV incidence observed in Mwanza over the two years of follow-up was 38% (95% CI, 15-55) after adjustment for potential confounding variables [Hayes *et al.* 1995a]. In the simulations, a reduction of 30% was achieved over the first 2 years (Table 7.2), which is well within the confidence interval of the trial. Apart from random error, several factors may have contributed to the simulated impact being slightly lower than the point estimate from the trial:

(i) Some reproductive tract infections treated in the Mwanza intervention such as trichomoniasis, candidiasis, bacterial vaginosis and non-specific urethritis were not incorporated in the model;
(ii) Syndromic management in Mwanza covered not only the symptomatic infection presented by the patient but also concurrent, possibly asymptomatic, STDs, but this was not the case in the model;
(iii) The time between infection and cure may in reality have been shorter than assumed, reflecting an improvement in treatment-seeking behaviour in the intervention arm;
(iv) In the simulations, patients were assumed immediately susceptible to re-infection for all STDs considered, and re-infection may therefore have occurred earlier than in reality in some cases;
(v) The model assumed identical cofactor effects for asymptomatic and symptomatic STDs.

On the other hand, omission from the model of untreated STD such as HSV-2, and of immigration and mobility, which re-introduce STD from outside the study population, may have worked in the opposite direction, leading to overestimation of impact on HIV in Mwanza.

In the Rakai trial, periodic mass treatment resulted in only a small and non-significant reduction in HIV incidence (relative risk 0.97; 95% CI, 0.81-1.16) over the first two rounds [Wawer *et al.* 1999], which is much smaller than the reduction in our simulation (36% over 2 years). A number of factors may explain this apparent discrepancy:

(i) Our model fitted the demographic and epidemiological situation in Mwanza rather than Rakai, and the two situations are different. In particular, the HIV epidemic in Rakai has reached maturity, with an HIV prevalence and incidence of 16% and 1.5/100 person-years, compared with 4% and 1/100 person-years in Mwanza. In the later stages of an HIV epidemic, transmission may depend to a lesser extent on the enhancing effect of STDs [Robinson *et al.* 1997];
(ii) Incurable STDs, such as HSV-2, and genital tract infections only temporarily cured by single dose mass treatment, such as bacterial vaginosis, may have played a substantial role in ongoing HIV transmission in Rakai. More than

40% of genital ulcers in Rakai were due to HSV-2 [Wawer *et al.* 1999], and bacterial vaginosis is highly prevalent [Sewankambo *et al.* 1997]. Neither of these infections was incorporated in *STDSIM*;

(iii) In the model, mass treatment was given throughout the population at a single point in time. In Rakai, mass treatment of a cluster of villages took several weeks, as it was delivered at household level in order to achieve high coverage [Wawer *et al.* 1998]. In a situation of extended sexual networks, the time taken to deliver mass treatment may influence the reinfection rate;

(iv) The model ignored inward migration and may have underestimated the rate of re-introduction of infection from outside the study population. Mobility may reduce the long-term impact of STD mass treatment on HIV incidence by increasing STD re-infection rates [Korenromp *et al.* 1998]. In a mass treatment trial for the control of trachoma in The Gambia, ocular chlamydial infection was reintroduced rapidly by returning residents, visitors and migrants, in spite of high coverage and the use of effective antimicrobials [Mabey *et al.* 1998].

Finally, considering the many uncertainties in its determinants, no firm conclusions can yet be drawn on the effectiveness of STD mass treatment for HIV prevention. Our simulations predicted that in a rural African setting in which syndromic STD treatment can reduce HIV incidence, single-round mass treatment may also be effective in the short-term. Mass treatment followed by sustained syndromic treatment would be particularly effective, both in the short and long term. The impact of mass treatment on syphilis is complex and requires further investigation. As we have shown, the impact of mass treatment relative to syndromic treatment depends on the relative prevalence and cofactor effects of symptomatic and asymptomatic curable STD. However, the effectiveness and cost-effectiveness of different STD treatment strategies are also affected by many other epidemiological and non-epidemiological determinants which were beyond the scope of this study. Simulation modelling of alternative STD control strategies in different settings may help to identify those determinants, estimate their relative importance, and identify needs for further empirical research. We will use the *STDSIM* model to address these issues using the population-based longitudinal data of the trials of STD control for HIV prevention in Mwanza, Rakai and Masaka. The results may have major implications for the design of effective STD and HIV control strategies in populations in Africa, Asia and Latin America exposed to high STD prevalences.

7.6 Appendix - Demography and sexual behaviour in *STDSIM*: model structure and parameter values used in the simulation of rural Mwanza

The microsimulation model *STDSIM* simulates the spread and control of HIV and four bacterial STDs (gonorrhoea, chlamydia, syphilis and chancroid) over time in a population consisting of hypothetical individuals in a computer program [Van der Ploeg *et al.* 1998, Korenromp *et al.* 2000c]. Each individual is represented by a number of characteristics, of which some remain constant during simulated life (e.g. sex and date of birth), whereas others change (e.g. number of sexual partners and infection status). Changes in personal characteristics result from events such as the start and end of sexual relationships, or the acquisition of infection. These events are stochastic: if and when an event occurs is determined by Monte-Carlo sampling from probability distributions. Model outcomes for a simulated population are generated by aggregating the characteristics of the simulated individuals. *STDSIM* is event-driven: all events are listed and performed in chronological order. At the occurrence of an event, the characteristics of the individual and/or relationship to which the event pertains are updated. In addition, events can generate new events, which occur either immediately - for example, the death of an individual terminates all relationships of this individual - or later in the simulation - for example, acquisition of HIV infection advances a person's earlier scheduled moment of death.

Aspects affecting the transmission and control of STDs are grouped into six modules. The modules: Transmission, Natural history, Health care and Interventions are described in Section 7.3, subsections 'Biomedical Parameters' and 'Coverage and effectiveness of STD treatment'. Below, we describe the structure and parameter quantification for the modules Demography and Sexual behaviour. For all parameter specifications, the distribution functions, numbers and borders of age groups and values listed are those used to represent rural Mwanza in this chapter. The modeller can however change these in an input file, for example to base assumptions on differently structured datasets, or to do projections for populations with other endemic conditions.

Demography

Fertility is simulated by attributing pregnancies to sexually active females on the basis of user-specified fertility rates. The duration till each subsequent pregnancy in a certain age group a is sampled from an exponential distribution with mean $b_a * F_a(t)$, where: b_a is the user-specified birth rate for age group a and $F_a(t)$ the number of females in age group a at time t. Each new pregnancy is attributed randomly to a female in the age group concerned who is engaged in a sexual rela-

Table 7.A1 **Specification of fertility and mortality among HIV-negatives in *STDSIM*, and parameter values used to represent rural Mwanza.**

Age group (years, upper limits)	Birth rate per woman per year	Survival probability	
		Males	Females
-1	0	0.90	0.90
-5	0	0.85	0.85
-15	0	0.80	0.80
-20	0.143	0.784	0.787
-25	0.288	0.771	0.772
-30	0.270	0.752	0.756
-35	0.239	0.722	0.733
-40	0.192	0.683	0.722
-45	0.097	0.644	0.711
-50	0.040	0.602	0.667
-55	0	0.560	0.622
-60	0	0.506	0.620
-70	0	0.33	0.46
-80	0	0.1	0.2
-90	0	0	0

tionship and not already pregnant. All pregnancies result in life births 9 months after their start. The period of pregnancy can be used to simulate the effects of STD on pregnancy outcomes, for example, still-birth due to syphilis, but this option was not used in the current study. The fertility rates used to simulate rural Mwanza in this study were based on the 1996 Demographic Health Survey of rural Tanzania [Bureau of Statistics & Macro-International 1997] and are listed in Table 7.A1. We assumed half of all births to be males. At the birth of a simulated person, the moment of his or her death is sampled from a stepwise linear life table specifying the proportion still alive at certain ages. For the simulation of rural Mwanza, the lifetable was specified according to mortality estimates for HIV-uninfected individuals in the trial cohort (Table 7.A1) [Todd *et al.* 1997]. If a simulated persons contracts HIV, a moment of HIV-attributable death is sampled from the survival distribution of HIV patients (see Section 7.3, subsection 'Biomedical Parameters' and Table 7.A1). If the moment of HIV-attributable death is earlier than that of non-HIV-attributable death, the actual moment of death is advanced to the former, and this event is recorded as an HIV-attributable death. Although *STDSIM* can simulate migration into and out of the population, this option was not used in this study.

Sexual behaviour

Sexual contacts and relationships between men and women in *STDSIM* constitute a dynamic network through which STDs can be transmitted. We consider three types of (exclusively hetero-)sexual contact: steady relationships ('marriages'); short relationships; and one-off contacts between a small group of females, who may or may not define themselves as prostitutes, and a larger group of males. In the remainder of this Appendix, we will refer to these individuals as prostitutes and clients, respectively.

Formation of relationships is simulated using the concepts of availability for (supply) and search (demand) of new partners [Le Pont & Blower 1991]. Figure 7.AI illustrates this process. New relationships are formed between available men and available women. People become available for relationships for the first time at sexual debut (t_1 in Figure 7.AI). At each subsequent change in the number of current partners, a new duration till availability is determined. This duration (e.g. the interval between t_5 to t_7) may be shorter than the duration of an ongoing relationship (t_5 to the end of the horizon in Figure 7.AI), thus allowing for concurrent relationships (t_8 to t_9). Availability temporarily ends when a new relationship is formed. This happens either when someone is selected by a new partner (t_5 in Figure 7.AI), or when a full 'period of availability' (t_1 to t_2) has elapsed and the person selects a partner from the pool of available people of the opposite sex in a preferred age group (e.g. at t_2). The mechanisms of availability and partner selection do not reflect actual (psychological, behavioural or social) processes,

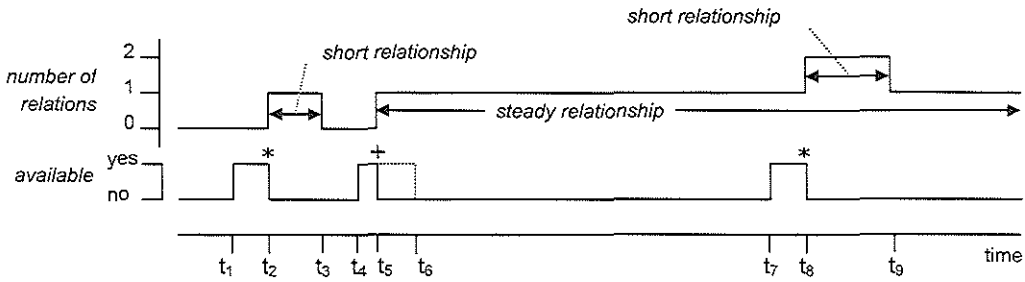

Figure 7.AI. **Example of the relationship history of a young male in *STDSIM*.** The man becomes first available at t_1 (sexual debut). Because he is not selected during his 'period of availability' between t_1 and t_2, he selects a partner himself (*) and starts a short relationship at t_2. This relationship ends at t_3. After a delay, he becomes available again at t_4 for a period which might have lasted until t_6. During availability, the man is selected (+, at t_5) by a female for a steady relationship, which terminates this period of availability (the no longer applicable remainder is indicated with a dashed line). During this relationship, he becomes available again at t_7. After this period of availability, at t_8, he selects (*) a partner for a concurrent short relationship which ends at t_9. On top of the relationships depicted in this figure, one-off contacts with female prostitutes can occur (see text).

but allow us to steer the representation of behaviour from both the male and the female population.

Sexual debut

Sexual debut is defined as the start of a first 'period of availability' for sexual relationships. In the representation of Mwanza, the timepoint of first availability was drawn from a uniform probability distribution with a range of 12-18 years for males, and 12.5-18.5 years for females.

Sexual relationships: availability and partner selection

At each change in an individual's number of current partners, a new duration τ till availability for a new relationship is drawn from an exponential distribution with mean $\delta_{s,r} / (r_{s,a} * p_i)$, where: $\delta_{s,r}$ is the mean duration till availability, which depends on the person's sex (s) and relationship status (r) (currently engaged in a steady, short or no relationship); $r_{s,a}$ is the sex (s) and age (a) group specific promiscuity factor; and p_i is the personal promiscuity level. In this study, the values of $\delta_{s,r}$ were set at 10 and 25 years for males and females, respectively, at the start of a steady relationship; at 2 and 4 years for unmarried males and females, respectively, at the start of a short relationship; and at 0.5 years for both sexes at the end of a last relationship, i.e. if becoming single again. The values of $r_{s,a}$ are listed in Table 7.A2. Every time an individual passes an age border at which an age-specific parameter that affects a waiting time (e.g. $r_{s,a}$) changes value, a new duration is drawn according to the parameter value of the new age group. This applies also to the duration of availability (see below).

The personal promiscuity level p_i of individual i, which reflects the heterogeneity in promiscuity within age groups, is determined by a gamma distribution with mean 1.0 and shape parameter α:

$$f(p_i) = \frac{\alpha}{\Gamma(\alpha)} \cdot (\alpha \cdot p_i)^{\alpha - 1} \cdot e^{-\alpha \cdot p_i} \qquad \text{Eq. (1)}$$

Variation in promiscuity within age groups decreases with increasing values of α. In this study, α equalled 1.5.

While being available for new relationships, an individual can be selected by someone of the opposite sex who has just ended his/her period of availability. If a person has not been selected by the end of his/her period of availability, he/she him-/herself then selects a partner from the pool of available people of the opposite sex. This period of availability is drawn from by an exponential probability distribution with a mean of $\varepsilon / (r_{s,a} * p_i)$, with ε=0.25 yr in this study. See Table 7.A2 for quantification of $r_{s,a}$ and Eq. 1 for p_i.

Table 7.A2 **Values of parameters describing partnership formation in the *STDSIM* representation of rural Mwanza.**

Age group (years)	Age- and sex-dependent promiscuity levels ($r_{s,a}$)		Probability that a new relationship is steady, depending on the age of the male partner	
	Males	Females	Neither partner already in a steady relationship	One or both partners already in a steady relationship
<15	3.5	4.0	0	0
15-19	3.5	4.0	0.1	0
20-24	4.0	2.5	0.3	0.1
34-39	3.0	1.5	0.6	0.15
30-34	2.0	1.0	0.8	0.2
35-44	1.0	0.6	0.8	0.15
45-54	0.4	0.4	0.8	0.1
55+	0.2	0.2	0.8	0.1

Sexual relationships: partner preferences

Partnership formation is guided by age preference matrices (one for each sex, Table 7.A3) specifying the probability to select a partner from a certain age class. In case no potential partner is available in the preferred age class, a partner is selected in another age class by immediate renewed sampling among the remaining age classes for which the preference is larger than zero (e.g. in Table 7.A3a, for males aged 15-19 years: the 3 female classes <24 years, but not the older female age classes). If no partner is available in any of the preferred age classes, the person remains available for another period sampled as described above. This cycle repeats until the person has found a new partner.

As the age preference matrices determine age differences at the start of simulated relationships, the realized age differences in partnerships existing at a single point in time - in which long relationships are relatively overrepresented - do not necessarily match the user-specified preferences. In the present simulations, the matrices specified males to prefer on average 5 years younger females and females on average 5 years older males (Table 7.A3), in line with reported age difference between spouses in Mwanza [Munguti *et al.* 1997]; realized age differences in the model population on cross-section averaged only 2 years. Apart from assortativeness by age, no other preferences apply. Thus, promiscuous individuals have no explicit preference for promiscuous partners.

Types and durations of relationships

The probability that a new relationship is steady depends on whether or not at least one of the partners is already engaged in a steady relationship, and on the age of the male partner (Table 7.A2). At the start of a new relationship its dura-

Table 7.A3 Age preferences in partner selection in the *STDSIM* representation of rural Mwanza. a) males and (b) females.

(a) age of male (years)	age of female (years)							
	<15	15-19	20-24	25-29	30-34	35-44	44-54	55+
<15	0.8	0.2	0	0	0	0	0	0
15-19	0.6	0.3	0.1	0	0	0	0	0
20-24	0.3	0.4	0.2	0.1	0	0	0	0
25-29	0.1	0.25	0.4	0.2	0.05	0	0	0
30-34	0	0.1	0.25	0.4	0.2	0.05	0	0
35-44	0	0	0.1	0.25	0.4	0.2	0.05	0
45-54	0	0	0	0.1	0.25	0.4	0.2	0.05
55+	0	0	0	0	0.1	0.25	0.4	0.25
(b) age of female (years)	age of male (years)							
	<15	15-19	20-24	25-29	30-34	35-44	44-54	55+
<15	0.4	0.3	0.2	0.1	0	0	0	0
15-19	0.15	0.25	0.3	0.2	0.1	0	0	0
20-24	0	0.1	0.2	0.35	0.25	0.1	0	0
25-29	0	0	0.1	0.2	0.35	0.25	0.1	0
30-34	0	0	0	0.1	0.2	0.35	0.25	0.1
35-44	0	0	0	0	0.1	0.2	0.35	0.35
45-54	0	0	0	0	0	0.1	0.3	0.6
55+	0	0	0	0	0	0	0.2	0.8

tion is drawn, in this study from gamma distributions with shape parameter 0.5 and means of 25 years for steady relationships and 0.5 years for short relationships. This distribution function and parameter values were chosen to obtain fit against the data of Mwanza [Munguti *et al.* 1997] for the proportions of males and females married in different age groups (Fig. 7.1a), simultaneously with the total number of partners during the past year of males in different age groups (Fig. 7.1b).

In the current version of *STDSIM*, the frequency of intercourse in relationships varies with the age of the male partner, but does not depend on the number and type of ongoing relationships. For this study, we assumed frequencies of once a week for relationships in which the male was <15 or between 35-54 years of age, 1.5 times weekly for males aged 15-34, and 0.5 times weekly for males aged 55 and over, consistent with data from factory workers in Mwanza town [Borgdorff *et al.* 1994].

One-off contacts / Prostitution

The occurrence of one-off contacts between male 'clients' and female 'prostitutes' is specified by defining a number of frequency classes of prostitute visiting, and

Table 7.A4 **Frequency of prostitute visits of males assumed in the *STDSIM* representation of rural Mwanza.**

frequency (contacts per year)	fraction of unmarried males	fraction of married males
0	40%	70%
1	55%	25%
6	5%	5%

subsequently specifying the proportions of married and unmarried males (up to a maximum age, in this study 50 years) in each class. A personal inclination to visiting prostitutes, assigned to each male at birth, determines to which classes a male belongs for the married and unmarried parts of life. As the inclination remains the same throughout life and does not depend on relationship situation, frequency of prostitute visiting is always the same before and after marriage. For the distribution of males in this study (Table 7.A4), this means that 5% of males visits prostitutes 6 times per year irrespective of marital status. Of the 55% visiting prostitutes once yearly while unmarried, 30% quits this practice upon marriage, but would take up prostitute visiting again in case of divorce. The other 25% visiting prostitutes once yearly does so irrespective of marital status. At each prostitute contact as well as at sexual debut, the time interval till the client's next contact is determined according to the exponential distribution with mean φ, where $1/\varphi$ is the personal frequency of prostitute visits.

Prostitutes are recruited according to the male demand from all sexually active females within a user-specified age range, in this study 15-30 years. A prostitute's 'career' lasts at least 1 year and ends somewhere before a user-specified maximum age (in this study 35 years), according to a uniform distribution. In this study, the frequency of client contacts per prostitute averaged 1 per week. In the absence of adequate data, we believe this is not unreasonable for rural Mwanza, and it allowed us to achieve adequate fit of numbers of partners of males - which includes each one-off contact as a separate partner - (Figure 1b) and STD epidemiology (Figures 2 and 3). In this study, client contacts were divided over the pool of prostitutes in time order.

Each year, the model checks, and - if necessary - adapts the number of prostitutes to match the user-specified frequency number of client contacts per prostitute as closely as possible, given the number of visits by clients and the frequency of client contacts of prostitutes. If the number of prostitutes is too small, additional women are recruited. If the number of prostitutes is too large, a randomly selected prostitute terminates her career before the scheduled date. In addition, every time a woman in the starting age range (15-30 years) becomes widowed (i.e. loses a steady partner), a similar check for the number of prostitutes is per-

formed; and if there is a shortage, the widow is recruited as a prostitute.

Start of the simulation

At start of a simulation, an initial population is created; the population used in this study is given in Table 7.A5. All individuals start as singles; formation of sexual relationships and one-off contacts then occurs as described above. STD infections are attributed to the initial population at user-specified prevalences, in this study 3.5% for gonorrhoea, 5% for chlamydia, 9% for syphilis and 1.2% for chancroid. Initial STD infections are randomly distributed only among individuals with a high individual promiscuity level (p_i>1) who have had their sexual debut. Simulations are started in a user-specified year (here 1930) well in advance of the introduction of HIV. This allows the model population to reach dynamic equilibria with respect to demography, partnership formation and STD epidemiology, before the simulated start of HIV spread. Neither the chosen composition of the initial population nor the user-specified STD rates in the initial population are critical to the situation of equilibrium. HIV is introduced into the model population by randomly infecting one prostitute, in a user-specified year (here 1983). In applications of the model in which one-off contacts are not assumed, HIV introduction occurs by simultaneous infection of 10 sexually active males and 10 sexually active females in the general population.

Table 7.A5 **Specification of the initial population (in absolute numbers) in *STDSIM*, and values used to represent rural Mwanza, for starting year 1930.**

Age group (years)	Males	Females
0 - 9	500	500
10 - 19	375	375
20 - 29	223	223
30 - 39	150	150
40 - 49	100	100
50 - 59	80	80
60 - 69	40	40
70 - 79	20	20
80 - 89	10	10

chapter 8

HIV/STD dynamics and behaviour change as determininants of the impact of STD treatment on HIV spread over the Rakai epidemic

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8.1 SUMMARY

Objective: To assess how the impact of STD treatment on HIV incidence varies between stages of the HIV epidemic.
Methods: We simulated the spread of curable STDs, herpes simplex virus type 2 and HIV in the dynamic transmission model *STDSIM*. Parameters were quantified to represent a severe HIV epidemic as in Rakai, Uganda, using demographic, behavioural and epidemiological data from its recent STD treatment trial.
Results: The model fitted the HIV epidemic in Rakai adequately if we assumed a considerable behavioural risk reduction starting at the end of the Ugandan civil war in 1986. Improvement of STD treatment was projected to reduce HIV incidence in this population by 35% over 2 years if implemented in 1981, but by only 11% and 8% in 1988 or 1998. This trend resulted in part from the hypothesized behaviour change, which markedly reduced the prevalences of bacterial STDs. In a simulated epidemic without behavioural change, the corresponding impacts in 1988 and 1998 would be 19% and 15%. Enhanced herpetic ulceration in immunocompromised HIV-patients contributed little to the falling impact of treatment of bacterial STDs over time.
Conclusions: In HIV epidemics beyond the first decade, the impact of STD treatment programmes on HIV transmission may depend more on whether a behavioural risk reduction occurred, than on the stage of the epidemic. Preceding behavioural change associated with civil stability may have contributed to the lack of impact of STD treatment on HIV in the Rakai trial. In advanced epidemics with less behaviour change, STD treatment may still be important in HIV prevention.

8.2 INTRODUCTION

Epidemiological and clinical studies suggest that the sexually transmitted diseases (STDs) act as cofactors for the sexual transmission of HIV [Moss & Kreiss 1990, Laga *et al.* 1991, Wasserheit 1992, Fleming & Wasserheit 1999]. If STDs are highly prevalent, as in sub-Saharan Africa, and STD cofactor effects are strong, improved treatment of STDs may be a strategy for HIV prevention. The effectiveness of STD treatment for HIV prevention has been tested in two randomized community-based trials in Uganda and Tanzania, which had very different outcomes [Wawer *et al.* 1999, Grosskurth *et al.* 1995a]. Improved clinical management of symptomatic STD treatment in Mwanza, Tanzania, was associated with a reduction in HIV incidence by 38% (95% confidence interval 15% - 55%) over 2 years [Hayes *et al.* 1995a, Grosskurth *et al.* 1995a]. Over a same interval, and with comparable proportional reductions in the treated STDs, periodic mass treatment in Rakai, Uganda did not reduce HIV incidence (i.e. a 3% HIV incidence

reduction, 95% CI -16% to 19%) [Wawer *et al.* 1999].

Several explanations have been proposed for this apparent discrepancy, including differences in the treatment strategy, study populations and the stage of the HIV epidemic, study design, and random chance [Wawer *et al.* 1999, Fleming & Wasserheit 1999, Grosskurth *et al.* 2000, Hudson 2001]. Among differences between the populations, one factor may be that STD cofactors play a larger role in early, concentrated HIV epidemics - as in Mwanza - than in mature epidemics - as in Rakai. Early in HIV epidemics, infections are thought to take place primarily in core groups of highly sexually active individuals, who have high rates of STDs. Later in HIV epidemics, more HIV transmissions will occur in stable relationships between low-risk individuals, few of whom have STDs. An additional mechanism may be that, due to selective HIV-attributable mortality among high-risk individuals, STD prevalences in the population fall over the evolution of the HIV epidemic [Korenromp *et al.* 2000c].

The decreasing importance of STD cofactors during the HIV epidemic has been demonstrated in several modelling studies, in which the impact of hypothetical programmes was simulated for various time points in the HIV epidemic [Robinson *et al.* 1997, Korenromp *et al.* 1999b]. However, two aspects that may influence the role of STD cofactors were not taken into account in these studies. First, besides curable bacterial STDs targeted by STD treatment, the uncurable infection with herpes simplex virus type 2 (HSV-2) may act as a cofactor in HIV transmission. HSV-2 is highly prevalent in SSA populations with severe HIV epidemics, and its prevalence may be increasing due to increased reactivation in immunocompromised AIDS patients [Wasserheit 1992, O'Farrell 1999], possibly reducing the relative importance of curable STDs in HIV transmission. Second, it is becoming increasingly clear that several SSA countries, including Uganda, have experienced or are experiencing reductions in sexual risk behaviour, including decreases in casual sex and in prostitution, and increases in condom use [Ng'weshemi *et al.* 1996, Jackson *et al.* 1997c, Konde-Lule *et al.* 1997, Asiimwe-Okiror *et al.* 1997, Kilian *et al.* 1999, Kamali *et al.* 2000, Gregson *et al.* 1998, Meekers 2000, Fylkesnes *et al.* 2001]. Since such behaviour change will cause the prevalence of short-duration STDs like gonorrhoea, chlamydia and chancroid to fall [Korenromp *et al.* 2001a], it may also reduce the importance of these curable cofactors in HIV spread.

In this chapter, we assess how the impact of STD treatment on HIV transmission would vary over time during the Rakai HIV epidemic, taking into account the role of HSV-2 in ongoing HIV transmission and behavioural change. We used the dynamic transmission model *STDSIM* [Van der Ploeg *et al.* 1998, Korenromp *et al.* 2000b] to simulate the spread of HIV, curable STDs and HSV-2 in the Rakai population. To distinguish the influence of behaviour change from that of natural HIV/STD dynamics, we also simulated a hypothetical Rakai-like population without a behaviour change. The simulated intervention was syndromic STD treatment, which was felt most interesting with respect to the discrepant results and

policy implications of the Mwanza and Rakai trials. We discuss the importance of the respective phases of the HIV epidemics in the Mwanza and Rakai trials as an explanation for their discrepant outcomes, in the light of the simulation outcomes.

8.3 METHODS

STDSIM model

STDSIM simulates the natural history and transmission of STDs and HIV, in a dynamic population consisting of individuals with assigned characteristics that change over time [Korenromp *et al.* 2000b, Korenromp *et al.* 2000c]. The formation and dissolution of heterosexual partnerships and transmission of STDs during contacts between sexual partners, are modelled as stochastic events. Recently, the model was adapted to include the simulation of genital infection with HSV-2 and the effects of HIV infection on the natural history and transmission of HSV-2 [Korenromp *et al.* accepted]. The adapted model allowed us to study the impact of STD treatment on HIV spread, in varying scenarios of interactions between STDs and HIV.

Simulated populations

The simulation of the Rakai HIV/STD epidemic was based on data collected in the context of the STD treatment trial and preceding cohort studies [Wawer *et al.* 1991, Wawer *et al.* 1994, Wawer *et al.* 1997, Serwadda *et al.* 1992]. Some additional quantifications followed from previous simulations [Korenromp *et al.* 2000c] of the trial in Mwanza, which also involved a rural population [Grosskurth *et al.* 1995a, Grosskurth *et al.* 2000]. Few data are available on sexual behaviour in either Rakai or Mwanza prior to 1988. Two assumptions were made to explain the much higher prevalence of HIV in Rakai (15-25% [Serwadda *et al.* 1992, Wawer *et al.* 1997]) as compared to Mwanza (2.5% [Barongo *et al.* 1992]) in 1988. First, we estimated that HIV spread started relatively early in Rakai. Because the time of HIV introduction in Uganda is not precisely known and the first AIDS cases were observed in Rakai in 1982 [Serwadda *et al.* 1985, Sewankambo *et al.* 1987], this timepoint was set at 1978, i.e. around the time of the Tanzanian invasion which marked the start of the Ugandan civil war. Second, we assumed that partner change rates had been higher in Uganda during the period of civil war between 1978 and 1986, due to social disruption, relative to Tanzania. Compared to the first Ugandan surveys around 1988, behavioural risk reductions have been observed during the 1990s, including reductions in numbers of partners,

increased condom use, and possibly delays in the age of first sex [Konde-Lule *et al.* 1997, Asiimwe-Okiror *et al.* 1997, Kilian *et al.* 1999, Kamali *et al.* 2000, Ministry of Health *et al.* 1989, Statistics Dept. Uganda 1996]. There is anecdotal evidence that in Rakai, commercial sex had become less common in the 1990s as compared to the 1980s [Serwadda *et al.* 1992]. These changes are compatible with the restored stability after the end of the Ugandan civil war, and the adoption of a national AIDS control policy including IEC programmes and voluntary HIV testing and counselling. In line with earlier models of Uganda [Stoneburner *et al.* 1996, Kilian *et al.* 1999], the behavioural change was represented in *STDSIM* as a 50% reduction in the proportion of males having one-off sexual contacts with female sex workers after 1986. In addition, a 25% reduction in partner change rates in the whole population was assumed after this time point. This quantification resulted in adequate fit of the model with respect to proportions married, numbers of recent partners of males, and age/sex patterns in data from the trial baseline survey (not shown). In addition, we simulated a hypothetical Rakai-like population in which the assumed behavioural changes in 1986 were omitted.

Assumptions on STD natural history and transmission

The *STDSIM* representations of the natural history and transmission of curable STDs were based on literature review [Korenromp *et al.* 2001a] and are summarized in Table 8.1.

The representation of HSV-2, which resulted in realistic age/sex patterns in simulated HSV-2 seroprevalence, has been described elsewhere [Korenromp *et al.* accepted]. In brief, the infection was specified to start with a primary ulcer lasting on average 3 weeks [Cone *et al.* 1991, Koelle *et al.* 1992, Corey *et al.* 1983]. After healing of this lesion, symptomatic and asymptomatic ulcers were assumed to recur at an average 6 months interval [Wald *et al.* 2000, Langenberg *et al.* 1989] for a period of on average 15 years denoted as the 'early latent stage'. In line with their relative clinical severity [Corey *et al.* 1983], herpetic recurrences were assumed to be less severe in terms of perceived symptoms, infectivity and cofactor effects on HIV transmission than primary ulcers. In between recurrences, a low continuous level of infectivity was assumed which represented the regular occurrence of sub-clinical HSV-2 shedding [Adam *et al.* 1979, McCaughtry *et al.* 1982, Wald *et al.* 1997]. At the end of the HSV-2 'early latent stage', patients were assumed to no longer suffer recurrences nor to be infectious, but to remain seropositive for life.

HIV infection was specified as four subsequent stages, named primary HIV infection, asymptomatic (latent) stage, symptomatic pre-AIDS stage, and AIDS. It was assumed that symptomatology [Morgan *et al.* 1997b] and effects on herpetic ulcerations (see below), differed with HIV progression. HIV transmission

Table 8.1 **Representation of natural history and transmission of HIV and STDs in the *STDSIM* simulation of the Uganda HIV epidemic.**

Infection & stage	Mean duration[1]	Transmission probability [2]		Cofactor effect on HIV transmission[2,3]	Proportion symptomatic	
		M→F	F→M		M	F
HIV						
Primary	10 weeks	0.045	0.015	na	na	na
Asymptomatic	5 years	0.00225	0.00075	na	na	na
Symptomatic pre-AIDS	2 years	0.00225	0.00075	na	na	na
AIDS	40 weeks	0.01125	0.00375	na	na	na
Syphilis						
Infectious	6 months	0.3	0.2	10x	80%	50%
Latent	15 years	0	0	na	na	na
Chancroid	10 weeks	0.20	0.15	25x	90%	70%
HSV-2						
Primary ulcer	3 weeks	0.30	0.15	25x	30%	
Early latent (with recurrent ulcers)	15 years[4]	0.005[4]	0.0025[5]	na[5]	na[5]	na[5]
Recurrent ulcer	1 week[4]; Interval between ulcers: 6 months[4]	0.20	0.10	10x	15%	7.5%
Late latent	Lifelong	0	0	na	na	na
Gonorrhoea	M 9 weeks; F 13 weeks	0.22	0.15	5x	50%	20%
Chlamydia	M 12 weeks; F 16 weeks	0.20	0.12	5x	30%	15%

[1] Individual stage durations were sampled from a Weibull distribution function with shape parameter 2, except for the duration of the early latent stage of HSV-2 and the interval between recurrent HSV-2 ulcers, which used exponential distribution functions. [2] Per contact; equal for recognized and unrecognized episodes. [3] Both for susceptibility (in HIV-negative partner) and infectivity (in HIV-positive partner). [4] Except in symptomatic HIV patients, for whom the values are 30 years, 2 weeks, and 3 months. [5] Except during recurrent ulcers. M = male; F = female; na = not applicable.

probabilities were modelled in a 'bath-tub' pattern, with infectivity being highest during primary HIV disease and, secondly, during AIDS [Jacquez *et al.* 1994, De Vincenzi 1994, Quinn *et al.* 2000, Gray *et al.* 2001].

Biomedical interactions between STD and HIV

We assumed that STDs enhance the infectivity with HIV and the susceptibility to HIV, by a factor varying with the disease stage (Table 8.1). In the absence

of knowledge on STD cofactor magnitudes from experimental studies, we estimated these variables from mathematical calculations based on observational studies among commercial sex workers and clients in Nairobi [Hayes *et al.* 1995c, Korenromp *et al.* 2001b]; the resulting cofactor values were lower than those assumed in previous simulations [Korenromp *et al.* 2000c]. The relative cofactor magnitude for the different ulcerative STDs were chosen in line with their relative clinical severity. For the infectious stage of syphilis during which several ulcer episodes may occur intermittently [Holmes *et al.* 1999], an average cofactor effect of 10-fold was applied throughout. Chancroid and primary HSV-2 were assumed to enhance HIV transmission 25-fold, but only for the duration of the ulcer.

HIV disease may enhance the frequency and duration of herpetic ulcerations, as is inferred from studies observing 3- to 4-fold increases in the number of HSV-2 culture-positive days [Augenbraun *et al.* 1995, Schacker *et al.* 1998, Mbopi-Keou *et al.* 1999] and increases in the incidence rate of clinical ulcers [Kaul *et al.* 1997, Schacker *et al.* 1998]. In line with these data, we assumed that during the symptomatic stages of HIV infection (Table 8.1), the duration and the frequency of recurrent herpetic ulcers are doubled.

Simulation of STD intervention

The simulated STD intervention increased the cure rate of symptomatic episodes of gonorrhoea, chlamydia, syphilis and chancroid from 5% to 38% [Buvé *et al.* 1998]. As a simplification in the model, only the symptomatic STDs for which the patient sought treatment was cured; concurrent asymptomatic infections were not. The simulated intervention was initiated in 1981, 1988 or 1998 (the 3rd, 10th or 20th year of the simulated HIV epidemic), and was sustained throughout the simulation period.

Simulation design

Simulations were done for several scenarios: (a) Rakai; (b) hypothetical Rakai-like population without behaviour change; (c) Rakai with STD intervention implemented in year 3, 10 or 20 of the HIV epidemic; (d)) hypothetical Rakai-like population without behaviour change, with STD intervention in year 3, 10 or 20 of the HIV epidemic. In order to reduce random fluctuations associated with stochastic simulations, for each scenario 100 simulation runs were conducted. All outcomes are reported as averages over 100 runs in the general adult population aged 15-49 years.

Sensitivity analyses

To assess the robustness of results, we repeated simulations for alternative quantifications of parameters known to affect the rapidity of saturation of HIV epidemics and interactions between STDs and HIV. In addition to the parameter of interest, in each alternative simulation, the transmission probability of HIV was re-adjusted, if necessary, to fit the 16% point prevalence of HIV in Rakai at start of the trial in 1995.

8.4 RESULTS

Figure 8.1 shows the simulated prevalences of curable STDs and HSV-2 during the HIV epidemic in Rakai and in the population without behaviour change. The simulated Rakai epidemic fitted data from the trial reasonably well with respect to the prevalence of gonorrhoea, chlamydia and syphilis (Figure 8.1a-d). Also, the simulated stage distribution in syphilis cases [Wawer *et al.* 1999], and age- and sex-specific seroprevalences of HSV-2 matched the empirical data (not shown). After 1986, STD prevalences fell in the Rakai simulation, following the assumed behavioural risk reduction (Figure 8.1a-e). The simulated decline in syphilis prevalence matched that observed in Rakai between 1992 and 1996, although it was somewhat earlier. The prevalence fall in the model was fastest and largest for chancroid. Because chancroid has the lowest reproductive number [Brunham & Plummer 1990], behavioural change will have most impact on this STD; however no empirical data are available on *Haemophilus ducreyi* to validate this prediction. The decline was comparatively slow and small for HSV-2 seroprevalence (from 48% to 40%), for two reasons. Since HSV-2 is a lifelong infection with a high baseline prevalence and recurrent nature, a reduction in herpetic ulceration can only follow from reductions in new infections in the youngest age groups. Therefore, reduced HSV-2 transmission takes a long time to impact HSV-2 seroprevalence at a population level. Furthermore, the behavioural effect is to some extent counterbalanced by the assumed enhancement of herpetic ulceration in HIV patients, which increases HSV-2 transmission.

HIV prevalence in the Rakai simulation peaked at 16% around 1990. Therafter, it stabilized and started a slow decline (Figure 8.1f), in line with trends in risk behaviour and epidemiological observations in Rakai [Wawer *et al.* 1991, Wawer *et al.* 1997] and other parts of Uganda [Mulder *et al.* 1995, Kamali *et al.* 2000, Kilian *et al.* 1999, Stoneburner *et al.* 1996].

In the hypothetical population without behavioural change, prevalences of the bacterial STDs also slightly fell during the 1990s (Figure 8.1a-d), due to selective HIV-attributable mortality in high-risk groups. The simulated prevalence of HSV-2, in contrast, remained stable at around 47% throughout the HIV epidemic

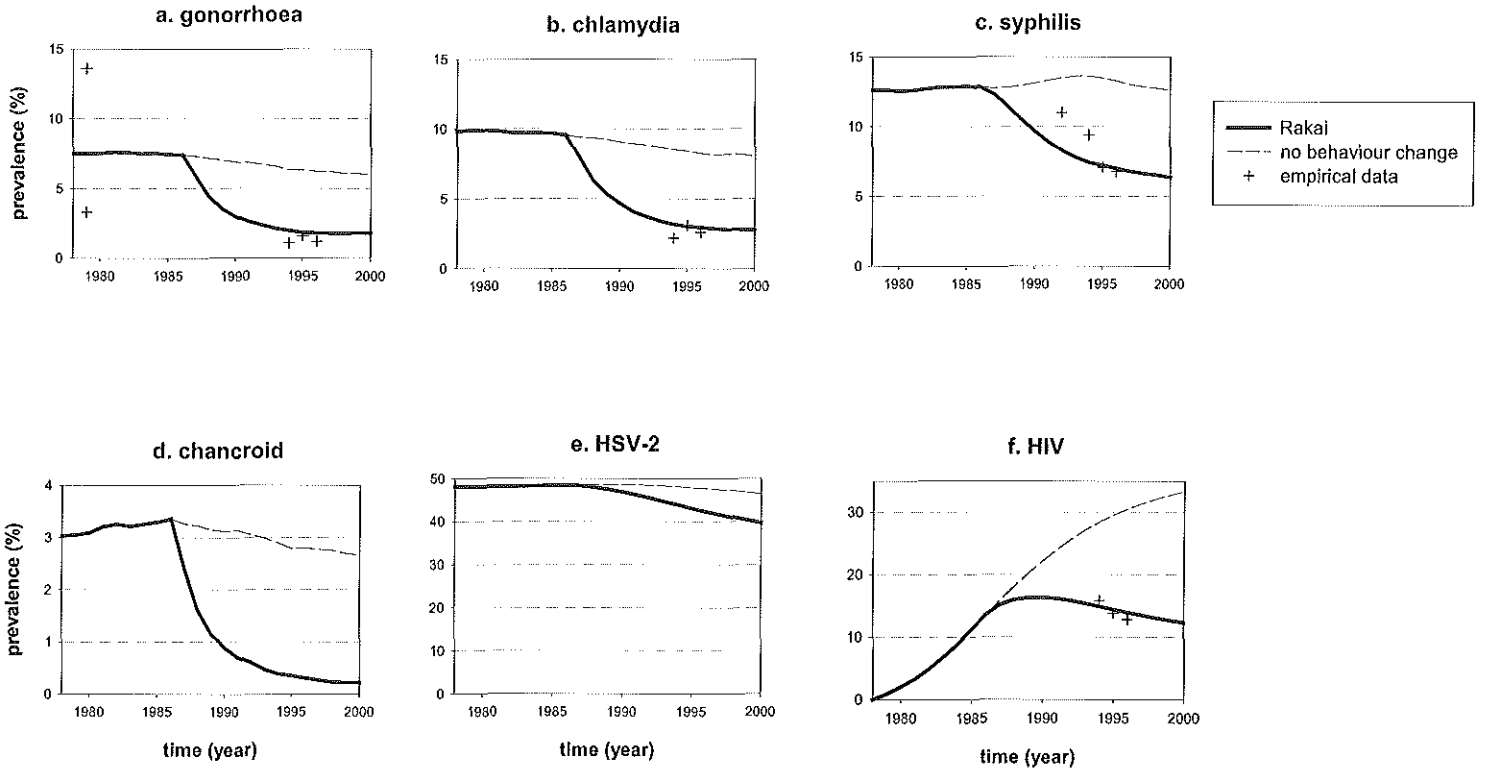

Figure 8.1 **Simulated prevalences (%) of STDs and HIV in adults (15-49 years), for rural Rakai and a hypothetical Rakai-like population without a behaviour change.** Syphilis: $RPR^+/TPHA^+$ any titer [Wawer *et al.* 1999]; HSV-2: seroprevalence. Mean of 100 simulated populations. Empirical data, for comparison, for 1992-1996 from the comparison arm of the STD treatment trial at baseline and pre-trial cohort studies in Rakai; for gonorrhoea and chlamydia 1994-6: subsample aged 15-29 years; gonorrhoea data 1979: random subsamples of general population in 1971-2 in rural Ankole and Teso districts [Arya *et al.* 1973].

(Figure 8.1e), due to the counterbalancing effect of enhanced herpetic ulceration in HIV patients. In the absence of behaviour change, HIV prevalence continued to increase till after 2000, albeit at decreasing pace (Figure 8.1f). HIV incidence stabilized earlier, around 1995 (Figure 8.2c). This reflects a saturation due to HIV viral dynamics: later in the HIV epidemic, fewer HIV patients are in the primary, most infectious, disease stage, and most new infections occur outside the high-transmitter core groups.

Impact of STD treatment over time

In the population with unchanged behaviour, improvement of STD treatment reduced the prevalences of curable STDs considerably; the magnitude of these reductions was independent of the timepoint of implementation (Figure 8.2a).

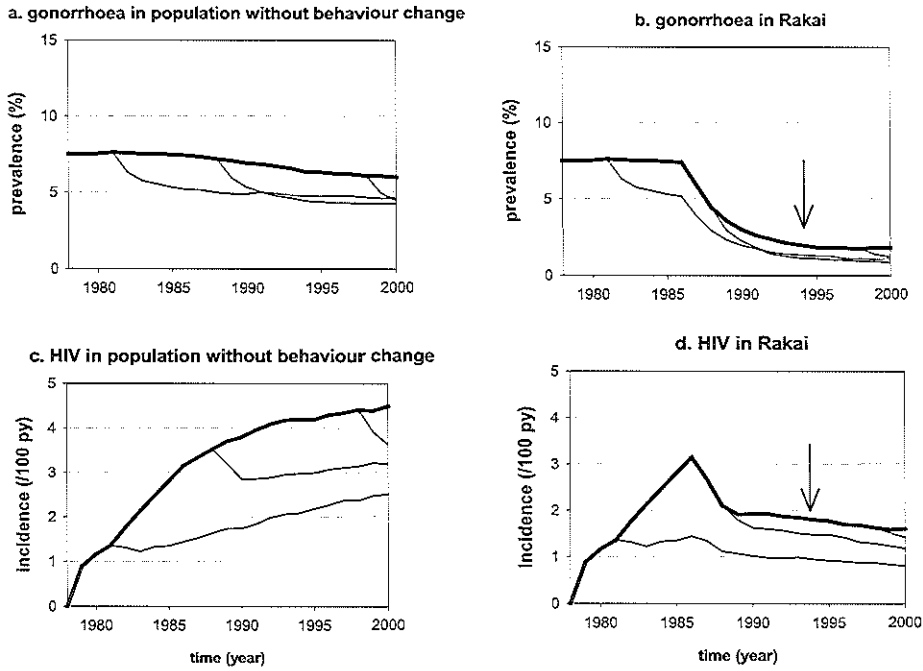

Figure 8.2 **Simulated impact of improved STD treatment intervention implemented in different stages (year 3, 10 and 20) of the HIV epidemic on: (a) gonorrhoea prevalence (%) in population without behaviour change, (b) gonorrhoea prevalence (%) in Rakai (c) HIV incidence (/100 person-years) in population without behaviour change, (d) HIV incidence (/100 person-years) in Rakai, in adults (15-49 years). Mean of 100 simulated populations.** The arrows in figures (b) and (d) indicate the timing of the actual trial in Rakai.

In the Rakai simulation, the intervention caused STD prevalences to decrease at rates comparable to those in the population without behaviour change, if implemented in 1981. After 1986, the combination of improved STD treatment and behavioural change achieved lower equilibrium prevalence levels for all STDs than in the simulation without changing behaviour (Figure 8.2b). Other curable STDs showed similar responses to STD treatment as gonorrhoea, but the prevalence of HSV-2, which is not curable, was unaffected by improved syndromic treatment (not shown).

The impact of the simulated intervention on HIV incidence varied with the timepoint of implementation. In the population without behaviour change, with implementation in 1981, improved STD management slowed - but did not stop - the projected increase over time in HIV incidence (Figure 8.2c). If STD management was implemented at later times, when HIV incidence had already exceeded 3 per 100 person-years, the intervention resulted in a decrease in HIV incidence to approximately 3 per 100 person-years. In the Rakai simulation, impact on HIV of the intervention in 1981 was initially comparable to that in the population without behavioural change (Figure 8.2d). At start of the behavioural change in 1986, the combination of these two interventions would result in a stabilization of HIV incidence at around 1 per 100 person-years. With implementation at later stage of the HIV epidemic more close to the timing of the actual trial in 1995 (arrow in Figure 8.2), STD treatment decreased HIV incidence to this same equilibrium level, but over a longer time period.

For comparison with the Rakai and Mwanza trial outcomes, we calculated the simulated intervention impact as the proportional reduction in HIV incidence over the first 2 years of the intervention. In the model, the STD intervention reduced HIV incidence over the first 2 years by 35% if implemented in 1981. However, when implemented in 1988 or 1998, the reduction in HIV incidence fell to 19% or 15%, respectively, in the simulation without behaviour change. In the Rakai epidemic, simulated impact in the 10th and 20th year of the HIV epidemic was 11% or 8%, respectively.

Sensitivity analyses

Table 8.2 shows the simulated impact of STD treatment for alternative scenarios varying in the quantification of possibly critical parameters. Across all scenarios, the fall in impact in the absence of behaviour change was largest between years 3 and 10. After year 10, falls over time in impact were always much larger for the Rakai epidemic than for the population with unchanged behaviour. This supports the robustness of these conclusions with respect to the Rakai simulations.

To single out the influence of the dynamics of HSV-2 infection during the HIV epidemic on the impact of treatment of bacterial STD, separate simulations were run in which HSV-2 was omitted as a cofactor for HIV, or in which herpetic ulcer-

Table 8.2 **Sensitivity analysis on the proportion (%) of new adult HIV infections averted by improved STD treatment implemented in year 3, 10 or 20 of the HIV epidemic in Uganda and a Uganda-like population without behaviour change.** Evaluation period is the the first two years of implementation of the intervention. Simulations are shown for the base-case as well as for alternative scenarios differing in the values of critical parameters. Base-case outcomes correspond to the results shown in the Figures. Outcomes are the mean of 100 simulated populations.

Scenario	Assumptions	Proportional reduction in HIV incidence over 2 years				
			population without behaviour change		Rakai	
		year 3	year 10	year 20	year 10	year 20
Base-case	**(see Table 8.1)**	**35%**	**19%**	**15%**	**11%**	**8%**
Lower/higher cofactors	Gonorrhoea/chlamydia: 2x Syphilis/recurrent HSV-2: 5x Chancroid/primary HSV-2: 10x	31%	16%	12%	7%	4%
	Gonorrhoea/chlamydia: 10x Syphilis/recurrent HSV-2: 30x Chancroid/primary HSV-2: 100x	44%	27%	22%	17%	10%
HSV-2 less/more important	HSV-2 removed as cofactor for HIV transmission	38%	20%	17%	15%	8%
	HSV-2 stronger cofactor effects: Primary ulcers: 100x; Recurrent ulcers: 25x	32%	16%	11%	8%	4%
No/stronger bathtub pattern in HIV infectivity over the course of infection	Constant HIV infectivity ('no bathtub')	39%	18%	13%	12%	5%
	Primary HIV 100x (instead of 20x) and AIDS 20x (instead of 5x) as infective as asymptomatic / pre-AIDS phase.	30%	22%	17%	11%	5%

ations were a more important cofactor than the bacterial ulcers. In both alternative scenarios, the fall in impact of STD treatment during the HIV epidemic was similar to the base-case.

8.5 DISCUSSION

The simulations confirmed that the proportion of new HIV infections that can be prevented with STD treatment decreases during the evolution of severe HIV epidemics. In populations with unchanged risk behaviour, the most marked decline in impact occurs with STD intervention over the first 10 years of the epidemic (Table 8.2). This relates mainly to a rapid initial change in the types of relationships in which most new HIV infections take place: from high-risk partnerships of short duration between individuals among whom STDs are prevalent, to stable relationships with a higher sexual contact frequency and lower concurrent STD exposure. Previous simulations suggested this outcome to hold true for a range of populations with varying patterns of sexual behaviour [Korenromp *et al.* 1999b, Robinson *et al.* 1997]. Furthermore, our sensitivity analysis (Table 8.2) supports that this conclusion is robust across a range of scenarios varying in HIV/STD transmission dynamics and the rapidity of saturation of the HIV epidemic.

The simulated slight decline in STD prevalences over time in the scenario without behaviour change (Figure 8.1a-d) indicates that selective HIV-attributable mortality contributes only modestly to the changing impact of STD treatment. Magnitudes of STD declines during HIV epidemics have however not been measured empirically, precluding a validation of this model prediction [Korenromp *et al.* 2001a]. The sensitivity analyses suggest that the dynamics of HSV-2 spread also contribute little to the falling impact of treatment of bacterial STDs on HIV incidence during the HIV epidemic. In line with this, HSV-2 seroprevalence increased little due to increased herpetic ulceration in HIV patients (Figure 8.1e). This is firstly because the majority of HSV-2 patients are not HIV-infected, because of the high prevalence of HSV-2 (48%) relative to HIV (around 16%), and those who are infected die earliest, which limits concurrent infection with HIV and HSV-2. Furthermore, the majority of partners of HSV-2/HIV patients are already infected with HSV-2, so that increased infectivity does not always increase HSV-2 transmission in the population. The predicted stability of HSV-2 seroprevalence throughout the simulated HIV epidemic is in line with the similar HSV-2 seroprevalences measured in the severe, mature HIV epidemic in Rakai and the earlier, less severe epidemic in Mwanza [Orroth *et al.* 2001]. Although the simulated prevalence of herpetic *ulcers* increased relatively more than HSV-2 seroprevalence (from 2.1 to 3.3 in the scenario without behaviour change between years 3 and 20), this increase was insignificant at a population level.

The simulations suggest that behavioural risk reduction as occurred in Uganda after the end of its civil war is a powerful determinant of the HIV epidemic and of the potential impact of subsequent STD treatment programmes on HIV spread (Table 8.2). By reducing the prevalences of curable STDs, behavioural risk reduction limits the importance of STD cofactors in HIV transmission. An additional mechanism is that, following a reduction in high-risk contacts, an increasing proportion of HIV transmissions will take place in lower-risk, stable relationships, in which due to the longer duration and more regular sexual contact, HIV is likely to be transmitted regardless of cofactor STDs. Importantly, the effect of behavioural risk reduction on the impact of STD treatment programmes may occur at any stage of the HIV epidemic.

Caution is however warranted in the interpretation of this model outcome. Although a number of data sources from Uganda indicate that a rapid decline in risk behaviours has occurred, and this effect would be consistent with the end of the civil war and sociopolitical stabilization after 1986, the actual magnitude of this change is not known. For the period 1970s through late 1980s, data are lacking. Behavioural surveys conducted in later years have methodological limitations, such as cross-sectional design, varying sampling frames, and weak measures of risk, e.g. 'ever use' of condoms. Outcomes are also prone to reporting biases, which may have changed over time as an effect of the very health education programmes which advocated behavioural change - obscuring actual trends. Although there was almost certainly substantial behavioural change after 1986, it is impossible to determine the relative contributions of the end of the civil war and the contemporaneous implementation of the national AIDS Control program. Finally, although the assumed time trends in risk behaviours resulted in adequate fit of observed HIV and STD epidemiological patterns, we cannot exclude the possibility that in reality other mechanisms ignored in the model contributed also to these patterns. For example, the model did not allow for changes in HIV infectivity over time, by which the virus may have been more virulent and infectious in the early years of the epidemic than it is currently [Ewald 1994]. Due to such effects, we may have overestimated the extent the effects of risk behaviour in Uganda in the early 1980s and/or and the magnitude of the consequent subsequent risk reduction.

Implications for the interpretation of the Mwanza and Rakai trials

Our results shed light on the discrepant outcomes between the Rakai and Mwanza trials, if we consider their timing relative to the onsets of the respective HIV epidemics. For Rakai, we estimated the trial started at around the 17th year of the HIV epidemic; and for Mwanza, assuming HIV spread to have begun around 1983 [Korenromp *et al.* 2000c], we situate the trial in 1992-4 to have been around the 10th year of the epidemic. The expected influence of this differ-

ence in HIV epidemic on the impact of STD treatment is approximated by the difference between the simulated 19% and 15% HIV reduction in years 10 and 20 for the population without behaviour change, and by the difference between 11% and 8% HIV reduction in years 10 and 20 for Rakai. Thus, it appears that the stage of the epidemic on its own cannot fully explain the discrepancy in observed impacts of STD control between Mwanza and Rakai (38% and 3% reduction in HIV incidence, respectively). However, if we also consider the behavioural risk reduction in Uganda [Konde-Lule *et al.* 1997, Asiimwe-Okiror *et al.* 1997, Kilian *et al.* 1999, Kamali *et al.* 2000, Ministry of Health *et al.* 1989, Statistics Dept. Uganda 1996] and the apparent absence hereof in Mwanza [Grosskurth *et al.* 1995a], the simulated difference in impact (19% reduction for a population without behaviour change in year 10 vs. 8% in Rakai in year 20) is more comparable with the actual discrepancy between the trials. The simulated 8% impact for Rakai in year 20 is in line with the observed 3% HIV incidence reduction in the trial, the slight excess simulated impact being possibly due to random chance (the 95% confidence interval around the empirical estimate was -16% to 19%). It is of note that the excess simulated impact is unlikely to be due to the difference in simulated and actual type of STD treatment (syndromic treatment vs. periodic mass treatment), because the simulated STD prevalence reductions (Figure 8.2b) approximated the actually observed STD reductions in the mass treatment trial [Wawer *et al.* 1999].

Model fit was less satisfactory with respect to the simulated impact of STD treatment in the 10th year of the HIV epidemic with unchanged behaviour (19%) in comparison to the outcome of the Mwanza trial (38%) - although the simulation still fitted the empirical confidence interval of 15-55%. Considering the similarity between simulated and observed magnitudes of STD reductions (Figure 8.2 and [Mayaud *et al.* 1997a]), the following factors are the most likely contributors to this sub-optimal fit:

- The model represented the behavioural and epidemiological situation in Rakai rather than Mwanza, and these two situations were different also in other aspects than those discussed above. Notably, in the 10th year of the respective HIV epidemics, HIV prevalence in Rakai had reached and was stabilizing at a 16% prevalence [Wawer *et al.* 1991, Wawer *et al.* 1997], whereas the actual prevalence in Mwanza was only 4% and still rising [Grosskurth *et al.* 1995a]. Because of the lower HIV prevalence in Mwanza, fewer HIV transmissions were likely taking place in stable relationships, rendering STDs more important. In addition, due to the lower HIV prevalence, the effects of AIDS-related selective mortality and enhancement of herpetic ulceration may have been less pronounced;
- Observed impact in the Mwanza trial may have been biased upward by a coincidental higher baseline prevalence of HIV, some STDs and some HIV risk factors in the intervention arm as compared to the control arm [Grosskurth *et al.*

1995a, Mayaud *et al.* 1997a], and this factor was ignored in these simulations [Korenromp *et al.* 2000a];
- Some reproductive tract infections that may be cofactors in HIV transmission, such as trichomoniasis and candidiasis, were treated in the Mwanza intervention but not incorporated in the model.

In conclusion, the impact of STD treatment on HIV incidence decreases over time due to the natural dynamics of the HIV epidemic, but this effect is mainly important within the first decade of the HIV epidemic. The simulations suggest that the cofactor role of HSV-2 increase littly in importance during the HIV epidemic. A stronger contributor to a decreasing role of curable STDs in HIV transmission in advanced HIV epidemics can be behaviour change. The lack of impact of STD treatment in the Rakai trial may thus relate to the behavioural change following cessation of civil disruption in Uganda before the trial. By implication, improved STD treatment may be more effective than in the Rakai trial not only in earlier-stage HIV epidemics - like India -, but also in advanced HIV epidemics in which no strong behaviour change has yet occurred - like South-Africa.

chapter 9

Can behaviour change explain increases in the proportion of genital ulcers attributable to herpes in sub-Saharan Africa? A simulation modelling study

Korenromp EL, Bakker R, De Vlas SJ, Robinson NJ, Hayes R, Habbema JDF. Can behaviour change explain increases in the proportion of genital ulcers attributable to herpes in sub-Saharan Africa? A simulation modelling study. *Sex.Transm.Dis.*, in press. Reused with permission of the American Sexually Transmitted Diseases Association.

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9.1 Summary

Objective: To assess the contributions of HIV disease and behavioural response to the HIV epidemic to the increasing proportion of genital ulcer disease (GUD) attributable to herpes simplex virus type 2 (HSV-2) in sub-Saharan Africa.
Study design: Simulations of the transmission dynamics of ulcerative sexually transmitted diseases and HIV using the model *STDSIM*.
Results: In simulations, 28% of GUD was caused by HSV-2 prior to a severe HIV epidemic. If HIV disease was assumed to double the duration and frequency of HSV-2 recurrences, this proportion rose to 35% by year 2000. Assuming stronger effects of HIV, this proportion rose further, but due to increased HSV-2 transmission, this would shift the peak in HSV-2 seroprevalence to an unrealistically young age. A simulated 25% reduction in partner change rates increased the proportion of GUD caused by HSV-2 to 56%, following relatively large decreases in chancroid and syphilis.
Conclusion: Behavioural change may make an important contribution to relative increases in genital herpes.

9.2 Introduction

The distribution of aetiologies of genital ulcer disease (GUD) differs widely between countries within Africa. The proportion of GUD attributable to herpes simplex virus type 2 (HSV-2) appears to be higher or increasing in countries with severe HIV epidemics [Morse 1999, O'Farrell 1999, Chen *et al.* 2000]. For example, the proportion of GUD cases that was herpes-positive on culture increased from 11% in 1986-8 to 21% in 1990-2 among HIV-positives in Rwanda [Bogaerts *et al.* 1998], from 3% before 1981 to 14% in 1994 among gold miners in Johannesburg, South Africa [Htun *et al.* 1997], and from 7% in 1984 to 40% in 1998 in Durban, South Africa [O'Farrell 1999]. Increases have also been reported in the occurrence of genital herpes as a proportion of new diagnoses of sexually transmitted diseases (STD), e.g. in Durban (from 7% in 1989 to 11% in 1997) and Harare, Zimbabwe (6% in 1982, 10% in 1997). Moreover, GUD appears to constitute a larger proportion of STD diagnoses in sub-Saharan African (SSA) countries with severe HIV epidemics than in West Africa [O'Farrell 2000].

Several explanations have been proposed for the apparent increase in HSV-2 as a cause of GUD in SSA. Immunosuppression during advanced HIV disease can increase the duration, severity and incidence of herpetic recurrences, leading to an increased herpes ulcer load [Wasserheit 1992, Wald *et al.* 1993]. This effect may be enhanced if the increased herpes ulcer load in HIV patients increases the transmission of HSV-2. Decreases in the prevalence of bacterial causes of GUD, in particular chancroid, may induce a relative increase in HSV-2 as a cause

of GUD. Bacterial GUD can decrease due to selective HIV-attributable mortality among high-risk groups [Korenromp *et al.* 2000d], and due to behaviour change as a result of HIV control programmes promoting safer sex [Asiimwe-Okiror *et al.* 1997, Kilian *et al.* 1999, Kamali *et al.* 2000, Gregson *et al.* 1998]. Improved management of bacterial STD may also contribute to decreases in bacterial GUD [Dangor *et al.* 1999, Steen *et al.* 1999, O'Farrell 1999, De Coito *et al.* 1999]. Finally, apparent increases in genital herpes may reflect changes in detection, rather than true shifts in GUD aetiology [Cowan *et al.* 1996, O'Farrell 1999]. Improved HSV-2 detection could result from increased awareness among clinicians and/or patients of herpes as a cause of GUD, and improved diagnostic possibilities such as PCR as a complement to viral culture and clinical appearance [Morse 1999].

Available data cannot directly distinguish between these explanations. Yet, their implications for the burden of disease and the control of ulcerative STD and possibly HIV in SSA may be different. This chapter presents simulations of the influence of these possible causes on the epidemiology of ulcerative STD. We used the stochastic microsimulation model *STDSIM* [Van der Ploeg *et al.* 1998, Korenromp *et al.* 2000c, Korenromp *et al.* 2000d] to simulate the spread of ulcerative STD and HIV for a typical SSA population with a severe HIV epidemic. Comparing simulation outcomes with empirical data, we discuss the likelihood and importance of the suggested explanations.

9.3 Methods

Microsimulation model *STDSIM*

STDSIM simulates the natural history and transmission of multiple STD and HIV in a population consisting of individuals with assigned characteristics that change over time. The formation and dissolution of (hetero-)sexual partnerships and transmission of STDs during contacts between sexual partners are modelled as stochastic events [Van der Ploeg *et al.* 1998, Korenromp *et al.* 2000c, Korenromp *et al.* 2000d]. Recently, the model was adapted to include the simulation of genital infection with HSV-2 and effects of HIV infection on the natural history and transmission of STD including HSV-2, allowing us to study the epidemiology of HSV-2 in relation to that of other ulcerative STD and HIV.

Simulated population

Assumptions on demography, sexual behaviour and health care were chosen to reflect conditions in a typical SSA city with a severe and advanced HIV epidemic.

For this, we adapted a previous model representation of a population in rural Tanzania [Korenromp *et al.* 2000d], by specifying a higher frequency of prostitute visits by men (25% more than in the Tanzania simulation), a higher frequency of client contacts per prostitute (average 2 per week), and an earlier time of introduction of HIV (1980). To adequately reproduce HSV-2 seroprevalence patterns observed in SSA cities [McFarland *et al.* 1999, Robinson & Hosseini 2000], the representation of sexual behaviour was further adapted by specifying: (i) larger age differences between sexual partners (males being on average 3.3 years older than their spouses), and (ii) an increase in the mean age of sexual debut to 18 years in men and a corresponding decrease to 15 years in women.

Representation of HSV-2

Figure 9.1 shows the model representation of HSV-2 infection; the corresponding parameter values are given in Table 9.1. Infection starts with a primary ulcer episode of on average 3 weeks duration [Rawls *et al.* 1971, Corey *et al.* 1983a, Cone *et al.* 1991, Koelle *et al.* 1992, Corey *et al.* 1983b]. The incubation period is ignored, because it is short [Corey *et al.* 1983a, Cone *et al.* 1991] and unlikely to influence HSV-2 transmission dynamics.

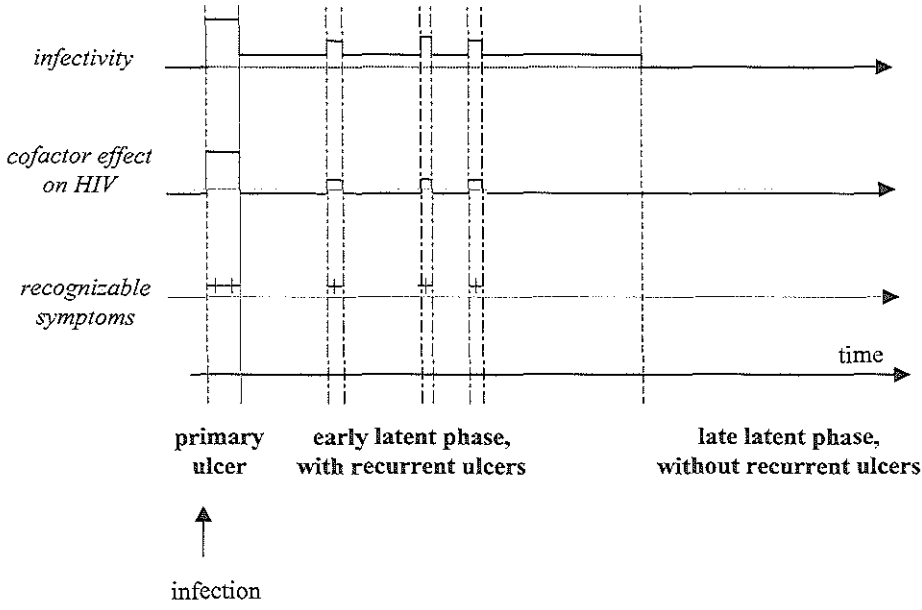

Figure 9.1 **Diagrammatic representation of the natural history of genital HSV-2 infection in the *STDSIM* model.** Drawing not to scale. Corresponding parameter values are given in Table 9.1.

Table 9.1 **STDSIM representation of natural history and transmission of ulcerative STD**

Stage	Mean duration[1]	Transmission probability[2]		Cofactor effect on HIV transmission[2,3]	% of ulcers that are recognized	
		M→F	F→M		M	F
HSV-2						
Primary ulcer	3 weeks	0.30	0.15	25x	30%	30%
Early latent	15 years[4,5]	0.005[5]	0.0025[5]	na[5]	na[5]	na[5]
Recurrent ulcer	1 week[4]; Interval between ulcers: 6 months[4]	0.20	0.10	10x	15%	7.5%
Late latent	Lifelong	0	0	na	na	na
Syphilis						
Infectious	6 months	0.30	0.20	10x	80%	50%
Latent	15 years	0	0	na	na	na
Chancroid	10 weeks	0.20	0.15	25x	90%	70%
HIV						
primary	10 weeks	0.045	0.015	na	na	na
asymptomatic	3 or 5 years[6]	0.00225	0.00075	na	na	na
symptomatic	4 or 2 years[6]	0.00225	0.00075	na	na	na
AIDS	40 weeks	0.01125	0.00375	na	na	na

[1] Individual stage durations were sampled from a Weibull distribution function with shape parameter 2, except for the duration of the early latent stage of HSV-2 and the interval between recurrent HSV-2 ulcers, which used exponential distributions. [2] Per contact; equal for recognized and unrecognized ulcers. [3] Both for susceptibility (HIV-negative partner) and infectivity (HIV-positive partner). [4] In scenarios 1 and 3 of no effects of HIV on the natural history of HSV-2, and in scenario 2 only for individuals not symptomatic with HIV. In scenario 2a, values of these parameters for symptomatic HIV patients are: 30 years, 2 weeks, 3 months; and in scenario 2b: 60 years, 4 weeks, 1.5 month. See also Section 9.3, subsection 'Scenarios of effects of HIV on the natural history of HSV-2'. [5] Except during recurrent ulcers. [6] For scenarios 1, 2a and 3, asymptomatic phase 5 years and symptomatic phase 2 years; for scenario 2b, asymptomatic phase 3 years and symptomatic phase 4 years; (see also Section 9.3, subsection 'Scenarios of effects of HIV on the natural history of HSV-2'). M = male; F = female; na = not applicable.

After the primary episode, patients progress to a long 'early latent' phase during which ulcers can recur. In the remainder of the chapter, the terms 'ulcer' and 'recurrence' denote both recognized and unrecognized genital lesions. The frequency of recurrences is known to decrease over the first years after primary infection [Jeansson & Molin 1974, Rattray *et al.* 1978, Knox *et al.* 1982, Mertz *et al.* 1988b, Brock *et al.* 1990, Koelle *et al.* 1992, Wald *et al.* 1995, Corey & Wald 1999]. Since no long-term patient follow-up studies have been conducted, it is however unknown whether recurrences stop after a certain period, or continue at a (much) lower frequency. Comparisons of age profiles in clinic presentations

with herpetic recurrences and in GUD reporting - which peak between age 30 and 40 years [Adam *et al.* 1979, Guinan *et al.* 1981, Knox *et al.* 1982, Mertz *et al.* 1988a, Mertz *et al.* 1988b, Brock *et al.* 1990, Wald *et al.* 1995, Wawer *et al.* 1999, Wald *et al.* 2000] -, HSV-2 seroprevalence - which peaks at older age [Nahmias *et al.* 1990, Kamali *et al.* 1999] - and HSV-2 incidence - which peaks between age 20 and 30 [Rawls *et al.* 1971, Kinghorn 1994] suggest that the majority of symptomatic recurrences occur within 15-20 years after infection.

Among clinic patients, frequencies of 5 to 8 recurrences annually are reported as typical [Knox *et al.* 1982, Mertz *et al.* 1988a, Brock *et al.* 1990, Wald *et al.* 1995, Wald *et al.* 1996, Wald *et al.* 2000], but these studies likely oversampled individuals with relatively severe and frequent recurrences [Benedetti *et al.* 1994, Wald *et al.* 2000]. Follow-up studies among HSV-2 infectees sampled from general populations observed recurrence frequencies of 2-4 annually [Wald *et al.* 2000, Langenberg *et al.* 1989]. In line with these observations, we estimated that the 'early latent phase' during which ulcers recur lasts for on average 15 years, during which ulcers recur at a mean interval of 6 months. To reflect the large heterogeneity between individuals [Wald *et al.* 1995], we assumed the duration of the 'early latent' phase and the interval between recurrences to vary randomly between episodes within individuals, according to exponential distributions. After the 'early latent' phase, simulated patients progress into a 'late latent phase', during which they count as prevalent on serologic tests, but no longer have recurrences.

Recurrences were specified to last for on average 1 week. As this duration appears to be relatively homogeneous [Rawls *et al.* 1971, Rattray *et al.* 1978, Guinan *et al.* 1981, Corey *et al.* 1983a, Wald *et al.* 2000], we assumed a Weibull distribution with shape parameter 2. During ulcers, patients are thought to be infectious; a proportion of patients recognizes symptoms. From their relative clinical severity [Rawls *et al.* 1971, Corey *et al.* 1983b], we infer that infectiousness and symptom recognition rates are higher for primary ulcers than for recurrences.

No data are available on per-contact transmission probabilities for HSV-2. Genital shedding, a likely correlate of infectivity, is higher during symptomatic episodes than during asymptomatic episodes or in between episodes, and higher during primary episodes than during recurrences [Rawls *et al.* 1971, Corey *et al.* 1983a]. Because it is not known how shedding levels translate into transmission probabilities, the latter were chosen from a range of estimates for other ulcerative STD [Plummer *et al.* 1983, Csonka & Oates 1990, Brunham & Plummer 1990]. Transmission was assumed to be twice as efficient from male-to-female relative to female-to-male [Mertz *et al.* 1990, Mertz *et al.* 1992, Bryson *et al.* 1993]. To account for episodes of viral shedding in the absence of clinical signs [Adam *et al.* 1979, McCaughtry *et al.* 1982, Corey 1994, Wald *et al.* 1995, Wald *et al.* 1997], a continuous low level of infectiousness throughout the early latent phase, i.e. in between recurrences, was specified.

Between 10% and 50% of HSV-2 seropositive individuals in Western settings report a history of genital herpes [Mertz 1993, Brugha *et al.* 1997], symptoms being more common in men than women [Jeansson & Molin 1974, Stavraky *et al.* 1983, Obasi *et al.* 1999]. In a Tanzanian population, 28% and 8% of HSV-2 seropositive men and women reported ulcers ever in the past, as compared to 3% and 2% of HSV-2 seronegatives; over the previous year, ulcers were reported by 11% and 6% of male and female HSV-2 seropositives, and by 1% and 2% of seronegatives [Obasi *et al.* 1999]. Based on these data, we estimated that 30% of primary herpetic ulcers, and 15% and 7.5% of recurrent herpetic ulcers in men and women, respectively, are recognized in SSA populations. Recognition was assumed to occur randomly and independently over different episodes and individuals, i.e. recognition at one episode did not influence recognition at subsequent episodes.

Scenarios of effects of HIV on the natural history of HSV-2

HIV disease is associated with 3- to 4-fold increases in the number of HSV-2 culture-positive days [Augenbraun *et al.* 1995, Hitti *et al.* 1997, Schacker *et al.* 1998, Mbopi-Keou *et al.* 1999] and the incidence of clinical ulcers [Kaul *et al.* 1997]. The level of HSV-2 shedding during symptomatic ulcers increases with decreasing CD4 count [Bagdades *et al.* 1992, Augenbraun *et al.* 1995]. In addition, herpetic recurrences may last longer and be more severe in HIV patients [Kamya *et al.* 1995, Chen *et al.* 2000, Schacker *et al.* 1998].

Translating these effects into model parameters is not straightforward. It is unknown how shedding levels and clinical signs quantitatively translate into infectivity, symptom recognition and cofactor effects. Studies likely oversample HIV patients in the later, symptomatic stages of disease. No prospective studies are available on the duration of untreated recurrences by HIV status. To reflect these uncertainties, we simulated several scenarios. In scenario 1, HIV was assumed not to affect the natural history of HSV-2. In scenario 2a, HIV doubled the duration and the frequency of herpetic recurrences during AIDS and the last 2 years of the AIDS incubation period. In addition, the (remaining) duration of the early latent phase was doubled from the onset of symptomatic HIV. This ensured that most simulated HIV patients continue to have recurrent ulcers until their death from AIDS. Thus, HSV-2 patients with HIV disease in this simulation suffered herpetic ulcers for on average 8 weeks per year, as compared to a mean 2 weeks for patients without HIV. In scenario 2b, stronger biological effects were assumed: HIV quadrupled the duration and frequency of recurrences and the (remaining) duration of the early latent phase during AIDS and the last 4 years of the AIDS incubation period. This corresponds to an average ulcer load of 32 weeks annually.

Representation of HIV, syphilis and chancroid

The *STDSIM* representations of syphilis, chancroid and HIV (Table 1) were based on the scientific literature. Syphilis was represented by two consecutive stages, with the first, "infectious" stage corresponding to primary and secondary syphilis [65]. For computations of ulcer incidence, we assumed that each syphilis infection causes two ulcers during the infectious stage. Chancroid was represented as a continuous ulcerative episode lasting on average 10 weeks [66, 67]. Transmission probabilities were specified at a lower level (15-20%;Table 1) than the single available empirical estimate (43%, for male-to-female transmission [45]). This was done in order to have the model predict a realistic prevalence level and a realistic fraction of ulcers attributable to chancroid (see Results). To allow for effects of HIV disease on HSV-2 natural history described above, the AIDS incubation period was split into 3 phases, named primary HIV disease, asymptomatic pre-AIDS and symptomatic pre-AIDS.

It was assumed that throughout the simulation period, 5% of symptomatic episodes of chancroid and the first syphilis stage were cured upon antibiotic treatment, which reduced episode duration to 2 weeks.

STD cofactor effects on HIV transmission

We assumed the presence of ulcers to enhance the infectivity of HIV and the susceptibility to HIV. In the absence of knowledge on STD cofactor magnitudes from controlled experimental studies, we estimated these based on observational studies among prostitutes and clients in Nairobi (Table 9.1 [Hayes *et al.* 1995c, Korenromp *et al.* 2001b]). In line with their relative clinical severity, herpetic recurrences were attributed a lower cofactor effect (10-fold per contact) than primary HSV-2 and chancroid (25-fold per contact). For the infectious stage of syphilis during which several ulcer episodes may occur [Holmes *et al.* 1999], an average cofactor effect of 10-fold was applied throughout. Identical cofactor effects were assumed for recognized and unrecognized ulcers.

Scenario of changing sexual behaviour

Several SSA countries have documented recent reductions in risk behaviour, including decreases in casual sex and in prostitution and increases in condom use [Ng'weshemi *et al.* 1996, Asiimwe-Okiror *et al.* 1997, Jackson *et al.* 1997c, Wawer *et al.* 1997, Gregson *et al.* 1998, Kilian *et al.* 1999, Kamali *et al.* 2000, Meekers 2000]. We assessed the influence of such behavioural change on the proportion of GUD attributable to herpes, in a scenario 3 with a 25% reduction in the proportion of men visiting prostitutes combined with a 25% reduction in

relationship formation rates after 1990. This type and magnitude of behaviour change provided good fit against survey data from Uganda [Konde-Lule *et al.* 1993, Asiimwe-Okiror *et al.* 1997, Wawer *et al.* 1997, Kilian *et al.* 1999, Kamali *et al.* 2000].

Simulation design

To reduce random fluctuations associated with stochastic simulations, 100 simulation runs were conducted for each scenario. All outcomes are reported as averages over 100 runs, and focus on the general adult population (15-49 years). In univariate sensitivity analyses, simulations were re-run for a set of alternative quantifications in which the values of HSV-2 biomedical parameters were doubled and halved.

9.4 Results

HSV-2 epidemiology before the HIV epidemic

The model provided a reasonable fit to data on HSV-2 seroprevalence by age and sex in Ndola, Zambia (Figure 9.2) and other SSA populations [McFarland *et al.* 1999, Robinson & Hosseini 2000]. Seroprevalence in women exceeds that in men, especially in the youngest age group. This reflects that (i) women become sexually active at younger ages than men; (ii) women typically have older sexual partners while men have younger partners [Garnett & Anderson 1993a, Gregson *et al.* 2000], so that women more often meet HSV-2 infected partners; and (iii) male-to-female transmission is more efficient than female-to-male transmission [Mertz *et al.* 1990, Mertz *et al.* 1992, Bryson *et al.* 1993]. This sex difference was somewhat smaller in the model than in the data, perhaps partly because simulated age differences between partners (e.g. mean 3.3 years in marriages) may have been less than in reality [Munguti *et al.* 1997, Glynn 2000].

Simulated incidence of primary herpetic ulcers was 2.6 and 2.7 per 100 person-years in men and women, respectively (in the total population including both HSV-2 positives and negatives), with corresponding peaks in age groups 20-24 years and 15-19 years. For recurrences including unrecognized episodes, simulated incidence was 41 and 53 per 100 person-years in men and women. Recurrences peaked at age 25-34 years for men, and 20-29 years for women. The overall simulated incidence of recognized herpetic ulcers was 5.9 per 100 person-years.

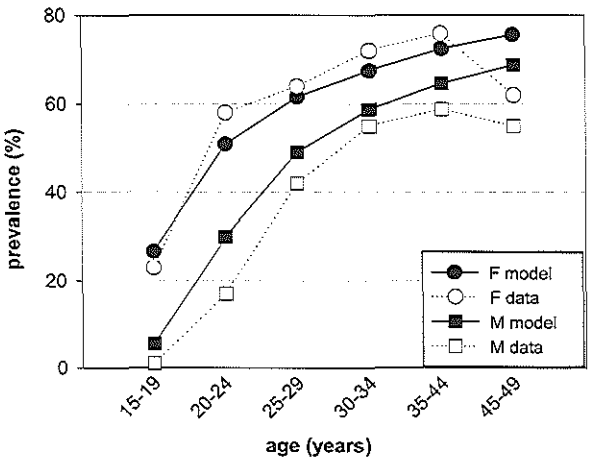

***Figure 9.2* Simulated HSV-2 seroprevalence (%) in the general population by age and sex in a hypothetical SSA city in year 1980.** In the absence of empirical data on HSV-2 seroprevalence from general SSA populations in the 1980s, we used data from Ndola, Zambia in 1997 [Robinson & Hosseini 2000], for comparison.

Ulcer aetiology before the HIV epidemic

Based on simulated incidence of herpetic ulcers, syphilis and chancroid, we derived a distribution of aetiologies of incident ulcers. Of all incident ulcers in 1980, 72% were attributable to HSV-2, 24% to chancroid and 4% to syphilis. For comparison with proportions reported in surveys or seen in STD clinics, we also derived the distribution for recognized ulcers only. Among recognized ulcers, 28% were attributable to HSV-2, reflecting the specified relatively poor recognition of herpetic recurrences (Table 9.1); 64% and 8%, respectively, were caused by chancroid and syphilis.

Trends in ulcer epidemiology during the HIV epidemic

The simulated HIV epidemic reached a prevalence of 31% in 2000 (Figure 9.4d), allowing a clear illustration of the possible effects of HIV on the epidemiology of HSV-2 and GUD.

Assuming no enhancing effect of HIV on HSV-2 (scenario 1), the simulated incidence of recognized herpetic ulcers was stable between 1980 and 2000 at around 6 per 100 person-years (Figure 9.3). The proportion of recognized ulcers attributed to HSV-2 remained roughly stable at 28%. HSV-2 seroprevalence decreased from 48% to 43%, due to excess HIV-related mortality in high-risk groups (Figure 9.4). Due to this same effect, the incidence of chancroid fell also during the HIV epidemic, and the proportion of recognized GUD attributable to chancroid decreased from 64% in 1980 to 59% by 2000. For syphilis, incidence and the contribution to GUD were fairly stable over time.

Moderately strong effects of HIV on HSV-2 (scenario 2a) increased the inci-

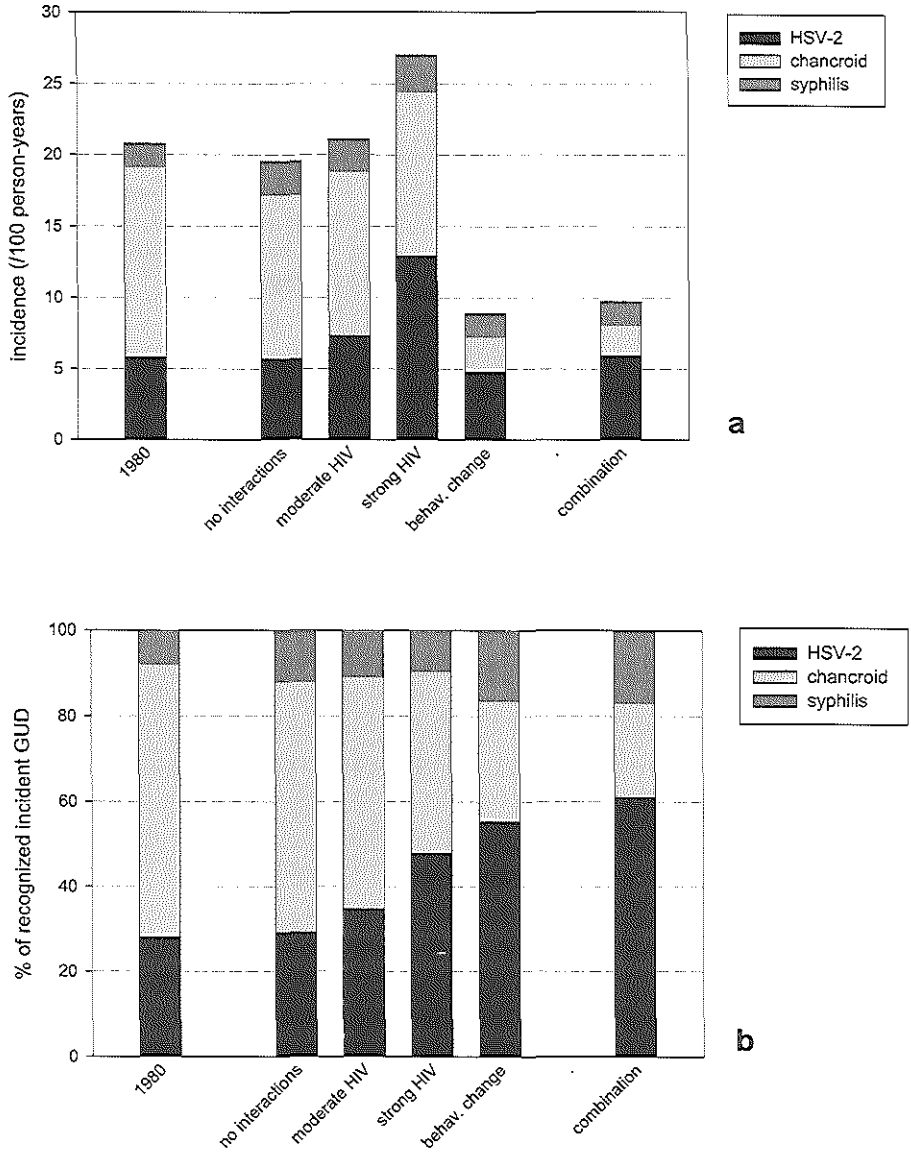

Figure 9.3 **Simulated incidence of recognized ulcers in the general population (15-49 years) by aetiology, in 1980 (most left bar) and 2000 (right bars). a) absolute incidence (/100 person-years); b) proportional contribution (%) to genital ulcer disease (GUD). Scenarios: 1) no interactions; 2a) moderate HIV: moderately strong effects of HIV on the natural history of HSV-2; 2b) strong HIV: very strong effects of HIV on the natural history of HSV-2; 3) beh. change: behaviour change starting in 1990; 4) combination = combination of behaviour change and moderately strong effects of HIV on HSV-2.** For description of scenarios, see Methods.

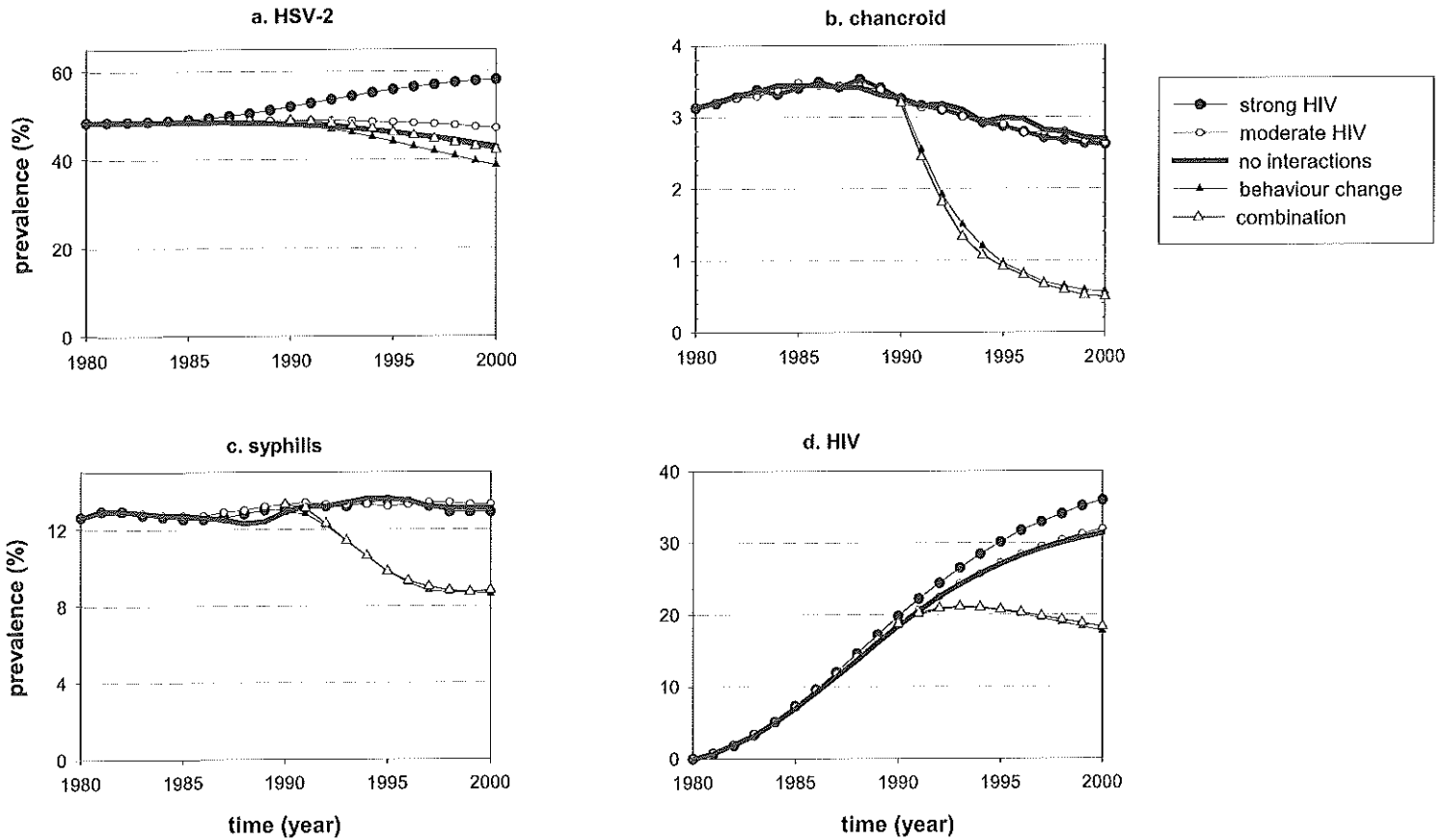

Figure 9.4 **Simulated prevalence (%) in the general population (15-49 years) over time of (a) HSV-2, (b) chancroid; (c) syphilis (ulcerative and non-ulcerative stages combined, corresponding to serological syphilis); (d) HIV in alternative scenarios.** For description of scenarios, see Methods.

dence of recognized herpetic ulcers from 5.9 to 7.4 per 100 person-years between 1980 and 2000. Combined with the relatively large fall in the incidence of chancroid due to selective AIDS mortality, this increased the proportion of recognized GUD attributable to HSV-2 from 28% to 35%. In absolute terms, the increase in herpetic ulcer incidence counterbalanced the decrease in GUD incidence due to selective HIV-attributable mortality. As a result, HSV-2 seroprevalence and the overall incidence of GUD (of any aetiology) remained stable between 1980 and 2000. Similar but more pronounced shifts in GUD aetiology were predicted for scenario 2b of very strong effects of HIV. Here, the fraction of GUD attributable to HSV-2 increased to 48%. The absolute incidence of herpetic ulcers increased from 6 to 13 per 100 person-years, while HSV-2 seroprevalence increased from 48% in 1980 to 58% in 2000.

Behaviour change (scenario 3) reduced the incidence and prevalence of chancroid and syphilis considerably and rapidly (Figures 9.3 and 9.4). Chancroid fell more markedly than syphilis, because of its lower reproductive number [Brunham & Plummer 1990]. Both HSV-2 seroprevalence and the incidence of herpetic ulcers fell relatively little (from 48% to 39%, and from 5.9 to 4.8 per 100 person-years, respectively). Since HSV-2 is a lifelong infection with a high baseline prevalence and recurrent nature, a reduction in herpetic ulceration can only follow from reductions in new infections in the youngest age groups. Therefore, reduced

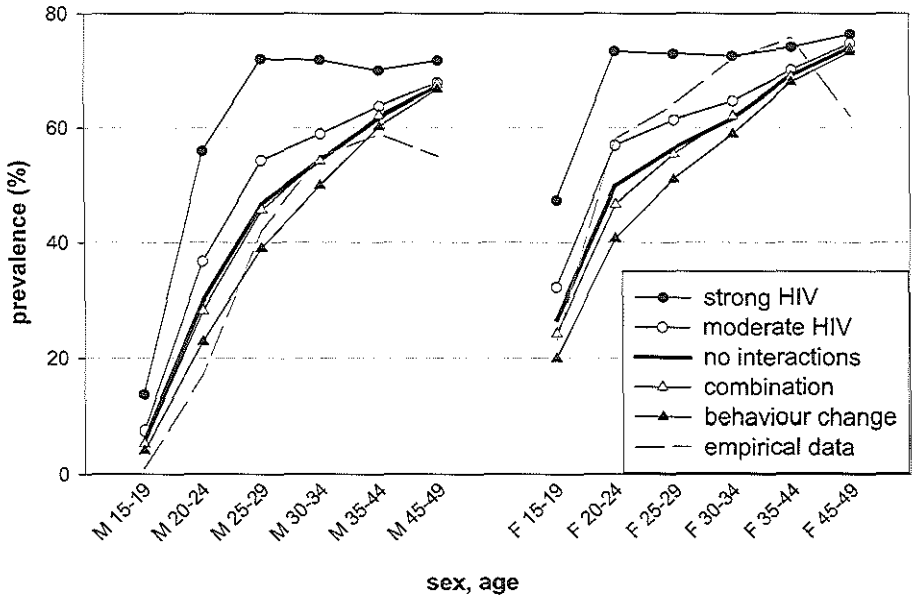

Figure 9.5 **Simulated HSV-2 seroprevalence (%) by age and sex in 2000 in alternative scenarios.** For description of scenarios, see Methods. Empirical data, for comparison, are from Ndola, Zambia in 1997 [Robinson & Hosseini 2000].

HSV-2 transmission takes a long time to impact the incidence of herpetic ulcers at a population level. As a result of the large fall in chancroid relative to herpes and syphilis, the proportion of recognized incident GUD attributable to HSV-2 increased from 28% in 1980 to 56% in 2000, while the proportion caused by chancroid decreased from 64% to 28%.

In a fourth scenario combining behaviour change and moderately strong effects of HIV, the incidence of herpetic ulcers remained unchanged over time, while chancroid and syphilis fell, increasing the proportion of GUD attributable to HSV-2 to 61% by year 2000.

Figure 9.5 shows the age and sex-specific seroprevalence of HSV-2 in year 2000 in the various scenarios. Effects of HIV on herpetic ulcerations increased HSV-2 seroprevalence especially in the younger age groups. Very strong effects of HIV (scenario 2b) would shift the peak from the oldest group to a plateau from age 25-29 years onwards for men and age 20-24 years for women, resulting in an unrealistic age pattern [McFarland *et al.* 1999, Robinson & Hosseini 2000]. Behaviour change, in contrast, slightly decreased HSV-2 seroprevalence in the younger age groups, who had the highest partnership change rates. The age pattern in the combined scenario 4 resembled that in scenario 1 of no interactions.

Sensitivity analyses

To explore the robustness of the results, we assessed their sensitivity to variations in model assumptions on HSV-2 and its possible interactions with HIV.

Of the parameters tested, the average duration of the early latent phase, the probability distribution function assumed for this duration, and the interval between recurrent ulcers were the most important determinants of HSV-2 seroprevalence and ulcer incidence levels. While halving durations considerably reduced HSV-2 seroprevalence, doubling them did not substantially increase seroprevalence, due to saturation. In all simulations, the gender difference in HSV-2 seroprevalence was insensitive to the relative efficiencies of male-to-female and female-to-male transmission, indicating that its population distribution is mainly determined by sexual behaviour patterns. Across all quantifications, behaviour change shifted GUD aetiologic distributions much more than moderately strong biological effects of HIV. Of the different possible effects of HIV, that on the frequency of herpetic recurrences impacted GUD aetiology most. Of the two assumed components of behavioural change, a 25% reduction in relationship formation rates impacted GUD aetiology more than a 25% reduction in prostitute visits.

9.5 Discussion

HSV-2 transmission dynamics

In order to simulate both observed adult HSV-2 seroprevalences in SSA (≥45%) and plausible frequencies of herpetic recurrences (<5 per 100 person-years), a high level of asymptomatic HSV-2 transmission had to be assumed. This finding supports the empirical evidence that a large proportion of herpetic ulcerations go unrecognized and these contribute substantially to transmission [Mertz *et al.* 1992, Mertz 1993, Brugha *et al.* 1997].

Simulated HSV-2 epidemiology and GUD aetiologic distribution were robust against most uncertainties in the natural history of HSV-2 (sensitivity analysis). This corroborates findings with simpler transmission models, in which interventions impacting HSV-2 infectivity and ulceration had little influence on seroprevalence levels [Blower *et al.* 1998, White & Garnett 1999]. The duration of the 'early latent phase' during which ulcers recur, and the variability of this duration within the population were however critical. Better knowledge of these parameters, from long-term follow-up studies in unselected populations, would help to better understand the transmission dynamics of HSV-2.

GUD incidence and aetiology

The model showed that realistic prevalence levels of HSV-2 and syphilis are consistent with an incidence of recognized GUD as high as 20 per 100 person-years. The simulated fraction of the population with recognized GUD in the last year, in contrast, was only 9% (scenarios 1 and 2), in line with fractions reported in SSA populations [Wawer *et al.* 1999, McFarland *et al.* 1999]. The difference between the incidence rate and the fraction with ulcers results from the occurrence of recurrent ulcers, such as for HSV-2, and repeat infections, such as for chancroid. Another reason is that ulcers caused by different STD cluster because of shared risk factors.

The simulated aetiologic distribution of recognized GUD in 1980 (Figure 9.3) matched data from the 1980s from SSA cities. Chancroid was the predominant cause of GUD [Haines *et al.* 1978, Fast *et al.* 1984, Hazlett *et al.* 1984, Plummer *et al.* 1985, Greenblatt *et al.* 1988, Bogaerts *et al.* 1989, Bogaerts *et al.* 1998, O'Farrell 1999]. Observed proportions should however be viewed with caution, because diagnosis was based on either culture methods with limited sensitivity - likely resulting in underestimation - or clinical appearance - possibly resulting in overestimation [Fast *et al.* 1984, Hazlett *et al.* 1984, Htun *et al.* 1998]. The simulated 28% attributable to HSV-2 is higher than values reported for Nairobi (2-16%) [Fast *et al.* 1984, Hazlett *et al.* 1984, Plummer *et al.* 1985, Greenblatt *et*

al. 1988], Kigali (11-19%) [Bogaerts *et al.* 1989, Bogaerts *et al.* 1998], Durban and Johannesburg (3-7%) [Htun *et al.* 1997, O'Farrell 1999]. These older studies all used culture to diagnose herpes, which due to low sensitivity may have caused underestimation [Morse 1999]. The low simulated proportion attributable to syphilis (8%) matches proportions found in Nairobi (3-10%) [Fast *et al.* 1984, Greenblatt *et al.* 1988] and Zimbabwe (6%) [Haines *et al.* 1978]. Studies in Johannesburg and Rwanda found proportions of 15% and 19% [Bogaerts *et al.* 1998, Duncan *et al.* 1981], but, being based on serologic diagnosis which remains positive for years after the disappearance of ulcers [Morse 1999, Holmes *et al.* 1999, Malonza *et al.* 1999], these may be overestimates.

Behavioural change versus biological effects of HIV

In both scenarios 2b and 3, the proportion of GUD attributable to HSV-2 increased considerably during the HIV epidemic (from 28% to 48% and 56%, respectively), resulting in GUD aetiologic distributions in year 2000 (Figure 9.5) in the range of those observed in advanced HIV epidemics. In Uganda, 75-85% of reported ulcers with known aetiology were attributable to HSV-2, 6-9% to chancroid and 4-17% to syphilis [Kamya *et al.* 1995, Wawer *et al.* 1999]. In Malawi, the three infections accounted for about equal proportions of GUD [Behets *et al.* 1995]. In rural Zimbabwe, 32% of diagnosed ulcers were attributable to HSV-2, 47% to chancroid and 22% to syphilis [Le Bacq *et al.* 1993].

Seemingly very strong biological effects (scenario 2b) had to be assumed to explain a shift in GUD aetiology approaching that caused by apparently realistic magnitudes of behaviour change (scenario 3), and only in scenario 2b would HSV-2 seroprevalence and GUD incidence increase in absolute terms. The limited sensitivity of HSV-2 epidemiology in the general population to enhancement of herpetic ulceration in HIV patients is firstly because not all HSV-2 patients are infected with HIV. Even in a severe HIV epidemic, not all HSV-2 patients contract HIV, and those who do die earliest, which limits the combined prevalence. Secondly, the majority of partners of HSV-2/HIV patients are already infected with HSV-2, so that increased infectivity does not always actually increase transmission in the population. Long-term follow-up studies in HIV-positive and HIV-negative populations could help to determine whether HIV truly enhances herpetic ulceration as strongly as assumed here.

We may have overestimated the increase in the proportion of GUD attributable to HSV-2 because the simulation did not allow for a possible enhancement by HIV disease of chancroidal ulceration [Wasserheit 1992]. Due to its low reproductive number [Brunham & Plummer 1990], the latter effect could markedly increase the spread of chancroid during HIV epidemics. It should also be noted that the simulated HIV epidemic was, at a prevalence of 31% in 2000, more advanced than in many SSA populations. For less severe epidemics, increases in

herpetic ulceration due to HIV would be less. Furthermore, we assumed sexual activity to be unaffected by symptoms. If many ulcer patients would temporarily abstain or reduce the frequency of intercourse [O'Farrell *et al.* 1992, Kamya *et al.* 1995], we may have overestimated the influence of herpetic ulceration on HSV-2 transmission. On the other hand, we ignored an effect of HIV on the severity of herpetic ulcers, which may lead HIV patients to more often recognize these. This may have caused our model to underestimate the shift in GUD aetiology possible among clinical cases in severe, advanced HIV epidemics.

The simulated shifts in GUD aetiology in scenarios 2b and 3 were mediated through different mechanisms, which had opposing effects on HSV-2 seroprevalence and the absolute incidence of herpetic ulcers, chancroid and syphilis (Figures 9.3-9.5). Does comparison of these predicted concomitant effects with empirical data allow inference as to which scenario best reflects reality?

No data are available on HSV-2 seroprevalence over time periods spanning the course of SSA HIV epidemics [O'Farrell 1999]. One study reports an increase in seroprevalence in urban and rural Zaire between 1959 and 1985 (from 21 to 60% and from 6 to 32%, respectively) [Nahmias *et al.* 1990]. But sampling for these surveys was among young men in 1959 [Motulsky *et al.* 1966] and in undefined general populations in 1985, leaving doubts about their comparability in terms of age and risk profile. Moreover, this putative time trend occurred largely before the HIV epidemic in this region. For herpetic ulcer incidence, longitudinal data allowing assessment of time trends in SSA are also lacking. The contrast between scenarios 2b and 3 in their effect on the absolute incidence of herpetic GUD and HSV-2 seroprevalence does therefore not allow proper validation. Future population-based surveillance on trends in these indicators may help to solve this issue.

Data on time trends in bacterial ulcerative and non-ulcerative STD in several SSA settings are available, and some match the simulated reduction in rates of syphilis, chancroid and recognized GUD in scenario 3. For example, the number of chancroid diagnoses fell 7-fold in Harare between 1990 and 1998 [O'Farrell 1999], prevalences of gonorrhoea, chlamydia and syphilis decreased 2- to 3-fold among women in Nairobi between 1992 and 1997 [Moses *et al.* 2000], Malawi saw 1.1- to 2-fold falls in the prevalence of syphilis, trichomoniasis, gonorrhoea and genital ulcers between 1990 and 1996 [Taha *et al.* 1998a], and factory workers in Mwanza, Tanzania, reported 35% less GUD in 1994 than in 1991 [Ng'weshemi *et al.* 1996].

Comparison between empirical data and simulations on age patterns in HSV-2 seroprevalence suggests that the true effect of HIV on herpetic ulceration is less strong than assumed in scenario 2b. The simulated saturation of HSV-2 seroprevalence at age 20-29 years in this scenario (Figure 9.5) is inconsistent with available data from SSA populations. For example in Ndola, Harare and Kisumu, HSV-2 seroprevalence peaked above age 45 or 35 years in both sexes [McFarland *et al.* 1999, Robinson & Hosseini 2000]. This inconsistency was apparent in spite

of conservative assumptions on the relationship between ulceration and infectivity, since we specified a non-zero infectivity throughout the early latent phase in between recurrences, and ignored a possibly higher infectivity during recognized (more severe) ulcers as compared to unrecognized episodes. If HSV-2 infectivity in SSA populations would correlate more strongly with (recognized) ulcers than in these simulations, the specified strong effects of HIV would result in even more unrealistic age patterns. Behaviour change, in contrast, did not produce unrealistic age patterns in HSV-2 seroprevalence, although the limited available epidemiological data did not allow us to check whether this scenario fitted better for populations with recorded behaviour change than for populations without. For Ndola, the simulated decrease in HSV-2 seroprevalence among the young upon behavioural risk reduction improved the fit for males, but worsened it for females (Figures 9.2 and 9.5). For this advanced HIV epidemic, scenario 4 combining behaviour change with moderately strong effects of HIV fitted observed age patterns in HSV-2 seroprevalence equally well as scenario 1 of no interactions.

Other explanations?

The large influence of behaviour change can explain why increases in HSV-2 as a cause of GUD are also pronounced in developing countries without severe HIV epidemics, like in South East Asia [Chua & Cheong 1995, Taylor *et al.* 1984, Beyrer *et al.* 1998]. For example, in Thailand the incidence of clinical syphilis and chancroid decreased 3- and 20-fold between 1987 and 1993 [Beyrer *et al.* 1998], the period of the 100% condom programme which succesfully constrained the spread of HIV [Hanenberg *et al.* 1994].

Of note, the simulated reduction in partner change rates is not the only form of behaviour change that can underly relative increases in herpes. With increased condom use, the shift in GUD aetiology could be even more marked than with partner reduction, because condom efficacy is likely lower against HSV-2 - which can cause lesions outside the condom-protected genital area - than against bacterial STD.

Not all countries with changes in GUD aetiology have evidence of behaviour change, with as example South Africa [Dangor *et al.* 1999, Steen *et al.* 1999, O'Farrell 1999, De Coito *et al.* 1999, Low-Beer *et al.* 2000]. Also, the only published reports on absolute increases in genital herpes - which according to our simulations could result in advanced HIV epidemics, if biological effects of HIV are strong and in the absence of behavioural responses - come from Singapore and India [Goh 1995, Kumar & Rajagopalan 1991]. As Singapore and India were at the time of these studies not in advanced HIV epidemics, these absolute increases cannot be explained from HIV-related immunosuppression. This suggests that risk reduction and, in severe HIV epidemics, HIV-related immunosup-

pression, are not the main explanations of (relative) increases in HSV-2 in all countries. Increased detection of genital herpes following higher awareness may well be another important factor.

Finally, improved antibiotic STD management may have contributed to relative increases in herpes, through falls in syphilis and especially chancroid. Improved STD care is a likely to have contributed to GUD epidemiologcal shifts in more developed, e.g. South-East Asian countries [Goh 1995]. For SSA populations, where besides treatment facilities also symptom recognition and treatment seeking behaviour are much poorer [Adler 1996], it is questionable whether STD treatment has so far played an important role. Yet, improvement of STD treatment coupled with population-based health education to improve clinic attendance certainly has the potential to enhance trends in GUD epidemiology ongoing in this region.

Conclusion and implications

Our results suggest that seeming increases in genital herpes in SSA are mainly relative, or artefacts reflecting changes in detection, rather than absolute. Even in severe HIV epidemics, the overall incidence of GUD and HSV-2 seroprevalence are unlikely to increase in absolute terms, because the effects of HIV-related enhancement of herpetic ulceration are at a population level easily offset by factors causing GUD to fall, such as HIV-attributable mortality. Behavioural response to the HIV epidemic is a particularly potent cause of relative increases in herpes among GUD, through rapid and large falls in chancroid.

The increasing proportion of HSV-2 as a cause of GUD presenting in clinics implies that, as long as antiviral therapy for HSV-2 is not evident in developing countries, education on the prevention of transmission and on avoiding possible consequences of ulcers including enhanced transmission of HIV, e.g. through temporary abstinence or condom use, becomes an increasingly important component of STD management.

chapter 10

General discussion

THROUGH A REVIEW of methods for estimating STD cofactor magnitudes and a reappraisal of two African trials of improved STD treatment, I have investigated whether and how much STD treatment may contribute to HIV prevention. In this final chapter of the thesis, I will try to integrate the findings and conclusions of the previous chapters. Section 10.1 focuses on estimates of the magnitude of STD cofactor effects on HIV transmission. Section 10.2 discusses the analyses of some of the determinants of the discrepant outcomes of the Mwanza and Rakai trials. The results of these investigations are reconsidered in the context of the original broader set of explanatory hypotheses (Table 1.2); the results of additional studies documented elsewhere are also summarised. On this basis, we estimate the comparative likelihood and importance of all possible factors. Section 10.3 reflects on the methodology of simulation and micro-simulation: i.e. (why) was *STDSIM* necessary for these studies? Which improvements to models such as *STDSIM* would help their use in decision support questions in HIV and STD control? Section 10.4 discusses the implications of the findings for future research into the role of STD and STD treatment in HIV prevention. Section 10.5 bring us back to the rationale for our research, and discusses the implications for practical HIV/STD control in sub-Saharan Africa. Section 10.6 concludes the chapter with a brief summary of findings and implications.

10.1 THE MAGNITUDE OF STD COFACTOR EFFECTS ON HIV TRANSMISSION

In Chapter 2, the magnitude by which STD enhance HIV transmission was estimated on the basis of observational (non-intervention) studies. Before the STD intervention trials, this was the most common way of estimating the importance of STD in HIV spread. After the Mwanza and Rakai trials had led to contrasting outcomes, research once more resorted to analyses of observational data.

Cofactor estimations derived from observational studies commonly adjust for confounding caused by shared risk factors for STD and HIV, using information on (for example) the number of recent sexual partners reported by study subjects. Because the adjustment is limited to the risk profile of the study subjects themselves and ignores wider, indirect effects through the sexual 'network' of which they are a part, it does not fully resolve the confounding. We illustrated the overestimation of cofactor effects that may result: for genital ulcers in prostitutes in Nairobi, Kenya [Hayes *et al.* 1995c], disregard of three common confounders may have inflated the cofactor estimate from a ('best estimate') 3-fold per sexual contact to 23-fold. Neither of these estimates is precise, since each is based on numerous assumptions, such as the duration of the STD, the effects of ulcer symptoms on sexual behaviour, and the sexual network of which the study subjects formed part. Therefore we did not succeed in our original aim of estimating the true

magnitude of STD cofactor effects.

The re-estimation nevertheless illustrated that previously, STD cofactor magnitudes had probably been overestimated, and that people may have been too optimistic about the potential for HIV prevention by STD treatment. In retrospect, we would say that this is likely to hold true for our simulations in Chapter 7 as well. There, we assumed cofactor values of a 100-fold per sexual contact for ulcers due to chancroid and syphilis, as well as for syphilis throughout the first half year, i.e. including the phase in between ulcers. On the basis of the insights stated in Chapter 2, the more recent simulations in Chapters 8 and 9 used lower cofactor values for ulcerative STD (10- to 25-fold, depending on the severity of the ulcer); values for the non-ulcerative STD were reduced correspondingly (from 10-fold to 5-fold). The resulting inconsistency between the simulations makes it clear that the predictions for the magnitude of impact of STD treatment in our studies should not be taken as precise quantitative outcomes. Since a range of cofactor values were consistent with the available data from observational studies and the trials, all simulations included sensitivity analyses exploring the robustness of the conclusions against uncertainty about cofactor magnitudes. In all cases, the main qualitative conclusions were robust against variation in cofactor assumptions, but the *absolute* predicted impacts of STD treatment were not. For example, in Chapter 7 we concluded that (if cofactor effects for asymptomatic and symptomatic STD are equal) one round of mass treatment in Mwanza would, in the short term, be *roughly as effective* against HIV as syndromic treatment, at all assumed cofactor values. Yet the reduction in HIV incidence achieved by the simulated STD treatments varied between 14% and 62% (Table 7.3).

Cofactor estimations from observational studies can be improved in various ways, for example by conducting them in more homogeneous populations and by following couples rather than individuals, so that outcomes can be corrected for the characteristics of each partner. A recent study of this kind on HIV-discordant marital couples in Rakai found a per-contact cofactor effect of GUD of 2.6 (95% CI: 1.0-5.7) [Gray *et al.* 2001], i.e. much lower than in earlier studies with less rigorous control for confounding, and well in line with our adjusted estimate. For other syndromes or laboratory-diagnosed STD, the Rakai study detected no significant cofactor effects. Nonetheless, cofactor studies are unlikely ever to yield precise answers, and it even remains possible that STD cofactor effects are insignificant, at least at a public health level. Another factor contributing to overestimation of cofactor magnitudes is a publication bias in favour of studies finding stronger associations [Garnett & Rottingen 2001]. On the basis of clinical and biological studies on HIV shedding and leukocyte involvement in inflammatory STD, we do however consider the existence of cofactor effects to be proven.

Section 10.4 addresses the implications to HIV prevention policy of downscaling cofactor estimates; in section 10.5 we discuss the options for and usefulness of additional studies.

10.2 The discrepant outcomes of the Mwanza and Rakai trials

The major part of this thesis has dealt with explaining the discrepancy in outcomes between the Mwanza and Rakai STD treatment trials (Chapters 3 through 9). However, we have not studied all the hypotheses that have been raised to explain the contrast (Table 1.2). Table 10.1 gives an overview of the hypotheses addressed in the respective chapters, and those investigated in studies documented elsewhere. This section discusses the results of these studies in the same order as that shown in Table 10.1. Where possible, I have tried to indicate the estimated importance of each factor.

Before proceeding to the discussion of hypotheses, I will explain three important general considerations.

First, an obvious determinant of the relationship between STD reduction and HIV reduction is the (unknown) magnitude of STD cofactor effects. This, however, is of little relevance to the Rakai-Mwanza discrepancy. The large reduction in HIV incidence associated with limited STD reductions in the Mwanza trial would suggest that cofactor magnitudes are large, while the lack of HIV reduction associated with significant STD reductions in Rakai might be interpreted as evidence for small cofactor magnitudes. In reality, the cofactor magnitude is likely to be the same across populations, as it reflects the biology of the pathogen-host interaction (i.e. the STD - human interaction) rather than population-specific characteristics. Therefore, when explaining the trial outcomes with simulation models, assuming higher cofactor values would improve fit against the Mwanza outcomes (although the improvement saturates at a still imperfect fit: see Table 7.3), but worsen fit for Rakai. Conversely, choosing lower cofactor values improves fit against the Rakai observations (Table 8.2), but worsens it for Mwanza.

Second, the main contrast in outcomes between the trials appears to lie in the impacts on HIV incidence, and not in the impact on STD. Comparison of the magnitudes of STD reductions in the two trials is not straightforward, as the definitions of STD rates and reductions they adopted were not exactly comparable (Chapter 5), and this analysis is still underway. However, preliminary results indicate that, overall, both interventions reduced STD rates by a similar fraction. Thus, a focus on the impact on HIV is warranted, and this means that explanations of the trial contrast which would act via the respective magnitudes of STD reduction are *a priori* not the most likely. More plausible are hypotheses that imply a difference in the relationship between *a given magnitude of STD reduction* and HIV reduction. This criterion would lend credence to the explanation that Mwanza was at a relatively early stage of the epidemic, when STD cofactor effects are more important than in late-stage epidemics such as that in Rakai, because this explanation is consistent with similar proportional STD reductions in both trials but a larger HIV reduction in Mwanza. In contrast, the hypothesis that syndromic treatment has better STD coverage than mass treatment is less likely to

Table 10.1 **Overview of the research on reasons for the difference in impact on HIV incidence of syndromic STD treatment (ST) in Mwanza trial and mass STD treatment (MT) in Rakai trial, and the relative estimated importance of these reasons.**

	Description of research	Estimated importance[1]	Affects mainly impact on STD, or on HIV given certain STD reduction?
Differences in the interventions			
ST but not MT continually provides treatment, improving coverage	Chapters 7 and 8	-	STD
Mobility/migration disturbs periodic MT more than continual ST	[Korenromp *et al.* 1999a]	-	STD
Some cofactors, such as bacterial vaginosis are more effectively treated by ST than by MT	not investigated	-?	HIV
Most STD episodes become symptomatic, therefore ST misses only few infections	Chapters 3 and 4	-	STD
Cofactor effects are higher for symptomatic STD, the focus of ST	Chapters 3 and 4	+?	HIV
The impact of ST on HIV in Mwanza is (in part) due to mechanisms other than a reduction in STD cofactor burden (such as patient counselling on safe sex)	not investigated	+ +?	HIV
Differences in the study populations			
Mwanza was in earlier stage of HIV epidemic, when STD cofactors are more important	Chapters 5 and 8	+	HIV
- Rates of incurable cofactor genital herpes (HSV-2) higher in Rakai[2]	Chapters 5, 8, 9	-	HIV
Behavioural response to HIV epidemic in Rakai had reduced rates of curable STD	Chapters 5 and 7	+ +	HIV
Greater population mobility in Rakai than in Mwanza	unpublished results (Richard White, LSHTM)	-	STD
Differences in study design			
Open cohort in Rakai included new participants enrolled halfway, diluting *apparent* impact, vs. closed cohort in Mwanza	not investigated	-	STD
The Rakai cohort but not the Mwanza cohort bordered non-intervention area, resulting in more impact dilution due to (re-)infection from outside	not investigated	-	STD
Random chance			
In Mwanza, intervention arm started out with lower HIV/STD rates than comparison arm, inflating *apparent* impact	[Korenromp *et al.* 2000a]	+	HIV and STD

[1] Meaning of scorings: -(?) = (possibly) not important; +(?) = (possibly) important, + +(?) = (possibly) very important. [2] This factor is considered one of the intermediate mechanisms behind the broader explanation proposed in the row above (stage of the HIV epidemic).

hold true, because it would imply larger proportional STD reductions in Mwanza. This evaluation criterion is indicated in the last column of Table 10.1 for all hypotheses considered.

Third, while it has been questioned whether a relevant reduction in STD cofactor burden should always be visible as a proportional STD prevalence reduction, this premise is not relevant to the interpretation of our simulation-based studies. The results of the Mwanza trial inspired the proposition that syndromic STD treatment reduced STD cofactor burden more than STD prevalence, because it primarily reduced the *duration* of STD episodes, and not so much their incidence [Hayes *et al.* 1995a]. Others have added that, due to the relatively high transmission probability of STD, STD may in many cases already have been transmitted before the patient receives treatment (limiting the population impact of treatment on STD prevalence in the population), while for transmission of the less infectious HIV, a shortening of STD episode duration is more influential [Hudson 1999]. While they are very real, these effects do not stand in the way of conclusions that arose from our simulation studies, as we automatically accounted for these effects by separate modelling of the transmission characteristics of STD and HIV infections.

10.2.1 Evaluation of hypotheses: differences in the interventions

Three hypotheses centered around the coverage of sustained syndromic treatment versus periodic mass treatment. These hypotheses are not *a priori* the most likely explanations, because they would imply an - unobserved - discrepancy in impact on STD, besides the - observed - one on HIV. Our simulations rendered these explanations even less likely. For Mwanza (Chapter 7), they predicted that a single round of mass treatment would, over the first two years of intervention, be roughly as effective against most STD and HIV as syndromic treatment would be. Predicted proportional reductions in HIV incidence over two years were 36% and 30%, respectively, under assumptions of very strong cofactor effects. For Rakai, syndromic treatment was predicted to be hardly more effective against HIV (an 8% incidence reduction) than was periodic mass treatment in the trial (Chapter 8). This section discusses the plausibility and importance of differential intervention coverage as an explanation for the Mwanza-Rakai discrepancy, by considering the validity of these simulation results.

Intervention coverage

The coverages assumed for both interventions in Chapter 7 (50% of symptomatic episodes covered by improved syndromic management and 80% of resident adults receiving mass treatment) were in retrospect higher than the most recent estimates derived from the respective trials: 38% [Buvé *et al.* 1998] and 70% [Wawer *et al.* 1999]. Therefore, both simulated impacts may have been slight over-

estimates. For comparison of the impact of mass treatment between the Mwanza simulation and the Rakai trial, we must however also consider that the simulated intervention was a single round, whereas the Rakai intervention covered two subsequent rounds (at a ten-month interval). This may have counterbalanced the excessively high simulated coverage per round. For syndromic treatment, in line with the excessively high coverage assumed in the Mwanza simulation, the corresponding simulated STD reductions were larger than the STD reductions actually observed in the trial.

Population mobility

Population mobility as an (indirect) determinant of intervention coverage deserves separate attention, as this phenomenon was not included in the simulations covered in this thesis. Simulations described elsewhere suggest that migration can considerably reduce the impact (on both HIV and STD) of mass treatment. However, this conclusion is specific to the case with a high coverage of between 80 and 95% [Habbema & Korenromp 1999]. At the 70% coverage achieved in Rakai, in contrast, the dilution of impact would be less, and hardly more than for a syndromic treatment intervention [Korenromp *et al.* 1999a]. Thus, the differential effect of population mobility on the impact of syndromic treatment vs. mass treatment is an unlikely explanation for the contrast in outcomes between the Mwanza and Rakai trials.

Differential efficacy against non-STD cofactors

As an additional difference between the interventions, it has been hypothesised that bacterial vaginosis (BV) (i) is a non-STD cofactor, (ii) responds better to multiple-dose syndromic treatment than to single-dose mass treatment. This hypothesis has not been investigated in this thesis*, and BV was not included as a cofactor for HIV transmission in the simulations. Examination of the literature suggests that BV is not a strong independent cofactor for HIV transmission. First, the cofactor effect of BV would be limited because the infection involves neither inflammation (such as gonorrhoea and chlamydia) nor ulceration (such as syphilis and chancroid). The mechanism supposed to account for an independent cofactor effect is the disturbance of vaginal flora and an increase in vaginal pH. These would result in a weakening of the barrier to invasion by pathogens including the HIV virus, but this seems to be a comparatively weak cofactor mechanism (see also 1.4). Second, the effect of disturbance of vaginal milieu on HIV transmis-

*The evaluation of the importance of the second part of this hypothesis would be difficult because in Mwanza, the impact of the intervention on BV rates had not been monitored. In Rakai, mass treatment reduced BV rates only little, a fact that was attributed to a rapid recurrence of the infection during the 10-month interval between treatment rounds. Thus, it remains unproven whether syndromic treatment reduced BV burden more than mass treatment.

sion may in part be indirect, through an increased susceptibility to other STD, such as gonorrhoea and chlamydia. This is supported by observational studies that found less strong associations between BV and HIV transmission after adjustment for correlations between BV and cofactor STD. Finally, still unpublished studies from discordant stable sexual couples in the Rakai trial cohort suggest that BV may also be a consequence of, rather than a predisposing factor to, HIV seroconversion (Ron Gray, personal communication).

Symptom probabilities

The predicted impact of syndromic treatment depended on the proportion of STD episodes that become symptomatic. Unlike intervention coverage, this determinant could not directly be derived from trial data. Also, there is little other direct empirical evidence (which should come from cohort studies of untreated and unselected patients followed from the moment of infection).

The symptom probabilities assumed in our simulations (Tables 7.1 and 8.1) were mainly derived from handbooks documenting expert opinion. An indirect check on their validity is provided by the fit of the simulations with respect to the STD reductions observed in the Mwanza trial: under realistic assumptions about symptom probabilities, the model should reproduce the empirically observed STD reductions (provided that it also uses correct rates for coverage and treatment effectiveness). Yet in all simulations of syndromic management (including an adaptation of Chapter 7 with reduced coverage; not shown), the reductions in the prevalence of gonorrhoea, chlamydia and syphilis were higher than had actually been observed in Mwanza, suggesting that the assumed symptom probabilities for these STD were on the high side.

Several independent analyses support this conclusion. For active syphilis, less than 20% of patients in the trial populations (as compared to a not insignificant fraction of those without syphilis) had recognised ulcers over the past half year - which is much lower than the symptom probability of 50-95% assumed in the simulations. For chancroid, studies in Manila, Nairobi and Bangkok suggest symptom probabilities per episode of between 40% and 90% [Lao & Trussel 1947, Plummer *et al.* 1983a, Viravan *et al.* 1996], i.e. also lower than the model assumed.

In Chapter 4, we estimated symptom probabilities for gonorrhoea and chlamydia, integrating data on symptom point prevalences and treatment patterns in the Rakai population with insights into the natural history of these STD in a natural history model. This yielded estimates of around 45% for males with gonorhoea, 11% for males with chlamydia, 14% for females with gonorrhoea, and 6% for females with chlamydia, i.e. lower than the symptom probabilities assumed in the Rakai and Mwanza simulations. When doing the same analysis done for the Mwanza trial population, using data on symptom prevalence among gonorrhoea-infected (or occasionally chlamydia-infected) male participants at follow-up [Mayaud *et al.* 1997a], symptom probabilities in the same order as in

Rakai result: at estimated treatment rates of symptomatic cases of 5% and 38% for the comparison arm and intervention arm, respectively [Buvé *et al.* 1998], the corresponding symptom probabilities would be 41% and 50%*. The difference between the Mwanza intervention arm, on the one hand, and the Mwanza comparison arm and Rakai†, on the other, may reflect the impact of the periodic population-based STD health education that was part of the Mwanza intervention package. At the same time, the outcome suggests that for gonorrhoea in males, the symptom probability assumed in the Mwanza trial simulations was in the right order.

The latter symptom estimates were lower than the estimates made in handbooks based on observations in Western populations. Probably, this is due to geographical differences in symptom recognition behaviour: in developed populations in Western, industrialised countries with good availability of and access to health services, the knowledge and perception of symptoms is generally high, whereas in under-serviced and poorly educated populations such as those in rural Rakai and Mwanza, symptom recognition and reporting is worse. In retrospect, we can therefore say that our models, which used symptom estimates based on observations in Western populations, probably overestimated the symptom probabilities for the trial populations for gonorrhoea and chlamydia. Overestimation of symptom probabilities may have contributed to overoptimistic predictions of the impact of syndromic treatment (especially in Chapter 7, for Mwanza). At any rate, these analyses indicate that our simulations are unlikely to have *underestimated* the coverage of STD under syndromic treatment.

In summary, the relative efficacies of the two treatment strategies in covering episodes of bacterial STD do not appear to be a main determinant of the contrast between the trials. As well as depending on coverage, however, the influence of the type of intervention also depends on whether cofactor magnitudes are similar for symptomatic and asymptomatic STD. Furthermore, we have not yet consid-

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* The symptom probability for gonorrhoea and/or chlamydia for Mwanza reduces to 14% and 17% in comparison and intervention arm, respectively, if symptom point prevalences are derived not from the follow-up but from the baseline survey. The reason for the apparent increase trial in symptom probability in the comparison arm during the Mwanza is unclear. An increase in symptom rates in both arms during the Mwanza trial was also apparent among male urethritis cases (Mayaud *et al.* 1997a), which was the reason why symptomatic urethritis was not considered in our analyses of STD reductions (Table 1.1). These considerations illustrate that the symptom probabilities we calculated are only rough estimates.

† In comparison to the estimated treatment rate of 5% for the comparison arm in Mwanza, the estimated 38% clinical treatment rate for Rakai (Chapter 4), in which this service had not been improved either, may now seem inappropriately high. Using 5% as the treatment rate in Rakai, estimated symptom probabilities for this population fall (from 44%) to 36% for gonorrhoea and (from 11%) to 8% for chlamydia.

ered possible effects of the respective interventions other than curing STD. These factors are therefore addressed in the following two subsections.

Cofactor magnitudes of symptomatic vs. asymptomatic STD

In the simulations, cofactor magnitudes were the same for symptomatic and asymptomatic STD episodes. This assumption influenced the simulated effectiveness of syndromic treatment (of symptomatic STD) relative to mass treatment (of symptomatic and asymptomatic STD): if the true cofactor effect of symptomatic STD were relatively higher, our simulations may have underestimated the impact of syndromic treatment.

The hypothesis that symptomatic STD facilitate HIV transmission more than asymptomatic STD, is based mainly on laboratory studies observing higher levels of HIV shedding in symptomatic STD than in asymptomatic STD. However, the relationship between shedding and transmission is unclear, complicating the interpretation of this finding. An important additional consideration is that 'symptomaticity' in shedding studies always relates to disease *signs* as they are detectable by the clinician upon genital examination. This criterion encompasses a larger fraction of patients than does the '*recognised* symptoms' criterion, which is nevertheless the factor of interest from the perspective of treatment seeking and, therefore, the meaning of the symptom probability parameters in *STDSIM*. As explained above, the occurrence of (objective) disease signs is only one of the determinants of the probability that symptoms will be recognised and reported. Our finding of large geographical variation in the probabilities of recognising symptoms for gonorrhoea and chlamydia (Chapters 3 and 4) in fact suggests that symptomaticity for these STD has little to do with the severity of the inflammation they underlie. In the Rakai population, only a subset of individuals with inflammatory gonorrhoea and chlamydia apparently report symptoms of these infections. We therefore conclude that in rural African populations, symptom reporting is unlikely to be an indicator of the severity of HIV cofactor effects that gonorrhoea and chlamydia patients may suffer.

For syphilis and chancroid, the two main other curable STD, the relationship between symptoms and cofactor magnitude is less of an issue. Ulceration, the main genital symptom of these STD and the likely mechanism of their effect on HIV transmission, is easily recognised. The temporal coincidence between the periods with cofactor effect and with recognised symptoms for these infections is reflected in their representation in *STDSIM*. (An example is given in Figure 9.1, the *STDSIM* representation of infection with HSV-2.) It is, however, conceivable that the subset of ulcers that go unrecognised by the patient are less severe, and facilitate HIV transmission less than the majority of ulcers that are recognised by the patient.

In summary, it is still unknown whether there is any significant association between symptom recognition and strength of cofactor effect on HIV transmission. In the rural SSA populations under study, symptom recognition is unlikely

to be an indicator of elevated cofactor magnitudes for non-ulcerative STD. For ulcerative STD, this possibility warrants further research.

Other mechanisms behind the impact of syndromic STD management

Syndromic STD management includes not only treatment of the possible causes of the symptom, but also patient education on sexual abstinence or the consistent use of condoms until treatment is completed, in order to prevent infection of partners, and counselling on how to prevent reinfection [WHO 1994]. It is therefore conceivable that the reduction in HIV incidence observed under the Mwanza intervention may partly have been due to the fact that patients were following recommendations of this type. This effect would be highly influential, as patients with STD infections may often have recently acquired HIV as well (e.g. from the same high-risk sexual contact), and infectivity with HIV is highest in the weeks immediately after infection [Jacquez *et al.* 1994]. It is true that behavioural change would reduce STD rates as well, but over the first few years, impact on HIV incidence might be more pronounced (Figure 8.2b+d and [Korenromp *et al.* 2001a]), resulting in a picture consistent with the Mwanza observations. The hypothesis is particularly attractive, because it would explain both why impact on HIV in Mwanza was so large relative to that in Rakai - where the intervention did not include health education - and the internal inconsistency within the Mwanza trial, in which the impact on HIV was relatively much greater than that on STD.

Analyses of available data on reported risk behaviour at follow-up in the two arms of the Mwanza trial did not clearly confirm or refute the hypothesis. The intervention had not increased reported condom usage; in line with this, the uptake of condoms given to patients in intervention clinics had been very low [Grosskurth *et al.* 1995a]. Among subsamples of adolescents, no differences were detected between arms in HSV-2 seroprevalence (unpublished analyses). However, whereas, at baseline, arms were similar in numbers of recent partners, participants in the intervention arm tended to report slightly fewer recent (casual) partners at follow-up than comparison arm participants [Grosskurth *et al.* 1995a]. And among a subset of men with STD symptoms interviewed at follow-up, a lower proportion (32%) in the intervention arm reported having had sex during symptoms than reported this in the comparison arm (50%, p=0.039 in 1-sided Fisher's exact test; unpublished data); this may be indicative of an intervention effect on temporary abstinence as a preventative behaviour. Among women, no difference was detected between arms in abstinence during symptoms (intervention: 46%; comparison: 43%; unpublished data). Importantly, these analyses could not exclude the possibility of more subtle behavioural effects. Changes may, for example, have been too small to be detected in the surveys, which were conducted on only subsamples of the population, thus limiting the power for comparison. Due to various biases in self-reports, surveys on sexual behaviour are known to be unrealiable and therefore liable to miss trends [Susser *et al.* 1998,

Morris 1993, Wadsworth *et al.* 1996]. Thus, on the basis of the available data we cannot make any conclusions with regard to the presence or absence of behavioural effects in the Mwanza trial. However, if they exist, even very modest behavioural changes could have marked effects on the spread of HIV (see also Chapters 6 and 9).

It is of note that all hypotheses on differences in interventions pertain to the contrast between periodic mass treatment and clinical services for symptomatic patients - whether syndromic or not. In other words, the same comparative advantages and disadvantages would apply with a test-based, 'aetiological' treatment instead of with the syndromic approach - and the inferred benefits of syndromic treatment would hold only over mass treatment, but not over test-based algorithms that may become available in future (see 10.4.2).

10.2.2 Evaluation of hypotheses: differences in the populations

Three hypotheses on the contrast between the trial outcomes related to the populations in which the interventions were delivered.

More mobility in Rakai?
The hypothesis that the Rakai trial had less impact because it was diluted by greater mobility than the Mwanza study is similar to the hypothesis discussed above, i.e. that mobility is more critical to trials of mass treatment than to syndromic treatment. This new hypothesis is unsatisfactory for the same reasons. First, it would imply a contrast in impact not only on HIV, but also on STD. Second, at the coverages achieved in the trials, population mobility would cause only a small dilution of impact [Korenromp *et al.* 1999a]. In addition, a comparative analysis of demographic data from both trials has indicated that there is no evidence of greater mobility in Rakai*.

Stage of the HIV epidemic, HSV-2 and behaviour change
The studies in Chapters 5, 8 and 9 addressed other possibilities that centred around the lower prevalences of curable STD in Rakai relative to Mwanza. Systematic comparisons of trial data demonstrated gonorrhoea, chlamydia, trichomoniasis and active syphilis to be considerably less prevalent in Rakai than in Mwanza (Chapter 5). In contrast to *active* (recently acquired) syphilis - which was more prevalent in Mwanza - *late* syphilis was prevalent at similar levels in both sites,

* On closer examination, any indications of greater mobility in Rakai turned out to relate to methodological differences in eligibility criteria and definitions of mobility (unpublished results by Richard White *et al.*, London School of Hygiene & Tropical Medicine, spring 2001).

and, among older participants, was even more prevalent in Rakai.

One of the explanations for the lower prevalences of curable STD in Rakai is found in the respective levels of risk behaviours in both sites. At the time of the trials, numbers of recent and ongoing sexual partnerships were higher in Mwanza than in Rakai, while condom use in casual contacts was reportedly lower. The excess numbers of partners in Mwanza was, however, lower for lifetime partners*. This suggests that sexual promiscuity may have been higher in Rakai in the 1980s than in the 1990s, and also than in Mwanza throughout the HIV epidemic.

Another explanation lies in the relatively late stage of the HIV epidemic in Rakai. Chapters 8 and 9 explored which of these two explanations was the most important in quantitative terms. Chapter 8 compared the impact of STD treatment over stages of the HIV epidemic, for Rakai and a hypothetical Rakai-like population without behaviour change. Impact on HIV transmission was largest at the beginning of the epidemic, when HIV transmission was still confined to high-risk groups of individuals with high rates of partner change and STD. A shift toward transmission in lower-risk relationships caused the impact to fall over time, this effect being mostly pronounced before the tenth year of the epidemic. In the interval between the tenth and the twentieth year, which approximates the difference in epidemic stages between the Mwanza and Rakai trial populations, impact fell only moderately, from 19% to 15%. This suggests that the natural dynamics of the HIV epidemic contributed to the contrast in outcomes between the trials, but not much.

Interactions in epidemiology between HSV-2 and HIV hardly affected the simulated impact of STD treatment over time. The reason for this was explored further in Chapter 9, where we considered the distribution of cofactor ulcers over the HIV epidemic. In contrast to the prevailing thought, increased herpetic ulceration in immunocompromised HIV patients was predicted to cause, at population level, only a moderate increase in herpes incidence - even in an HIV epidemic that was more advanced and severe than that in Rakai. Furthermore, in populations with sexual behaviour allowing for severe HIV epidemics, genital herpes constitutes only a small proportion of prevalent ulcers and of prevalent cofactor STD; therefore, any change in herpes incidence hardly affects the importance of curable STD in ongoing HIV transmission.

For Rakai-like populations, the decline in impact of STD treatment between year 10 and 20 of the epidemic was larger if also the behavioural change in Uganda was considered: then simulated impact fell to 8% in year 20, i.e. well within the confidence interval around the impact estimate of the Rakai trial (Chapter 8). The considerable influence of behaviour change is explained by the shifts it causes in the aetiological distribution of cofactor ulcers (Chapter 9):

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* Unpublished results, Kate Orroth *et al.*, London School of Hygiene & Tropical Medicine, spring 2001.

behaviour change greatly and rapidly decreases rates of, especially, chancroid - which is of short duration and sensitive to control efforts - relative to HSV-2 - an infection lasting lifelong and responding slow to intervention.A further contribution to the reduction in the proportion of curable cofactor STD is made by similarly large and rapid reductions in the rates of the curable cofactors gonorrhoea and chlamydia.

In summary, simulations and comparative analyses of empirical data suggest that the behavioural risk reduction that has occurred in Uganda since the late 1980s is an important explanation of the limited impact of STD treatment on HIV incidence in Rakai. This effect was enhanced by the late stage of the HIV epidemic at the time of the Rakai trial.

10.2.3 Evaluation of hypotheses: differences in study design

Two hypotheses related to differences between the trials in their design with respect to impact measurement. First, in Mwanza, impact on HIV incidence was measured in a closed cohort while in Rakai it was measured in an open cohort, which also included new immigrants who had not yet benefited from previous rounds of treatment*. Second, in Rakai, both the intervention area and the cohort for each community consisted of the whole village, or the 1000 households closest to the main road. Because of this, cohort members were always close to non-intervention area, and thereby relatively much exposed to reinfection. In Mwanza, in contrast, the cohort included only individuals living in the midst of a larger intervention area, which for each community comprised the whole, broader geographical area served by the health centre where STD management was strengthened. The effect of these differences in study design were not addressed specifically in the previous chapters, but we can note several points.

As with the hypotheses on intervention coverage, these are *a priori* not the most satisfying explanations for the difference between Rakai and Mwanza, as they would imply an equal discrepancy between the two trials in impact on STD and HIV, rather than mainly on HIV. Furthermore, design factors could dilute impact in the cohort only if there were a true impact in the target population. In Rakai, where the impact of STD reductions on HIV incidence was probably truly limited because the prevalence of STD was already low, dilution would

* Specifically, HIV/STD measurement in Rakai at round two (10 months after onset) included participants of round 1 as well as residents who had immigrated in to the area between rounds 1 and 2, and had thus not participated in the mass treatment at round 1. The round 3 evaluation (20 months after onset) included repeaters of round 1, of round 2 and of rounds 1 and 2, as well as new immigrants who had not yet been exposed to the intervention. HIV incidence calculations therefore included participants who participated in any of (at least) two rounds: round 1 and 2, 1 and 3 or 2 and 3.

therefore seem unimportant. In other words, even with a design that allowed less reinfection and larger STD reductions in the evaluation cohort, observed impact in Rakai on HIV incidence would have been limited. The design factors are therefore important mainly for the interpretation of impact observed in Mwanza.

With respect to the size and location of the HIV incidence cohort relative to the intervention area, it is of note that the large-scale set-up of the intervention tested in Mwanza guaranteed outcomes relevant to the case of large-scale implementation, the target of practical health policy. In contrast, the small-scale set up of Rakai, which would limit the impact of any effective intervention, does not constitute a true determinant of intervention impact, but must rather be seen as an artefact. From this perspective, it is fortunate that the way in which intervention effects are simulated in *STDSIM* resembled the Mwanza design more than it resembled the Rakai design*.

Regarding the type of cohort, however, the limitation of Mwanza to a closed cohort may have given a misleading impression of the true impact that occurred in the entire population. Overestimation of impact is likely, because a closed cohort commonly misses relatively mobile individuals, who are at higher risk of STD and HIV and at the same time less able to benefit from improved health services. In addition, compared to Rakai, Mwanza may have overlooked a relatively high number of mobile individuals, because the survey schedule included fewer repeat visits to catch individuals who had not been present at a first visit. From this perspective, the Mwanza trial and the simulations may have been optimistic about the population effect of STD interventions.

10.2.4 Evaluation of hypotheses: random chance

The trial outcomes were subject to random chance, the importance of which is reflected in the large confidence intervals around the point estimates of their impact. The influence of chance was probably great especially for HIV incidence, as there were small numbers of incident cases in either trial cohort, and both trials included only a limited number of community pairs (six in Mwanza, five in Rakai). Results relating to STD rate reductions were also imprecise, as STD rates were monitored only in subsamples of the trial cohorts and also because diagnostic methods for STD measurement were imperfect (especially in Mwanza; see Chapter 5). The influence of random chance can by definition not be estimated from the (single) trials themselves, and it is common to attribute all variation not

* Like most epidemiological models, *STDSIM* largely ignores the influences of exposure of the closed, small model population to the outside-world, as would in reality occur due to frequent temporary movements, circulatory migration, and sexual relationships with individuals living far away. In the simulations in this thesis, such disregard was further enhanced because the options for simulating migration were not used.

explained by specific other determinants, to random chance.

In contrast with the actual trials, the simulations - the intermediate in our conclusions on the trial outcomes - were hardly subject to random error. Although they were produced stochastically, the model outcomes were aggregates of large numbers of simulations. In other words, had the simulation started at a different random number, the overall outcomes would have been nearly the same. In some of the simulation results presented (e.g. Table 7.2), this is illustrated in the narrow confidence intervals surrounding averages, which indicate the variation between multiple runs of the same input specification. These simulation confidence intervals should not be confused with statistical confidence intervals around single field observations as the trials are, or with intervals around point estimates of intervention impact based on multivariate statistical modelling. When comparing simulations with actual trial outcomes, it must also be borne in mind that the simulations identified differences between the Mwanza and Rakai trials that contributed to their contrasting outcomes, but did not precisely state the quantitative role of all explanations in comparison. As a result, the simulations could not either attribute an exact amount of remaining lack-of-fit to 'random chance' (see 10.3.1).

If we consider the overall fit of the various simulations, bearing in mind that, for Mwanza, the simulated syndromic treatment interventions (whatever the coverage and cofactor magnitudes assumed) either produced STD reductions that were too large, or an HIV incidence reduction that was too small (Chapter 7), the main lack-of-fit would appear to lie in the Mwanza trial outcome rather than in the Rakai outcome. From this perspective, a chance factor ignored in the simulations in this thesis, becomes interesting. In the Mwanza trial, the communities randomised to the intervention arm started out with higher rates of HIV and with certain HIV risk factors higher than those randomised into the comparison arm. In particular, HIV prevalence in the cohort was 4.4% in the intervention arm and 3.8% in the comparison arm [Grosskurth *et al.* 1995a, Habbema & De Vlas 1995]. Preliminary simulations of the influence of this 'imbalance' suggested that, if the study arms truly differed this much in baseline HIV prevalence, this could have given a considerable upward bias to the difference in HIV incidence between the arms during the follow-up: e.g. from 17% to 28-32%* [Korenromp *et al.* 2000a]. In reality, however, the true difference in HIV prevalence between the arms was

* The exact value of the simulated bias depended on the assumed cause underlying the imbalance: a difference between arms in the average time of onset of HIV spread, or in the underlying level of risk behaviour. Given that behavioural surveys conducted during the trial did not identify clear differences between arms in numbers of partners or other STD risk behaviours (see 10.2.1), the first factor might be considered a more likely cause. On the other hand, the tendency toward lower baseline rates of, besides HIV, also ulcer reporting, syphilis, gonorrhoea and chlamydia in the intervention arm (Mayaud *et al.*, 1997a) might point at a true - but subtle and otherwise undetectable - difference in risk level.

probably only around 72% of that measured in the cohort, because the cohort consisted of only a subset of the residents living in both study areas so that 'regression to the mean' must be taken into account (Richard Hayes, personal communication). Yet, these results illustrate that random imbalances at baseline can considerably affect the 'impact' observed in trials.

As an alternative approach to account for the imbalances at baseline in risk factors, the imbalance in baseline HIV prevalence was included as a covariate in a direct statistical analysis of the trial outcomes. This resulted in a reduction of estimated impact from 42% to 38% [Hayes *et al.* 1995a]*, i.e. a smaller correction than suggested by our simulations. A reason for this difference may be that the statistical correction did not account for the parallel imbalances in the prevalences of STD. Alternatively, the closed model may have overestimated the dependence of HIV/STD exposure in a population on its HIV/STD prevalence. It may also just be a matter of random chance, i.e. that in the trial the correlation between realised HIV incidence and baseline HIV prevalence on the community level was coincidentally very low, despite the fact that HIV prevalence is generally a good indicator of HIV exposure in epidemics such as the one studied in Mwanza.

10.3 Simulation modelling of STD/HIV spread and control

The greater number of the studies in this thesis were conducted with the aid of a model, *STDSIM*, simulating the transmission dynamics of STD and HIV across populations. This section reflects on the need for and use of such analytical tools, the problems encountered in applying them, and areas for their future application.

10.3.1 Modelling in this thesis

The modelling allowed us to explore the long-term impact of STD interventions including that of programmes not actually performed, e.g. mass treatment and combinations of mass and syndromic STD treatment in Mwanza, and to identify critical determinants of intervention impact (e.g. cofactor magnitudes as determinant of absolute impact; see sensitivity analyses in Chapters 7 and 8). Conclusions from such explorations, however, did not prove to be the most revealing in explaining the contrast between the Mwanza and Rakai trials. In hindsight, the

* HIV imbalance corrected for regression to the mean; imbalances in STD rates not included except for the indicator 'history of self-reported STD ever' (Grosskurth *et al.* 1995a, Hayes *et al.* 1995a).

findings most pertinent to explaining this discrepancy seem predictable even without modelling. This is true particularly for the criterion we proposed, i.e. that explanatory hypotheses should deal primarily with the relationship between STD and HIV reduction, and not with the (proportional) magnitude of STD reductions themselves. Yet, the most insightful non-model-based conclusions (Chapters 2, 4, 5 and section 10.2) were reached only after the first simulation studies had been carried out (Chapter 7; [Korenromp *et al.* 1998, Korenromp *et al.* 1999a]). While this was not a coincidence, it illustrates the main use of the modelling. First, modelling forced us to make explicit all assumptions commonly made in evaluating these community-trials and study them in one comprehensive framework, while continually adopting the necessary population perspective. Secondly, mismatches between the model and empirical observations stimulated the formation of new hypotheses, and identied needs for further analyses of existing data or gaps in data. For example, the criterion that explanations of the Mwanza-Rakai discrepancy must deal primarily with the relationship between STD and HIV reduction, was based on the conclusion of Chapter 7 that, over a two-year period, mass treatment reduces STD prevalences by proportions similar to those achieved by syndromic treatment. In addition, the modelling served to explain unexpected outcomes of direct data analyses. For example, contrary to original hypotheses, the seroprevalence of HSV-2 was found not to be higher in Rakai than in Mwanza (Chapter 5), and this was corroborated and explained by simulations in Chapter 9.

In the light of the above, was it necessary to use a model as sophisticated as *STDSIM*? Theoretically, to structure viewpoints and thoughts and to systematically arrange hypotheses, simple models would have sufficed - and have been preferable. For our predictions of the impact of STD treatment on HIV in the trials, it seems questionable whether the level of detail of separately representing four curable and one incurable STD was warranted, given that trichomoniasis, another cofactor STD targeted by the interventions, was not simulated. Yet, working with a model that could be adapted *ad libitum* to our interests and thoughts may have been very helpful to the generation of new ideas and the initiation of new analyses on existing data. A nice illustration of this can be found in the conclusions on the differential effects of mass treatment and syndromic treatment on the epidemiology of syphilis (Chapter 7). These would probably not have been drawn without the detailed representation of this STD in *STDSIM*, but they were thereafter reproduced in a simpler compartmental model [Garnett & Brunham 1999]. In contrast, in our simulations of trends in the aetiology of genital ulcers (Chapter 9), the intuitive and flexible representation of different individual STD was certainly indispensable. Finally, the typical flexibility of microsimulation models to match the empirical data with respect to the structure of its output (e.g. the STD infection stages that count as prevalent on certain diagnostic tests) also proved a great advantage in validating model outcomes (see for example Chapter 9).

10.3.2 Problems in modelling

Like any model of infectious disease spread, *STDSIM* has its limitations, and some of the limitations relevant to the simulation of STD/HIV interventions must therefore be considered.

First and foremost, the modelling did not provide quantitative conclusions on the impact of STD treatment or other HIV control options. This had little to do with technical limitations in *STDSIM* building, but should instead be imputed to our imperfect knowledge of the determinants of intervention impact. There are various reasons for this, particularly uncertainty about the magnitude of STD cofactor magnitudes, the impossibility of disentangling random effects from systematic effects in the two trials, and the fact that the trial data were not best suited for testing hypotheses that arose only after their collection. In other words, these limitations hold equally for non-model-based studies.

Second, we are uncertain about the correctness of model representations of the 'sexual network', i.e. the patterns of sexual contacts in populations. While individual-based models can account for these critical aspects of sexual behaviour [Kretzschmar *et al.* 1995, Morris & Kretzschmar 1995, Ghani *et al.* 1998], when fitting *STDSIM* to the trial populations, we limited model verification with respect to sexual behaviour largely to some basic measures, such as the proportion of people that were married and their numbers of partners. With regard to sexual network aspects, only age differences between marital partners were considered - which the model fitted rather poorly. This lack of attention was in part unavoidable, because data on sexual network structure were limited, especially for Mwanza. It is also of note that the model representation might not have been better even with more behavioural data: this would have produced dilemmas if improving fit for epidemiology and for sexual behaviour had required opposing adjustments*. Fortunately, the uncertainty about modelling sexual networks was probably not critical to the interpretation of the STD treatment trials, which centred on the relationship between magnitudes of STD and HIV reductions: most determinants of this relationship (Table 10.1) have little to do with network effects. The single determinant that might be seen as a sexual network effect, i.e. population mobility, was studied without *STDSIM* (see 10.2.1 and 10.2.2). However, correctness of the sexual network representation may be critical to future modelling of behavioural/structural interventions and vaccine trials. The same may apply for the evaluation of STD mass treatment programmes in relevant populations (where STD are important in HIV transmission). For such studies, the model would need to be run repeatedly with alternative options for the representation of this (and other) uncertain features, to verify the robustness of predic-

* Such conflicts were already encountered within the restricted set of data used. For example, age patterns in STD prevalences suggested a later onset of sexual activity in men than data on reported sexual debut.

tions.

A third possible limitation is that - in all existing models of HIV spread so far - the phenomenon of evolution of the virus over time has been overlooked. As is common with viruses newly entering the human community, HIV is believed to have been more virulent and lethal in the early years of its spread than it is now [Ambroziak & Levy 1999, Morgan *et al.* 1997a]. Higher virulence may mean that in earlier days, recently infected HIV patients were more infectious than they are now, which has obvious implications for explaining and modelling the onset of HIV epidemics. Notably, for Uganda, a higher initial infectivity would mean that behavioural risk may have been less elevated during the late 1970s and 1980s than we inferred in Chapter 8.

Finally, a problem specific to the stochastic modelling of infectious disease spread is the interpretation of variation between simulation runs in relation to the single actual situation. *STDSIM* produced large variation between runs in the onset and pace of initial STD spread and in the consequent pattern of epidemics. Particularly for HIV, a relatively new, relatively non-infectious disease which was introduced into model populations by randomly attributing one infection to one prostitute*, variation between simulations was impressive. This model feature is thought to reflect a real-world phenomenon - possibly also explaining why in apparently similar populations, HIV started to spread early and rapidly in some, but only much later in others [Buvé *et al.* 1995] - but for application to single real-world epidemics, it poses a problem. In *STDSIM* simulations of the Mwanza HIV epidemic, even though the average simulation outcome adequately fitted the actual epidemic, some individual runs produced HIV prevalences that were totally inconsistent with the empirical data (Chapter 7). We solved this problem by systematically dropping all simulated epidemics that fell outside a predetermined range of HIV prevalence for the trial starting year (which was derived from the prevalence measured in the trial baseline survey). This procedure avoided calculations of intervention impact based on non-existing (0% prevalence) HIV epidemics - of which there were several (around 25% of runs) in the simulation of this low prevalence epidemic. The exclusion algorithm did not alter the main outcomes of the intervention evaluation; and in simulations of the more severe Rakai epidemic (Chapter 8), such exclusion was not needed.

Care should be taken that exclusion of outlier runs is not used inappropriately. In simulations of the spread of HSV-2 for a generic population [Blower *et al.* 1998], this infection was not sustained in 28% of simulated populations, which were therefore excluded from subsequent intervention evaluations. Since HSV-2 is in reality present in all real-world populations [Nahmias *et al.* 1990], this exclusion may have served to mitigate the effects of an incorrect specification of the disease model.

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* Except in simulation of populations with no prostitution, such as Profile 3 in Chapter 6.

An alternative method for avoiding reliance on unrealistic simulation runs would be to, retrospectively, adjust the time line of each simulation until it fits one or more known points on the actual epidemic. This method is based on the consideration that, since for most real-world epidemics the onset is not exactly known, each simulation that can fit the limited empirical data on recent years is equally valid. Or, specifically for the study of HIV epidemics, stochastic variation could be constrained by increasing the number of individuals in whom the infection is seeded (e.g. to several prostitutes, or several prostitutes and prostitute clients).

10.3.3 Future use of models

In a review on the influence of the mathematical modelling of HIV control policies in the developing world, Stover *et al.* concluded that, while modelling has played a major role in increasing our understanding of the dynamics of the epidemic and in identifying gaps in our knowledge, its impact on policies and programs has been limited. The authors recommended a better translation of modelling findings to policy action [Stover 2000]. The use of modelling in our analyses of the STD treatment trials nicely illustrates this first statement. In future, the interpretation of new community-randomised HIV prevention trials (such as trials on the introduction of HSV-2 treatment in developing countries and on HIV and HSV-2 vaccination) may be a promising application of microsimulation models; at the time of writing, however, few trials that would benefit from model-based analysis are underway.

Also outside the realm of trials, there have been few breakthroughs over the past decade that decisively altered the spread or the prospects for controlling HIV and STD in developing countries. In the same period, the modelling business has grown explosively. In the short-term, there thus seems to be little need for scientific modelling to further our understanding. To enhance rational control policy, however, the ongoing publication and dissemination of existing work is certainly indicated. Such educational modelling exercises may elaborate on the cost-effectiveness of alternative interventions (whether single or in combination) in different geographical settings, a subject highly relevant to decision makers faced with the task of distributing or redistributing health care budgets.

At the same time, new theoretical research may be useful in providing insight into the biases and distortions inherent to field observations in STD/HIV epidemiology. While common statistical models cannot fully grasp these, sophisticated microsimulation models employing advanced modern options of computing demand and output, e.g. individual-level databases, can. Recent simulation studies using these techniques have illustrated the difficulties in interpreting data on STD/HIV clustering [Boily & Anderson 1996] and on sexual networks surrounding STD patients [Ghani *et al.* 1998]. Furthermore, on the natural history, epide-

miology and intervention response of viral STD, such as infection with HSV-2 and human papilloma virus (HPV), new lessons are likely to be learnt through modelling. These infections behave differently from the better-known bacterial STD, options for their control differ and are in development, and because of the long duration of these infections, modelling provides an attractive alternative for difficult and lengthy field studies (see as an example Chapter 9).

With regard to forecasting the future course of the HIV epidemic, one subject of interest is the global impact of and prospects for highly active antiretroviral therapy (HAART). Since its introduction in around 1995, HAART has considerably changed the Western HIV epidemic, grossly reducing AIDS mortality. Because HAART reduces HIV viral loads, it may also prevent HIV transmission [Blower *et al.* 2000, Garnett & Anderson 1996b, Ferguson *et al.* 2000]. With the falling costs of the relevant drugs and the continued expansion of HIV in developing countries, HAART is now being advocated for resource-poor countries as well. However, due to the high demands on health infrastructure, logistics, patient education and compliance, this is unlikely to be a successful intervention: most patients treated will probably quickly develop resistance against the drugs, while the majority of patients will remain untreated [Forsythe 1998, Jha *et al.* 2001]. Although the impact of HAART on the HIV epidemic in developing countries is thus likely to remain limited, a consequent possible spread of drug-resistant HIV strains to Western countries may critically alter the prospects of the epidemic there.

10.4 Implications for future research

10.4.1 STD treatment for HIV prevention?

The simulation-aided analyses of the Rakai and Mwanza STD treatment trials suggested three factors to be important in explaining their contrasting outcomes:

- the behaviour change in Uganda preceding the Rakai trial, which reduced risk behaviour and rates of curable STD to below the level in Mwanza;
- the relatively late stage of the HIV epidemic in Rakai, compared to the rising epidemic in Mwanza;
- an imbalance at baseline in HIV prevalence, STD rates and their risk factors in Mwanza.

In the model, these factors were sufficient to explain the lack of impact STD treatment had on HIV in Rakai - behaviour change in Rakai probably having made the largest contribution. They could not, however, fully explain the finding of considerable impact on HIV without large STD reductions in Mwanza. An alternative

explanation for the latter may be alternative (or subsidiary) behavioural effects of the Mwanza intervention on HIV incidence; this could, however, not be ascertained from the trial data.

Although the different approaches to antibiotic treatment (mass or syndromic) and their comparative effects on the magnitude of STD reductions thus appear unrelated to the trial discrepancy, considerations of feasibility, sustainability and cost-effectiveness argue that clinic-based, syndromic treatment is the most practical option for STD management (at least in rural Africa) [Islam *et al.* 1994, Costello Daly *et al.* 1998a, Adler 1996]. This section therefore focuses on further research into clinical STD management.

From a scientific perspective, highest priority would have the conduct of new trials of syndromic management. The aim of such trials would be to find the mechanism behind its impact and resolve the internal inconsistency between the HIV and STD reductions in the Mwanza trial. Trials would have to be conducted in relevant populations, in which STD are not already of reduced importance due to behavioural responses to the HIV epidemic. They might, for example, be conducted either in early HIV epidemics, such as those in some parts of India, or in later ones where there has been no behaviour change, such as in South Africa. Care should be taken to closely monitor intermediate outcome measures, including both STD (with reliable diagnostic tests) and risk behaviour (with validated indicators). To facilitate our ability to distinguish between behavioural and treatment effects, STD measurements should preferably include both curable and incurable infections - reductions in the latter would prove that part of the effect is mediated through behavioural responses.

One barrier to the conduct of such trials - and one that may be decisive - is ethics: the Mwanza trial proved that syndromic STD management combined with health education is - somehow - effective against HIV. From this perspective, it may be unacceptable to withhold (part of) this intervention from future trial comparison groups. However, an alternative worth considering might involve a trial of improved counselling of STD patients alone versus improved counselling combined with improved syndromic treatment [Hudson 2001]. In this respect, the ongoing debate on the ethics of intervention trials in developing countries, where the local standard of care (which could define the comparison group) is less than the best proven option available elsewhere (which would form the comparison group were the study conducted in a richer country) is of interest.

Even if the efficacy of syndromic STD management is deemed proven, trials on its cost-effectiveness may be indicated. Cost-effectiveness varies between settings, so it may not be possible to generalise the cost-per-averted-HIV-case estimated in Mwanza. Furthermore, cost-effectiveness could be assessed separately for the behavioural and the medical sides of STD patient management, possibly with important implications for their relative priorities. And comparisons in cost-effectiveness between STD management and other (e.g. behavioural) interventions may be worthwhile.

Currently, the results are awaited of a recent trial of syndromic treatment on top of education on risk reduction that was conducted in Masaka, a district of Uganda neighbouring Rakai. This trial was designed to answer another highly relevant question, that on the impact of STD treatment as a possible complement to a behavioural intervention. As with the trial in Rakai, which Masaka resembles closely in terms of the stage of the HIV epidemic, the occurrence of behaviour change and low STD prevalences [Mulder *et al.* 1995, Kamali *et al.* 2000], the Masaka study is however unlikely to provide the desired outcome. Evaluation is also ongoing of programmes of selective mass treatment, delivered at high frequency (e.g. monthly) to high-risk groups such as prostitutes, as an effort to maximise the benefits of mass treatment while limiting its costs [Holmes *et al.* 1996, Fonck *et al.* 2000, Steen *et al.* 2000]. Whereas targeting high-risk groups is generally an appropriate way of maximising benefits while limiting the costs of STD interventions (see also Chapter 6 [Brunham 1997]), this may apply less to mass treatment: the primary benefit of mass treatment lies in the simultaneous treatment of all infectees in order to reduce STD (re-)infection in the whole sexual network. Selective mass treatment may therefore be less promising than hoped. However, if the channels for treatment delivery are simultaneously used for health education and condom provision, the overall (cost-)effectiveness of such combined interventions may be high.

Further studies should also include a re-simulation of the Mwanza trial, after correcting *STDSIM* for some limitations relevant to the outcomes of Chapter 7. First, the cofactor STD trichomoniasis, which was treated and reduced in Mwanza, should be added to the model. This will improve the fit for small reductions in each single STD on the one hand, and the large reduction in HIV on the other. Second, the recently improved representation in *STDSIM* of syndromic treatment, which allows for the simultaneous treatment for all possible causes of a specific syndrome and other coinfections - must be used. In the light of the results of Chapter 4, the assumed durations of episodes of gonorrhoea - in males - and especially chlamydia - in both sexes - may require (upward) adjustment. Combined with a (downward) adjustment of the transmission probabilities - which would be needed to maintain fit to observed prevalence levels - these alternative specifications may result in larger predicted impacts of syndromic treatment on STD prevalences. Since the STD reductions in the current simulations were, at the estimated coverage, already on the high side, these adaptations may worsen fit to the data and stimulate a further reflection on the actual coverage achieved in the trial. The anticipated worsening of fit may however be compensated by the need, identified in Chapter 4 and in the previous section, to downwardly adjust symptom probabilities for chlamydia, syphilis and perhaps gonorrhoea and chancroid. A relevant feature of the Mwanza trial which was ignored in Chapter 7 is the round of 'mass treatment' for syphilis for all participants in both study arms with suspected active syphilis (by RPR-positivity) at the start of the trial. Finally,

adaptation may be required with respect to the magnitude of STD reductions achieved, depending on the outcomes of ongoing trial data analyses. In particular, the limitations of the diagnostic tests used in Mwanza (Chapter 5) deserve further consideration, because they may have diluted observed impact.

Re-simulations will help delineate the magnitude of the inconsistency in effects on STD and HIV in the Mwanza trial. It must however be realised that the additional gain in knowledge is ultimately restricted by the uncertainty inherent to the data of this single study.

10.4.2 STD cofactor effects

As discussed above, further observational studies are unlikely to reveal the true magnitude of STD cofactor effects. The only option for answering this question would be a trial of an STD intervention that targeted STD alone (i.e. not targeting risk behaviour and HIV directly), and that resulted in large STD reductions. Mass treatment in a relevant population with high STD baseline rates, and preferably at a higher coverage and in a larger implementation area than Rakai, would come closest to these criteria. However, in view of the criticism of mass treatment that has followed the dissemination of the Rakai results, i.e. that it is neither feasible nor sustainable [Hitchcock & Fransen 1999, Handsfield 1999, Boily *et al.* 2000, Hudson & Smith 2000], such a second mass treatment trial is unlikely to be ever conducted.

Nonetheless, several types of observational and laboratory studies can still help our understanding of the effects of STD on HIV transmission and of relevant HIV prevention strategies based on these effects. One question has clear priority: whether cofactor magnitudes are larger for recognised (symptomatic) than for unrecognised (subjectively asymptomatic, as opposed to clinically detectable) STD. An interesting subsidiary question may be whether the correlation between symptoms and HIV transmission increases when health education campaigns take place. While scientifically, the ideal design would be to evaluate not only HIV shedding but also actual transmission, the ethical acceptability of this is debatable. Another area of interest is the effect on HIV shedding and HIV transmission of bacterial vaginosis - with a correction for its clustering with other STD - in order to test the current insight that BV is not an independent cofactor. Furthermore, in view of the increasing proportion of genital ulcers that are due to HSV-2 in many developing countries [O'Farrell 1999], the strength of the cofactor effect of herpetic recurrences relative to syphilis, chancroid and primary HSV-2 may be worth investigating.

10.5 Implications for HIV prevention policy

10.5.1 STD treatment vs. behavioural intervention

The cofactor studies demonstrated that cofactor values remain uncertain and are possibly lower than previously thought. The simulations suggested that the reduction in HIV incidence following the Mwanza intervention is unlikely to have been fully mediated by reductions in STD cofactor burden brought about by the STD treatment. These combined results suggest that the expectations of the role of STD cofactor burden reduction in HIV prevention should be tempered.

A question not yet explicitly addressed is how STD treatment fares as an HIV prevention strategy in comparison with alternative control options, notably reductions in sexual risk behaviour. In sub-Saharan Africa, strikingly few 'primary prevention programmes' have been evaluated for their effects on STD and HIV rates in randomised trials [Laga *et al.* 1994, Aral & Peterman 1998, Oakley *et al.* 1995]. Simulations described in chapters 6, 8 and 9 and elsewhere [Worldbank 1997] indicated that behaviour change in high-risk groups - including decreased partner change rates, reduced prostitution, or postponement of first sexual activity by adolescents - at response levels actually found in African populations [Asiimwe-Okiror *et al.* 1997, Ng'weshemi *et al.* 1996, Konde-Lule *et al.* 1997, Jackson *et al.* 1997c], is very effective against both HIV and STD*. Importantly, behavioural change is relatively powerful as compared to STD treatment at the level achieved in the Mwanza and Rakai trials, irrespective of the magnitude of STD cofactor effects. This is because behaviour change, by preventing both HIV and STD, also benefits from the cofactor effect. In terms of cost-effectiveness, the primacy of primary prevention over STD treatment may be even more pronounced, because of the high costs of STD clinic set-up, maintenance, drugs, and staff training, relative to education programmes and media campaigns [Moses *et al.* 1991, Worldbank 1997]. The costs and cost-effectiveness of behavioural interventions have, however, proven difficult to estimate quantitatively [Sweat *et al.* 2000, Jha *et al.* 2001]; and they may vary between populations, depending on what types and frequencies of activities are most appropriate.

Inspired by the recent expansion of possible types of control activities, including antiviral HIV therapy and STD screening, there are now calls to re-prioritise (targeted) behavioural interventions [Aggleton *et al.* 1994, Ainsworth & Teokul 2000, Jha *et al.* 2001, Merson *et al.* 2000]. The idea is that, where implementation capacity is weak, focusing on a smaller, core set of the most cost-effective

* For comparison with the STD treatment interventions: simulated proportional HIV incidence reductions over the first two years of interventions reducing the rate of partner change or the occurrence of prostitution ranged between 19% and 58%.

activities is most likely to have an impact. In most African countries, efforts on promoting behavioural change can - with the aid of international donor money - be upscaled [Over & Piot 1996, Worldbank 1997, Ainsworth & Teokul 2000]. Meanwhile, further research on behavioural interventions in SSA is being both advocated and conducted [Aral & Peterman 1998, Ainsworth & Teokul 2000, Merson *et al.* 2000]; these include intervention trials, qualitative and sociobehavioural studies on the optimisation of education sessions, media messages and condom distribution campaigns in terms of groups targeted and context-specificity [Steen *et al.* 2000].

Concluding that behavioural interventions always have more potential than STD treatment would, however, depend on several additional considerations. It is questionable whether behavioural changes at the intensities that occurred in Uganda and featured in the success stories that formed the examples in Chapter 6, are to be expected in all populations. The Ugandan trend may have resulted from an intrinsic response in the population occurring independently of the national AIDS control programme, or it may have been just the effect of socioeconomic stabilisation after the end of the civil war in 1986 (Chapter 8 and [Low-Beer *et al.* 2000]). Thus, even though behavioural change would be the most effective response, it may be a more feasible goal for intervention programmes to improve the quality and use of STD treatment services. In addition, it is unclear whether a behavioural focus is recommended for countries where (spontaneous) behaviour change is already taking place. In such populations, more might be gained by improving the medical management of cofactor STD not rapidly responding to behavioural risk reduction, such as recurrent genital herpes.

These results do not imply that improving comprehensive STD management is unimportant for HIV prevention, since any association between STD and HIV, whether causal or due to shared risk factors, supports the strategy of targeting HIV prevention to STD patients. Although this remains to be evaluated, the Mwanza trial outcomes may be interpreted as evidence of a beneficial effect of comprehensive STD management on HIV incidence by other means than the reduction of STD cofactor burden. Regardless of cofactor magnitudes, STD management including counselling and education is therefore an important way to reach those individuals at highest risk of contracting and spreading HIV. In several SSA countries, these sociobehavioural aspects of clinic-based STD management receive comparatively little attention, and are amenable to improvement [Bryce *et al.* 1994, Harrison *et al.* 1998, Garcia *et al.* 1998, Harrison *et al.* 2000, O'Hara *et al.* 2001, Voeten *et al.* 2001, Chilongozi *et al.* 1996, Somse *et al.* 2000, Moses *et al.* 2000]. Finally, even though the comparative impact of STD management on HIV prevention may be limited, no single prevention strategy in isolation is sufficient to halt HIV spread in the countries worst affected.

The main limitation to the overall effectiveness of clinical STD management is probably its low coverage, which is due to low symptom probabilities. This

means that population-based STD health education to improve STD symptom recognition and health seeking behaviour is of paramount importance. In view of the large proportion of STD patients who, in the first instance, seek care from such non-medically-trained health care providers as drug peddlers, pharmacies or traditional healers [Mwabu 1986, Faxelid *et al.* 1998, Moses *et al.* 1994, Ward *et al.* 1997, Walker *et al.* 2001], there may be great potential for social marketing of pre-packaged self-help STD management kits containing, besides antibiotics for (syndromic) treatment, patient education material, condoms and partner referral cards [Kambugu *et al.* 2000, Castro *et al.* 2000, Harrison *et al.* 2000]. Training of staff in pharmacies may also be indicated [Garcia *et al.* 1998].

Two behaviour components to patient management are key to improving cure rates among symptomatic STD clinic attendants [Adler 1996]. The first is counselling on therapy compliance, i.e. on completing multiple-dose therapies and not sharing dosages with partners and friends - a practice which increases the development of drug resistance. Second, better notification and referral for treatment of infected partners may be desirable, for the prevention of (continual) STD re-infection (the so-called ping-pong effect). On the medical/technical site, options for improvement might be sought in the improvement of diagnostics and of therapies. With regard to improving the cost-effectiveness of clinical management in lower-prevalence populations, the challenges include the development of diagnostic tests that are cheap and easy to perform by unskilled staff working in less-well-equipped laboratories. An additional advantage of this alternative to the syndromic approach might be that it reduces the risk of development and spread of drug resistance caused by the overtreatment of uninfected patients [Steen & Dallabetta 1999]. Priorities for treatment options include the development of cheaper drugs, of alternative drugs for resistant STD strains (such as for gonorrhoea), and of single-dose regimens, the intake of which can be observed by the physician, ensuring compliance and thus reducing the risk of resistance development. Recently, attention has also turned to affordable forms for antiviral treatment of herpetic ulcers, especially for immunocompromised HIV/AIDS patients who may suffer severe and frequent herpetic recurrences [Chen *et al.* 2000].

The aims proposed for the improvement of clinical STD treatment are mostly long-term and, once achieved, are not likely to be the most cost-effective improvements to STD or HIV control. Nevertheless, their indirect effects should not be overlooked. Improved clinical management will improve patient satisfaction and lead to increased clinic attendance.

A consideration so far ignored is the effect of interventions on the disease burden caused by STD themselves. In comparison to the morbidity and mortality caused by HIV, this burden is small, especially in sub-Saharan Africa [Murray & Lopez 1996]; therefore, the ranking of interventions in terms of their impact on HIV will mostly outweigh the ranking in terms of impact on STD. In general, the intervention that is the most (cost-)effective against HIV is also the most (cost-

)effective against STD [Pettifor *et al.* 2000, Moses *et al.* 2000] - although there are exceptions (see for example section 7.5 on syphilis control).

10.5.2 Other HIV prevention strategies?

Relatively new fields of attention are 'structural intervention' and the 'multisectoral approach', which aim to address the environment in which risk behaviour takes place [Decosas & Pedneault 1996, O'Reilly & Piot 1996, Sweat & Denison 1995, Merson *et al.* 2000]. Structural interventions would focus on removing or mitigating structural and environmental risk factors, such as mobility and migration, including seasonal labour and family segregation, social disruption due to war and political instability, and the lack of education and income opportunities for women that underlies their economic and sexual dependence, as well as underlying overall economic underdevelopment and poverty. Though their feasibility and effectiveness remain to be demonstrated, these interventions are considered by some to have great promise - at least in the longer-term [Merson *et al.* 2000]. Yet it is questionable whether HIV prevention budgets should be diverted to these more general health and developmental interventions [Ainsworth & Teokul 2000], and this could not be decided by epidemiologists and health policy makers alone.

Probably more important for HIV prevention than a continued focus on HIV/STD interactions is the development of an HIV vaccine. This has progressed considerably over the last decade, and several candidate vaccines are being evaluated in phase III trials. Yet, in the short term, the prospects for the use of effective vaccination remain poor. Due to the large geographical variability between HIV viral strains and subtypes, vaccines which are effective in one population may not be useful in others. The implementation of vaccination will pose additional challenges: immunisation programmes targeting all sexually active adults require more upscaled and sophisticated logistics than the programmes of infant and child vaccination that are currently feasible [Stott & Hahn 1999, Esparza & Bhamarapravati 2000]. And even with universal vaccination against HIV, the need for behavioural programmes would remain: HIV vaccines are likely to be less than 100% protective, so a false sense of security and consequent upsurge in unsafe behaviours could easily have deleterious adverse effects [Blower & McLean 1994, Anderson *et al.* 1995]. Additionally, in theory at least, if there is no behaviour change, the countries now most affected and at risk will remain highly susceptible to similar epidemics of new sexually-transmitted viruses.

10.6 Conclusion

In conclusion, our studies on STD cofactor effects on HIV transmission demonstrated that, while the magnitude of these effects remains uncertain and cannot be estimated on the basis of observational studies, they are possibly much lower than previously thought. At the same time, this reanalysis confirmed that STD are good indicators of the risk of contracting and spreading HIV, and that, as such, STD clinics are an important access channel for targeting HIV prevention to those individuals most in need.

The simulation-aided analyses of the Rakai and Mwanza STD treatment trials suggested three factors to be important in explaining their contrasting outcomes:

- the behaviour change in Uganda preceding the Rakai trial
- the relatively late stage of the HIV epidemic in Rakai as compared to Mwanza
- an imbalance between study arms in HIV prevalence, STD rates and some of their risk factors at baseline in Mwanza.

These factors were sufficient to explain the lack of impact on HIV in Rakai, but could not fully explain the considerable impact on HIV - without large STD reductions - in Mwanza. Another explanation for the latter - apart from chance - may lie in behavioural effects of the Mwanza intervention on HIV incidence; this could however not be ascertained from the trial data. For a better quantitative understanding of the role of STD care in HIV prevention, new trials of syndromic management, allowing a distinction between cofactor-mediated and other (behavioural) effects, would therefore be needed.

The results suggest that the high expectations of the effectiveness of STD cofactor burden reduction in HIV prevention should be tempered. Lacking further evidence, this has three main implications for practical HIV control:

- More attention for the behavioural components of STD management, such as counselling on the prevention of re-infection and partner infection, and the distribution of condoms, is essential.
- To improve the use of STD management services, parallel population-based STD health education is indicated.
- The promotion of behavioural risk reduction remains the first priority in any setting; this should be addressed through education, skill-building, and through novel, possibly more structural, approaches.

Bibliography

Adam E, Kaufman RH, Mirkovic RR and Melnick JL (1979). Persistence of virus shedding in asymptomatic women after recovery from herpes genitalis. *Obstet Gynecol* **54**(2): 171-3.

Adler M, Foster S, Richens J and Slavin H (1996). Sexual health and care: sexually transmitted infections. Guidelines for prevention and treatment [occasional paper]. London, ODA Health and population.

Adler MW (1996). Sexually transmitted diseases control in developing countries. *Genitourin Med* 72(2): 83-8.

Aggleton P, O'Reilly K, Slutkin G and Davies P (1994). Risking everything? Risk behavior, behavior change, and AIDS. *Science* **265**: 341-345.

Ainsworth M and Teokul W (2000). Breaking the silence: setting realistic priorities for AIDS control in less-developed countries. *Lancet* **356**: 55-60.

Alani MD, Darougar S, Macd.Burns DC, Thin RN and Dunn H (1977). Isolation of Chlamydia trachomatis from the male urethra. *Brit.J.Vener.Dis.* **53**: 88-92.

Alary M, Laga M, Vuylsteke B, Nzila N and Piot P (1996). Signs and symptoms of prevalent and incident cases of gonorrhea and genital chlamydial infection among female prostitutes in Kinshasa, Zaire. *Clin Infect Dis* 22(3): 477-84.

Albrecht MA, DeLuca NA, Byrn RA, Schaffer PA and Hammer SM (1989). The herpes simplex virus immediate-early protein, ICP4, is required to potentiate replication of human immunodeficiency virus in CD4+ lymphocytes. *J Virol* 63(5): 1861-8.

Alexander ER, Chandler J, Pheifer TA, Wang S-P, English M and Holmes KK (1977). Prospective study of perinatal *Chlamydia trachomatis* infection. In: *Nongonococcal urethritis and related infections*. D Hobson and KK Holmes [Eds.]. Washington DC, Am.Soc.for Microbiology: 148-152.

Ambroziak J and Levy JA (1999). Epidemiology, natural history, and pathogenesis of HIV infection (Ch.18). In: *Sexually Transmitted Diseases*. KK Holmes, P-A Mardh *et al.* [Eds.]. New York, McGraw-Hill Companies, Inc.

Anderson RM and May RM (1988). Epidemiological parameters of HIV transmission. *Nature* 333(6173): 514-9.

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

Anderson RM (1991). Mathematical models of the potential demographic impact of AIDS in Africa. [Review]. *Aids* 5(1): S37-44.

Anderson RM and May RM (1991). *Infectious diseases of humans; dynamics and control*. Oxford, Oxford University Press.

Anderson RM (1994). The Croonian lecture, 1994. Populations, infectious disease and immunity: a very non-linear world.

Anderson RM, Swinton J and Garnett GP (1995). Potential impact of low efficacy HIV-1 vaccines in populations with high rates of infection. *Proc R Soc Lond B Biol Sci* 261(1361): 147-51.

Antal GM and Causse G (1985). The control of endemic treponematoses. *Rev.Inf.Dis.* 7(Suppl.2): S220-S226.

Aral SO and Peterman TA (1998). Do we know the effectiveness of behavioural interventions? *Sex.Transm.Dis.* **351**(Suppl.III): S33-S36.

Arya OP, Nsanzumuhire H and Taber SR (1973). Clinical, cultural, and demographic aspects of gonorrhoea in a rural community in Uganda. *Bull World Health Organ* 49(6): 587-95.

Asamoah-Adu A, Weir S, Pappoe M, Kanlisi N, Neequaye A and Lamptey P (1994). Evaluation of a targeted AIDS prevention intervention to increase condom use among prostitutes

in Ghana. *AIDS* **8**: 239-246.

Asiimwe-Okiror G, Opio AA, Musinguzi J, Madraa E, Tembo G and Carael M (1997). Change in sexual behaviour and decline in HIV infection among yount pregnant women in urban Uganda. *AIDS* **11**: 1757-1763.

Augenbraun M, Feldman J, Chirgwin K, Zenilman J, Clarke L, DeHovitz J, Landesman S and Minkoff H (1995). Increased genital shedding of HSV type 2 in HIV-seropositive women. *Ann.Int.Med.* **123**(11): 845-847.

Auvert B, Moore M, Bertrand WE, Beauchet A, Aegerter P, Lusamba D, Diong KT and Klinowski J (1990). Dynamics of HIV infection and AIDS in central African cities. *Int J Epidemiol* **19**(2): 417-28.

Bakir TMF, Hossain A, De-Silva S, Siddiqui A, Sengupta BS, El-Sheikh MM and Bakir AF (1989). Enzyme immunoassay in the diagnosis of Chlamydia trachomatis infections in diverse patient groups. *J.Hyg.Epid.Microbiol.Immunol.* **33**(2): 189-197.

Barnett SD and Brundage JF (2001). Incidence of recurrent diagnoses of Chlamydia trachomatis genital infections among male and female soldiers of the US Army. *Sex Transm Infect* **77**(1): 33-6.

Barongo LR, Borgdorff MW, Mosha FF *et al.* (1992). The epidemiology of HIV-1 infection in urban areas, roadside settlements and rural villages in Mwanza region, Tanzania. *AIDS* **6**: 1521-1528.

Bernstein RS, Sokal DC, Seitz ST, Auvert B, Stover J and Namaara W (1998). Simulating the control of a heterosexual HIV epidemic in a severely affected East-African city: computational modeling of single vs. combined intervention strategies with the iwgAIDS and simulAIDS models. *Interfaces* **28**(3): 101-126.

Bertrand JT, Makani B, Hassig SE, Lewu Niwembo K, Djunghu B, Muanda M and Chirhamolekwa C (1991). AIDS-related knowledge, sexual behavior, and condom use among men and women in Kinshasa, Zaire. *Am.J.Publ.Health* **81**(1): 53-58.

Blower SM and McLean AR (1994). Prophylactic vaccines, risk behavior change and the probability of eradicating HIV in San Francisco. *Science* **265**: 1451-1454.

Blower SM, Porco TC and Darby G (1998). Predicting and preventing the emergence of antiviral drug resistance in HSV-2. *Nat.Med.* **4**(6): 673-678.

Blower SM, Gershengorn HB and Grant RM (2000). A tale of two futures: HIV and antiretroviral therapy in San Francisco [see comments]. *Science* **287**(5453): 650-4.

Boily MC and Anderson RM (1996). Human immunodeficiency virus transmission and the role of other sexually transmitted diseases. Measures of association and study design. *Sex Transm Dis* **23**(4): 312-332.

Boily MC, Lowndes CM and Alary M (2000). Complementary hypothesis concerning the community sexually transmitted disease mass treatment puzzle in Rakai, Uganda. *Aids* **14**(16): 2583-92.

Borchardt KA, Hernandez V, Miller S, Loaiciga K, Cruz L, Naranjo S and Maida N (1992). A clinical evaluation of trichomoniasis in San Jose, Costa Rica using the InPouch TV test. *Genitourin Med* **68**(5): 328-30.

Borgdorff MW (1994). Epidemiology of HIV-1 infection in Mwanza region, Tanzania, University of Amsterdam.

Borgdorff MW, Barongo LR, Newell JN, Senkoro KP, Deville W, Velema JP and Gabone RM (1994). Sexual partner change and condom use among urban factory workers in northwest Tanzania. *Genitourin Med* **70**(6): 378-83.

Boyd JT, Csonka GW and Oates JK (1958). Epidemiology of non-specific urethritis. *Brit.J.Vener.Dis.* **34**: 40-43.

Brody S (1996). Incidence of HIV infection decreases because of nature of epidemics. *BMJ* **312**: 125.

Brunham RC and Plummer FA (1990). A general model of sexually transmitted disease epidemiology and its implications for control. *Med Clin North Am* **74**(6): 1339-52.

Brunham RC and Ronald AR (1991). Epidemiology of Sexually Transmitted Diseases in developing countries. In: *Research Issues un Human Behaviour and Sexually Transmitted Diseases in the AIDS era*. JN Wasserheit [Eds.]. Washington, American Society for Microbiology: 61-80.

Brunham RC (1997). Core group theory: a central concept in STD epidemiology. *Venereology* **10**(1): 34-39.

Bryce J, Vernon A, Brathwaite AR, Perry S, Figueroa JP and Emerson RB (1994). Quality of sexually transmitted disease services in Jamaica: evaluation of a clinic-based approach. Collaborative Working Group on Indicators of STD Case Management. *Bull World Health Organ* 72(2): 239-47.

Buhaug H, Skjeldestad FE, Backe B and Dalen A (1989). Cost effectiveness of testing for chlamydial infections in asymptomatic women. *Med Care* 27(8): 833-41.

Buimer M, van Doornum GJ, Ching S, Peerbooms PG, Plier PK, Ram D and Lee HH (1996). Detection of Chlamydia trachomatis and Neisseria gonorrhoeae by ligase chain reaction-based assays with clinical specimens from various sites: implications for diagnostic testing and screening. *J Clin Microbiol* 34(10): 2395-400.

Bureau of Statistics Tanzania and Macro-International (1997). Tanzania Demographic and Health Survey 1996. Calverton, MD, Bureau of Statistics and Macro International.

Burstein GR, Zenilman JM, Gaydos CA, Diener-West M, Howell MR, Brathwaite W and Quinn TC (2001). Predictors of repeat Chlamydia trachomatis infections diagnosed by DNA amplification testing among inner city females. *Sex Transm Infect* 77(1): 26-32.

Buvé A, Laga M, Crabbe F, Vuylsteke B and Van Lerberghe W (1993). A model for the operational assessment of case detection and management of STDs [abstract WRT 015]. VIIIth International Conference on AIDS in Africa, Marrakech.

Buvé A, Carael M, Hayes R and Robinson NJ (1995). Variations in HIV prevalence between urban areas in sub-Saharan Africa: do we understand them? [Review]. *AIDS* 9(Suppl.A): S103-109.

Buvé A, Gavyole A, Mugeye K, Mayaud P, Grosskurth H, Todd J and Hayes R (1998). A closer look at the intervention of the Mwanza trial: how many patients with an STD are cured by health services? 12th World AIDS conference, Geneva, Switzerland.

Cameron DW, Simonsen JN, D'Costa LJ *et al.* (1989). Female to male transmission of human immunodeficiency virus type 1: risk factors for seroconversion in men. *Lancet* 2(8660): 403-7.

Caraël M, Cleland J and Adeokun L (1991). Overview and selected findings of sexual behaviour surveys. [Review]. *Aids* 5(1): S65-74.

Caraël M (1995). Sexual Behaviour. In: *Sexual behaviour and AIDS in the developing world*. J Cleland and B Ferry [Eds.]. London, World Health Organization: 75-123.

Caraël M, Cleland J, Deheneffe J-C, Ferry B and Ingham R (1995). Sexual behaviour in developing countries: implications for HIV control. *AIDS* 9(10): 1171-1175.

Carpenter LM, Kamali A, Ruberantwari A, Malamba SS and Whitworth JAG (1999). Rates of HIV-1 transmission within marriage in rural Uganda in relation to the HIV sero-status of the partners. *AIDS* **13**: 1083-1089.

Carroll KC, Aldeen WE, Morrison M, Anderson R, Lee D and Mottice S (1998). Evaluation of the Abbott LCx ligase chain reaction assay for detection of Chlamydia trachomatis and Neisseria gonorrhoeae in urine and genital swab specimens from a sexually transmitted disease clinic population. *J Clin Microbiol* 36(6): 1630-3.

Carswell JW (1987). HIV infection in healthy persons in Uganda. *AIDS* **1**: 223-227.

Castro JR, D'Agnes L, Aquino C and Borromeo ME (2000). Breaking the HIV transmission cycle through social marketing of STI management kits in the Philippines. XIIIth International Aids Conference, Durban, South Africa.

Catterson ML and Zadoo V (1993). Prevalence of asymptomatic chlamydial cervical infectionin active duty army females. *Milit.Med.* **158**: 618-619.

Cave VG, Bloomfield RD, Hurdle ES, Gordon EW and Hammock D (1969). Gonorrhea in the obstetric and gynecologic clinic. *JAMA* **210**(2): 309-311.

Chen CY, Ballard RC, Beck-Sague CM *et al.* (2000). HIV infection and genital ulcer disease in South Africa. The herpetic connection. *Sex. Transm. Dis.* **27**(1): 21-29.

Chilongozi DA, Daly CC, Franco L, Liomba NG and Dallabetta G (1996). Sexually transmitted diseases: a survey of case management in Malawi. *Int J STD AIDS* 7(4): 269-75.

Choi K-H and Coates TM (1994). Prevention of HIV infection [Editorial review]. *AIDS* **8**: 1371-1389.

Chokephaibulkit K, Patamasucon P, List M, Moore B and Rodriguez H (1997). Genital Chlamydia trachomatis infection in pregnant adolescents in East Tenessee: a 7-year case-control study. *J. Pediatr. Adolesc. Gynecol.* **10**: 95-100.

Cleland J, Caraël M, Deheneffe J-C and Ferry B (1992). Sexual behaviour in the face of risk: preliminary results from first AIDS-related surveys. *Health Transition Rev* **2, suppl.**: 185.

Clemetson DBA, Moss GB, Willerford DM *et al.* (1993). Detection of HIV DNA in cervical and vaginal secretions. Prevalence and correlates among women in Nairobi, Kenya. *JAMA* **269**(22): 2860-2864.

Coale JA and Demeneny P (1966). *Regional model life tables and stable populations.* Princeton, New Jersey, Princeton University Press.

Cohen CR, Duerr A, Pruithithada N, Rugpao S, Hillier S, Garcia P and Nelson K (1995). Bacterial vaginosis and HIV seroprevalence among female commercial sex workers in Chiang Mai, Thailand. *AIDS* 9(9): 1093-1097.

Cohen MS, Hoffman IF, Royce RA *et al.* (1997). Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. *Lancet* **349**: 1868-1873.

Colebunders RL and Latif AS (1991). Natural history and clinical presentation of HIV-1 infection in adults. [Review]. *Aids* **5**(1): S103-12.

Colvin M, Abdool Karim SS, Connolly C, Hoosen AA and Ntuli N (1998). HIV infection and asymptomatic sexually transmitted infections in a rural South African community. *Int. J. STD&AIDS* 9: 548-550.

Cone RW, Hobson AC, Palmer J, Remington M and Corey L (1991). Extended duration of herpes simplex virus DNA in genital lesions detected by the polymerase chain reaction. *J Infect Dis* **164**(4): 757-60.

Corey L, Benedetti J, Critchlow C *et al.* (1983). Treatment of primary first-episode genital herpes simplex virus infections with acyclovir: results of topical, intravenous and oral therapy. *J Antimicrob Chemother* **12 Suppl B**: 79-88.

Costello Daly C, Franco L, Chilongozi DAT and Dallabetta G (1998a). A cost comparison of approaches to sexually transmitted disease treatment in Malawi. *Health Policy and Planning* **13**(1): 87-93.

Costello Daly C, Wangel AM, Hoffman IF, Canner JK, Lule GS, Lema VM, Liomba NG and Dallabetta GA (1998b). Validation of the WHO diagnostic algorithm and development of an alternative scoring system for the management of women presenting with vaginal discharge in Malawi. *Sex Transm Infect* 74 **Suppl 1**: S50-8.

Crawford C, Knapp JS, Hale J and Holmes KK (1977). Asymptomatic gonorrhea in men: caused by gonococci with unique nutritional requirements. *Science* **196**(4296): 1352-3.

Csonka GW and Oates JK (1990). Syphilis. In: *Sexually Transmitted Diseases; A textbook of genitourinary Medicine.* GW Csonka and JK Oates [Eds.]. London etc, Bailliere Tindall. **b0:** 227-276.

Cutler JC, Kvittingen J, Rose E and McCullough JC (1952). Mass treatment of syphilis in an Indian province. *Bull. World Hlth. Org.* **5**: 377-439.

Dada AJ, Ajayi AO, Diamondstone L, Quinn TC, Blattner WA and Biggar RJ (1998). A sero-

survey of Haemophilus ducreyi, syphilis, and herpes simplex virus type 2 and their association with human immunodeficiency virus among female sex workers in Lagos, Nigeria. *Sex Transm Dis* 25(5): 237-42.

Dallabetta GA, Gerbase AC and Holmes KK (1998). Problems, solutions and challenges in syndromic management of sexually transmitted diseases. *Sex.Transm.Dis.* 74(Suppl.1): S1-S11.

Darrow WW (1976). Venereal infections in three ethnic groups in Sacramento. *Am.J.Publ.Health* 66(5): 446-450.

D'Costa LJ, Plummer FA, Bowmer I, Fransen L, Piot P, Ronald AR and Nsanze H (1985). Prostitutes are a major reservoir of sexually transmitted diseases in Nairobi, Kenya. *Sex Transm Dis* 12(2): 64-7.

De Schryver A and Meheus A (1990). Epidemiology of sexually transmitted diseases: the global picture. *Bull.WHO* 68(5): 639-654.

De Vincenzi I, for the European study group on heterosexual transmission of HIV, (1994). A longitudinal study of HIV transmission by heterosexual partners. *New Engl.J.Med.* 331(6): 341-346.

Decosas J and Pedneault V (1996). Preventing STD through individual- and population-based public health approaches: social and political implications. *J.Inf.Dis.* 174(Suppl.2): S248-S52.

Dickerson MC, Johnston J, Delea TE, White A and Andrews E (1996). The causal role for genital ulcer disease as a risk factor for transmission of human immunodeficiency virus - an application of the Bradford Hill criteria. *Sex.Transm.Dis.* 5: 429-440.

Draper D, Parker R, Patterson E, Jones W, Beutz M, French J, Borchardt K and McGregor J (1993). Detection of Trichomonas vaginalis in pregnant women with the InPouch TV culture system. *J Clin Microbiol* 31(4): 1016-8.

Edwards D, Phillips D and Stancombe S (1985). Chlamydia trachomatis infection at a family planning clinic. *New Zealand Medical Journal* 98: 333-335.

Esparza J and Bhamarapravati N (2000). Accelerating the development and future availability of HIV-1 vaccines: why, when, where, and how? *Lancet* 355(9220): 2061-6.

Ewald PW (1994). Evolution of mutation rate and virulence among human retroviruses. *Philos Trans R Soc Lond B Biol Sci* 346(1317): 333-41; discussion p. 341-3.

Faxelid E, Ahlberg BM, Ndulo J and Krantz I (1998). Health-seeking behaviour of patients with STDs in Zambia. *East Afr.Med.J.* April: 232-236.

Ferguson NM, de Wolf F, Ghani AC *et al.* (2000). Antigen-driven CD4+ T cell and HIV-1 dynamics: residual viral replication under highly active antiretroviral therapy. *PNAS* 96(26): 15167-15172.

Feyisetan B and Pebley AR (1989). Premarital sexuality in urban Nigeria. *Studies in Family Planning* 20(6 Pt.): 343-354.

Fiscus SA, Vernazza PL, Gilliam B, Dyer J, Eron JJ and Cohen MS (1998). Factors associated with changes in HIV shedding in semen. *AIDS Res.&Hum.Retrovir.* 14(Suppl.1): S27-S31.

Fish ANJ, Fairweather DVI, Oriel JD and Ridgway GL (1989). Chlamydia trachomatis infection in a gynaecology clinic population: identification of high-risk groups and the value of contact tracing. *Europ.J.Obstet.Gynecol.Reprod.Biol.* 31: 67-74.

Fleming DT and Wasserheit JN (1999). From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex.Transm.Inf.* 75: 3-17.

Fonck K, Kaul R, Kimani J *et al.* (2000). A randomized, placebo-controlled trial of monthly azithromycin prophylaxis to prevent sexually transmitted infections and HIV-1 in Kenyan sex workers: study design and baseline findings. *Int J STD AIDS* 11(12): 804-11.

Forsythe SS (1998). The affordability of antiretroviral therapy in developing countries:

what policymakers need to know. *AIDS* **12**(Suppl 2): S11-S18.

Fouts AC and Kraus SJ (1980). Trichomonas vaginalis: reevaluation of its clinical presentation and laboratory diagnosis. *J Infect Dis* **141**(2): 137-143.

Fransen L, Nsanze H, D'Costa LJ, Brunham RC and Piot P (1985). Parents of infants with ophthalmia neonatorum: a high-risk group for sexually transmitted diseases. *Sex Transm Dis* **12**(3): 150-4.

Fylkesnes K, Musonda RM, Sichone M, Ndhlovu Z, Tembo F and Monze M (2001). Declining HIV prevalence and risk behaviours in Zambia: evidence from surveillance and population-based surveys. *Aids* **15**(7): 907-16.

Gao F, Bailes E, Robertson DL *et al.* (1999). Origin of HIV-1 in the chimpanzee Pan troglodytes troglodytes. *Nature* **397**(6718): 436-41.

Garcia PJ, Gotuzzo E, Hughes JP and Holmes KK (1998). Syndromic management of STDs in pharmacies: evaluation and randomised intervention trial. *Sex Transm Infect* **74 Suppl 1**: S153-8.

Garnett GP and Anderson RM (1993a). Factors controlling the spread of HIV in heterosexual communities in developing countries: patterns of mixing between different age and sexual activity classes. *Philos Trans R Soc Lond B Biol Sci* **342**(1300): 137-59.

Garnett GP and Anderson RM (1993b). Contact tracing and the estimation of sexual mixing patterns: the epidemiology of gonococcal infections. *Sex.Transm.Dis.* **20**(4): 181-191.

Garnett GP and Anderson RM (1995). Strategies for limiting the spread of HIV in developing countries: conclusions based on studies of the transmission dynamics of the virus. *J.Acq.Imm.Def.Syndr.Hum.Retrovirol.* **9**: 500-513.

Garnett GP and Anderson RM (1996a). Sexually transmitted diseases and sexual behavior: insights from mathematical models. [Review]. *J Infect Dis* **174**(2): S150-61.

Garnett GP and Anderson RM (1996b). Antiviral therapy and the transmission dynamics of HIV-1. *J.Antimicrob.Chemother.* **37**(Suppl.B): 135-150.

Garnett GP, Aral SO, Hoyle DV, Cates W and Anderson RM (1997). The natural history of syphilis. Implications for the transmission dynamics and control of infection. *Sex.Transm.Dis.* **24**(4): 185-200.

Garnett GP and Johnson AM (1997). Coining a new term in epidemiology: concurrency and HIV [editorial; comment]. *Aids* **11**(5): 681-3.

Garnett GP and Brunham RC (1999). Magic bullets need accurate guns - syphilis eradication, elimination, and control. *Microbes Infect* **1**(5): 395-404.

Garnett GP, Mertz KJ, Finelli L, Levine WC and St. Louis ME (1999). The transmission dynamics of gonorrhoea: modelling the reported behaviour of infected patients from Newark, New Jersey. *Phil.Trans.R.Soc.London* **354**: 787-797.

Garnett GP and Rottingen JA (2001). Understanding the dynamic consequences of infectious disease interactions and fractions attributable to STDs. *14th Meeting of the International Society for Sexually Transmitted Diseases Research*, Berlin, Germany.

Ghani AC, Swinton J and Garnett GP (1997). The role of sexual partnership networks in the epidemiology of gonorrhea. *Sex.Transmitted Dis.* **24**(1): 45-56.

Ghani AC, Donnelly CA and Garnett P (1998). Sampling biases and missing data in explorations of sexual partner networks for the spread of sexually transmitted diseases. *Stat.Med.* **17**: 2079-2097.

Ghys PD, Diallo MO, Ettiègne-Traoré V *et al.* (1995). Genital ulcers associated with human immunodeficiency virus-related immunosuppression in female sex workers in Abidjan, Ivory Coast. *J Infect Dis* **172**: 1371-1374.

Ghys PD, Fransen K, Diallo MP *et al.* (1997). The associations between cervicovaginal HIV shedding, sexually transmitted diseases and immunosuppression in female sex workers in Abidjan, Cote d'Ivoire. *AIDS* **11**: F85-F93.

Gilson L, Mkanje R, Grosskurth H *et al.* (1997). Cost-effectiveness of improved treatment

services for sexually transmitted diseases in preventing HIV-1 infection in Mwanza region, Tanzania. *Lancet* **350**: 1805-1809.

Goh CL. Epidemiology of sexualy transmitted diseases in Singapore, 1977 to 1993. *Ann Acad Med Singapore* 1995, **24**(4): 495-9.

Goldberg B and Stricker RB (2000). Bridging the gap: human diploid cell strains and the origin of AIDS. *J Theor Biol* **204**(4): 497-503.

Gray RH, Wawer MJ, Sewankambo NK *et al.* (1999). Relative risks and population attributable fraction of incident HIV associated with symptoms of sexually transmitted diseases and treatable symptomatic sexually transmitted diseases in Rakai district, Uganda. *AIDS* **13**: 2113-2123.

Gray RH, Wawer MJ, Brookmeyer R *et al.* (2001). Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. *Lancet* **357**(9263): 1149-53.

Gregson S, Zhuwau T, Anderson RM and Chandiwana SK (1998). Is there evidence for behaviour change in response to AIDS in rural Zimbabwe? *Soc Sci Med* **46**(3): 321-330.

Grin EI and Guthe T (1973). Evaluation of a previous mass treatment campaign against endemic syphilis in Bosnia and Herzegovina. *Brit J Vener Dis.* **49**(1): 1-19.

Grosskurth H, Mosha F, Todd J *et al.* (1995a). Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet* **346**(8974): 530-6.

Grosskurth H, Mosha F, Todd J *et al.* (1995b). A community trial of the impact of improved sexually transmitted disease treatment on the HIV epidemic in rural Tanzania: 2. Baseline survey results. *AIDS* **9**(8): 927-934.

Grosskurth H, Mayaud P, Mosha F *et al.* (1996). Asymptomatic gonorrhoea and chlamydial infection in rural Tanzanian men. *Bmj* **312**(7026): 277-80.

Grosskurth H, Gray R, Hayes R, Mabey D and Wawer M (2000). Control of STDs for HIV prevention: understanding the implications of the Mwanza and Rakai trials. [Viewpoint paper]. *Lancet* **355**: 1981-1987.

Gupta S, Anderson RM and May RM (1989). Networks of sexual contacts: implications for the pattern of spread of HIV. *Aids* **3**(12): 807-17.

Habbema JDF, Alley ES, Plaisier AP, Van Oortmarssen GJ and Remme JDF (1992). Epidemiological modelling for onchocerciasis control. *Parasitology Today* **8**(3): 99-103.

Habbema JDF and De Vlas SJ (1995). Impact of improved treatment of sexually transmitted disease on HIV infection [letter; comment]. *Lancet* **346**(8983): 1157-8 (discussion 1159-60).

Habbema JDF, De Vlas SJ, Plaisier AP and Van Oortmarssen GJ (1996). The microsimulation approach to epidemiologic modeling of helminthic infections, whith special reference to schisosomiasis. *Am J Trop Med Hyg.* **55**(5): 165-169.

Habbema JDF and Korenromp EL (1999). Chapter 6: Interpreting the Mwanza and Rakai results. In: *From knowledge to practice. STD control and HIV prevention.* K Attawell, H Grosskurth and L Fransen, EU HIV/AIDS programme in developing countries.

Handsfield HH, Lipman TO, Harnisch JP, Tronca E and Holmes KK (1974). Asymptomatic gonorrhea in men. Diagnosis, natural course, prevalence and significance. *N Engl J Med* **290**(3): 117-23.

Handsfield HH, Alexander ER, Pin Wang S, Pedersen AH and Holmes KK (1976). Differences in the therapeutic response of chlamydia-positive and chlamydia-negative forms of nongonococcal urethritis. *J Am Vener Dis Assoc* **2**(3): 5-9.

Handsfield HH (1999). Perspectives on presumptive therapy as a sexually transmitted disease control strategy. *Sex Transm Dis.* **26**(4 Suppl.): S21-22.

Hanenberg RS, Rojanapithayakorn W, Kunasol P and Sokal DC (1994). Impact of Thailand's HIV-control programme as indicated by the decline of sexually transmitted diseases.

Lancet 344(8917): 243-5.

Harms G, Iyambo SN, Corea A, Radebe F, Fehler HG and Ballard RG (1998). Perceptions and patterns of reproductive tract infections in a young rural population in North-West Namibia. *Int.J.STD&AIDS* 9: 744-750.

Harrison A, Wilkinson D, Lurie M, Connolly AM and Karim SA (1998). Improving quality of sexually transmitted disease case management in rural South Africa. *Aids* 12(17): 2329-35.

Harrison A, Karim SA, Floyd K, Lombard C, Lurie M, Ntuli N and Wilkinson D (2000). Syndrome packets and health worker training improve sexually transmitted disease case management in rural South Africa: randomized controlled trial. *Aids* 14(17): 2769-79.

Harrison WO, Hooper RR, Wiesner PJ, Campbell AF, Karney WW, Reynolds GH, Jones OG and Holmes KK (1979). A trial of mycocycline given after exposure to prevent gonorrhea. *NEJM* 300: 1074-1078.

Hart G (1986). Syphilis tests in diagnostic and therapeutic decision making. *Ann Intern Med* 104(3): 368-76.

Hawkes S, Morison L, Foster S, Gausia K, Chakraborty J, Peeling RW and Mabey D (1999). Reproductive-tract infections in women in low-income, low-prevalence situations: assessment of syndromic management in Matlab, Bangladesh. *Lancet* 354: 1776-1781.

Hayes RJ, Grosskurth H and ka-Gina G (1995a). Impact of improved treatment of sexually transmitted disease on HIV infection [Author's reply]. *Lancet* 346: 1159-1160.

Hayes RJ, Mosha F, Nicoll A, Grosskurth H, Newell J, Todd J, Killewo J, Rugemalila J and Mabey D (1995b). A community trial of the impact of improved sexually transmitted disease treatment on the HIV epidemic in rural Tanzania: 1. Design. *AIDS* 9(8): 919-926.

Hayes RJ, Schulz KF and Plummer FA (1995c). The cofactor effect of genital ulcers on the per-exposure risk of HIV transmission in sub-Saharan Africa. [Review]. *J Trop Med Hyg* 98(1): 1-8.

Hayes RJ, Wawer M, Gray R, Whitworth J, Grosskurth H, Mabey D and Group HSTW (1997). Randomised trials of STD treatment in HIV prevention: report of an international workshop. *Genitourin.Med.* 73: 432-443.

Hethcote HW and Yorke JA (1984). *Gonorrhea transmission dynamics and control.* Berlin, Springer-Verlag.

Hillis DM (2000). AIDS. Origins of HIV. *Science* 288(5472): 1757-9.

Hitchcock P and Fransen L (1999). Preventing HIV infection: lessons from Mwanza and Rakai. *Lancet* 353: 513-515.

Hogsborg M and Aaby P (1992). Sexual relations, use of condoms and perceptions of AIDS in an urban area of Guinea-Bissau with a high prevalence of HIV-2. In: *Antropological and socio-cultural studies in the transmission of HIV.* T Dyson [Eds.]. Liege, Ordina Publications: International Union for the Scientific study of the population: 29-36.

Holmberg SD, Stewart JA, Gerber AR, Byers RH, Lee FK, O'Malley PM and Nahmias AJ (1988). Prior HSV-2 infection as a risk factor for HIV infection. *JAMA* 259(7): 1048-1050.

Holmes KK, Johnson DW and Floyd TM (1967). Studies of venereal disease. I. Probenecid-procaine penicillin G combination and tetracycline hydrochloride in the treatment of "penicillin-resistant" gonorrhea in men. *Jama* 202(6): 461-73.

Holmes KK, Johnson DW and Trostle HJ (1970). An estimate of the risk of men acquiring gonorrhea by sexual contact with infected females. *Am J Epidemiol* 91(2): 170-4.

Holmes KK (1974). Gonococcal Infection. In: *Advances in Internal Medicine.* GH Stollerman and et.al., Year Book Medical Publisher.Inc.: 259-85.

Holmes KK, Johnson DW, Kvale PA, Halverson CW, Keys TF and Martin DH (1996). Impact of a gonorrhea control program, including selective mass treatment, in female sex workers. *J Infect Dis* 174(2): S230-9.

Holmes KK, Mardh P-A, Sparling PF, Lemon SM, Stamm WE, Piot P and Wasserheit JN, Eds. (1999). *Sexually transmitted diseases, 3rd edition*. New York, McGraw-Hill Companies, Inc.

Hook III EW, Richey CM, Leone P, Bolan G, Spalding C, Henry K, Clarke P, Smith M and Celum CL (1997). Delayed presentation to clinics for STD by symptomatic patients. A potential contributor to continuing STD morbidity. *Sex.Transm.Dis.* **24**(8): 443-448.

Hooper RR, Reynolds GH, Jones OG *et al.* (1978). Cohort study of venereal disease. I: the risk of gonorrhea transmission from infected women to men. *Am J Epidemiol* **108**(2): 136-44.

Horsburgh Jr. R, Jason J, Longini IM *et al.* (1989). Duration of HIV infection before detection of antibody. *Lancet* **8664**: 637-640.

Hudson CP (1999). Syndromic management for STDs: back to the drawing board [Review]. *Int.J.STD&AIDS* **10**: 423-434.

Hudson CP and Smith AN (2000). Ethics of mass STD treatment. *Lancet* **356**(9235): 1115.

Hudson CP (2001). Community-based trials of sexually transmitted disease treatment: repercussions for epidemiology and HIV prevention. *Bull.WHO* **79**(1): 48-58.

Hunter DJ, Maggwa BN, Mati JK, Tukei PM and Mbugua S (1994). Sexual behavior, sexually transmitted diseases, male circumcision and risk of HIV infection among women in Nairobi, Kenya. *Aids* **8**(1): 93-9.

Islam MQ, Latif A, Burton T and Piot P (1994). Analysis of the cost-effectiveness of approaches to STD case management. *Sex Transm Dis* **supplement 1994**: S138.

Jackson DJ, Rakwar JP, Bwayo JJ, Kreiss JK and Moses S (1997a). Urethral Trichomonas vaginalis infection and HIV-1 transmission [letter]. *Lancet* **350**(9084): 1076.

Jackson DJ, Rakwar JP, Chohan B, Mandaliya K, Bwayo JJ, Ndinya-Achola JO, Nagelkerke NJ, Kreiss JK and Moses S (1997b). Urethral infection in a workplace population of East African men: evaluation of strategies for screening and management. *J Infect Dis* **175**(4): 833-8.

Jackson DJ, Rakwar JP, Richardson BA *et al.* (1997c). Decreased incidence of sexually transmitted diseases among trucking company workers in Kenya: results of a behavioural risk-reduction programme. *AIDS* **11**(7): 903-909.

Jacobs NF and Kraus SJ (1975). Gonoccocal and nongonococcal urethritis in men. Clinical and laboratory differentiation. *Ann.Intern.Med.* **82**: 7-12.

Jacquez JA, Koopman JS, Simon CP and Longini I, Jr. (1994). Role of the primary infection in epidemics of HIV infection in gay cohorts. [Review]. *J Acquir Immune Defic Syndr* **7**(11): 1169-84.

Jekel JF (1968). Role of acquired immunity to T. pallidum in the control of syphilis. *Publ.Health Reports* **83**(8): 627-632.

Jessamine PG, Plummer FA, Ndinya Achola JO *et al.* (1990). Human immunodeficiency virus, genital ulcers and the male foreskin: synergism in HIV-1 transmission. [Review]. *Scand J Infect Dis Suppl* **69**: 181-6.

Jha P, Nagelkerke JD, Ngugi EN, Prasada Rao JV, Willbond B, Moses S and Plummer FA (2001). Public health. Reducing HIV transmission in developing countries. *Science* **292**(5515): 224-5.

Johannisson G, Sernryd A and Lycke E (1979). Susceptibility of Chlamydia trachomatis to antibiotics in vitro and in vivo. *Sex Transm Dis* **6**(2): 50-7.

Johannisson G, Lowhagen GB and Lycke E (1980). Genital Chlamydia trachomatis infection in women. *Obstet Gynecol* **56**(6): 671-5.

John GC, Nduati RW, Mbori-Ngacha D *et al.* (1997). Genital shedding of human immunodeficiency virus type 1 DNA during pregnancy: association with immunosuppression, abnormal cervical or vaginal discharge, and severe vitamin A deficiency. *J Infect Dis* **175**(1): 57-62.

John J and Donald WH (1978). Asymptomatic urethral gonorrhoea in men. *Brit.J.Vener.Dis.*

54: 332-323.
Judson FN (1981). Epidemiology and control of non-gonococcal urethritis and genital chlamydial infections: a review. *Sex.Transm.Dis.* 8(2): 117-126.
Judson FN (1990a). Gonorrhea. *Med.Clin.North America* 74(6): 1353-1366.
Judson NF (1990b). Clinical facilities for sexually transmitted diseases control. In: *Sexually Transmitted Diseases*. KK Holmes, P-A Mardh *et al.* [Eds.]. New York [etc], McGraw-Hill, Inc: 1047-1055.
Kamali A, Carpenter LM, Whitworth JA, Pool R, Ruberantwari A and Ojwiya A (2000). Seven-year trends in HIV-1 infection rates, and changes in sexual behaviour, among adults in rural Uganda. *Aids* 14(4): 427-34.
Kambugu FSK, Jacobs B, Lwanga A, Ochwo M, Cutler JR, Tifft S, Pool R and Whitworth JAG (2000). Evaluation of a socially marketed pre-packaged treatment kit for men with urethral discharge in Uganda. XIIIth International Aids Conference, Durban, South Africa.
Katz BP (1992). Estimating transmission probabilities for chlamydial infection. *Stat Med* 11(5): 565-77.
Kaul R, Kimani J, Nagelkerke NJD, Plummer FA, Bwayo JJ, Brunham RC, Ngugi EN and Ronald A (1997). Risk factors for genital ulcerations in Kenyan sex workers. The role of HIV-1 infection. *Sex.Transm.Dis.* 24(7): 387-392.
Kault DA (1995). Modelling AIDS reduction strategies. *Int.J.Epid.* 24(1): 188-197.
Keim J, Woodard P and Anderson MK (1992). Screening for Chlamydia trachomatis in college women on routine gynecological exams. *College Health* 41: 17-23.
Kelsey J, Thompson WD and Evans AS (1986). *Methods in observational epidemiology*. Oxford, Oxford University Press.
Kigadye RM, Klokke A, Nicoll A *et al.* (1993). Sentinel surveillance for HIV-1 among pregnant women in a developing country: 3 years' experience and comparison with a population serosurvey. *Aids* 7(6): 849-55.
Kilian AhD, Gregson S, Ndyanabangi B *et al.* (1999). Reductions in risk behaviour provide the most consistent explanation for declining HIV-1 prevalence in Uganda. *AIDS* 13: 391-398.
Koelle DM, Benedetti J, Langenberg A and Corey L (1992). Asymptomatic reactivation of herpes simplex virus in women after the first episode of genital herpes. *Ann Intern Med* 116(6): 433-7.
Konde-Lule JK, Musagara M and Musgrave S (1993). Focus group interviews about AIDS in Rakai district of Uganda. *Soc Sci Med* 37(5): 679-84.
Konde-Lule JK and Sebina AJ (1993). The impact of AIDS in a rural Ugandan community. *East Afr Med J* 70(11): 725-9.
Konde-Lule JK, Wawer MJ, Sewankambo NK, Serwadda D, Kelly RK, Li C, Gray RH and Kigongo D (1997). Adolescents, sexual behaviour and HIV-1 in rural Rakai district, Uganda. *AIDS* 11: 791-799.
Konings E, Blattner WA, Levin A, Brubaker G, Siso Z, Shao J, Goedert JJ and Anderson RM (1994). Sexual behaviour survey in a rural area of northwest Tanzania. *AIDS* 8: 987-993.
Koopman JS, Longini IM, Jacques JA, Simon CP, Ostrow DG, Martin WR and Woodcock DM (1991). Assessing risk factors for transmission of infection. *Am.J.Epid.* 133(2): 1199-1209.
Koopman JS and Longini IM (1994). The ecological effects of individual exposures and nonlinear disease dynamics in populations. *Am.J.Publ.Health* 84(5): 836-842.
Korber B, Muldoon M, Theiler J, Gao F, Gupta R, Lapedes A, Hahn BH, Wolinsky S and Bhattacharya T (2000). Timing the ancestor of the HIV-1 pandemic strains. *Science* 288(5472): 1789-96.
Korenromp EL, Van Vliet C, Gavyole A, Grosskurth H, Hayes RH and Habbema JDF (1998). Patterns of participation in mass STD treatment: model-aided evaluation of impact on

HIV incidence [oral presentation]. 12th World AIDS Conference, Geneva.

Korenromp EL, Grosskurth H, Hayes R, Meester EI, Wawer MJ and Habbema JDF (1999a). Modelling the impact of STD treatment on HIV in sub-Saharan Africa: use in the interpretation of trials [oral presentation]. 13th Meeting of the International Society for Sexually Transmitted Diseases Research, Denver, USA.

Korenromp EL, Meester EI and Habbema JDF (1999b). STD treatment for HIV prevention - model-based evaluation of the impact in different phases of the HIV epidemic [poster presentation]. 13th Meeting of the International Society for Sexually Transmitted Diseases Research, Denver, USA.

Korenromp EL, De Vlas SJ and Habbema JDF (2000a). The effect of imbalances in risk factors between arms at baseline in community-randomized HIV prevention trials. *XIII International AIDS conference*: Abstract nr. WePpP1313.

Korenromp EL, Van Vliet C, Bakker R, De Vlas SJ and Habbema JDF (2000b). HIV spread and partnership reduction for different patterns of sexual behaviour - a study with the microsimulation model *STDSIM. Math.Popul.Studies* **8**: 135-173.

Korenromp EL, Van Vliet C, Grosskurth H, Gavyole A, Van der Ploeg CPB, Fransen L, Hayes RJ and Habbema JDF (2000c). Model-based evaluation of single-round mass STD treatment for HIV control in a rural African population. *AIDS* **14**(5): 573-593.

Korenromp EL, Bakker R, Gray R, Wawer MJ, Serwadda D and Habbema JDF (2001a). The effect of HIV, behavioural change and STD syndromic management on STD epidemiology in sub-Saharan Africa - simulations of Uganda. *Sex.Transm.Inf.* **accepted**.

Korenromp EL, De Vlas NJ, Nagelkerke NJD and Habbema JDF (2001b). Estimating the magnitude of STD cofactor effects on HIV transmission - how well can it be done? *Sex.Trans.Dis.* **in press**.

Korenromp EL, Bakker R, De Vlas SJ, Robinson NJ, Hayes R and Habbema JDF (in press). Can behaviour change explain increases in the proportion of genital ulcers attributable to herpes in sub-Saharan Africa? A simulation modelling study. *Sex.Trans.Dis.* **in press**.

Kovacs GT, Westcott M, Rusden J, Asche V, King H, Haynes SE, Moore EK and Keterbey JW (1987). The prevalence of Chlamydia trachomatis in a young sexually-active population. *Med.J.Austr.* **147**: 550-552.

Kreiss J, Willerford DM, Hensel M *et al.* (1994). Association between cervical inflammation and cervical shedding of HIV DNA. *J.Inf.Dis.* **170**: 1597-1601.

Kreiss JK, Koech D, Plummer FA *et al.* (1986). AIDS virus infection in Nairobi prostitutes. Spread of the epidemic to East Africa. *N Engl J Med* **314**(7): 414-8.

Kretzschmar M, Reinking DP, Van Zessen G, Brouwers H and Jager JC (1993). Network models: from paradigm to mathematical tool. In: *Modeling the AIDS epidemic*. E Kaplan and M Brandeau [Eds.]. New York, Raven Press: 5610583.

Kretzschmar M, Jager JC, Reinking DP, Zessen Gv and Brouwers H (1995). A network modelling approach for assessing the efficiency of prevention strategies. *J Math Soc* **20**(4): 351-374.

Kretzschmar M, Van Duynhoven YT and Severijnen AJ (1996). Modeling prevention strategies for gonorrhea and chlamydia using stochastic network simulations. *Am J Epidemiol* **144**(3): 306-17.

Krieger JN, Tam MR, Stevens CE, Nielsen IO, Hale J, Kiviat NB and Holmes KK (1988). Diagnosis of trichomoniasis. Comparison of conventional wet-mount examination with cytologic studies, cultures, and monoclonal antibody staining of direct specimens. *Jama* **259**(8): 1223-7.

Laga M, Nzila N and Goeman J (1991). The interrelationship of sexually transmitted diseases and HIV infection: implications for the control of both epidemics in Africa. [Review]. *Aids* **5**(1): S55-63.

Laga M, Manoka A, Kivuvu M *et al.* (1993). Non-ulcerative sexually transmitted diseases as

risk factors for HIV-1 transmission in women: results from a cohort study. *AIDS* 7(1): 95-102.

Laga M, Alary M, Nzila N, Manoka AT, Tuliza M, Behets F, Goeman J, St Louis M and Piot P (1994). Condom promotion, sexually transmitted diseases treatment, and declining incidence of HIV-1 infection in female Zairian sex workers. *Lancet* 344(8917): 246-8.

Langenberg A, Benedetti J, Jenkins J, Ashley R, Winter C and Corey L (1989). Development of clinically recognizable genital lesions among women previously identified as having "asymptomatic" herpes simplex virus type 2 infection. *Ann Intern Med* 110(11): 882-7.

Lao DG and Trussel RE (1947). Chancroid in women in Manila. *Am.J.Syph.* 31: 277-288.

Larsen SA, Steiner BM and Rudolph AH (1995). Laboratory diagnosis and interpretation of tests for syphilis. *Clin Microbiol Rev* 8(1): 1-21.

Lauderdale TL, Landers L, Thorneycroft I and Chapin K (1999). Comparison of the PACE 2 assay, two amplification assays, and Clearview EIA for detection of Chlamydia trachomatis in female endocervical and urine specimens. *J Clin Microbiol* 37(7): 2223-9.

Lavreys L, Rakwar JP, Thompson ML, Jackson DJ, Mandaliya K, Chohan BH, Bwayo JJ, Ndinya-Achola JO and Kreiss JK (1999). Effect of circumcision on incidence of HIV type I and other STDs: a prospective cohort study of trucking company employees in Kenya. *J.Inf.Dis.* 180: 330-336.

Le Pont F and Blower SM (1991). The supply and demand of sexual behavior: implications for heterosexual HIV epidemics. *J.Acq.Imm.Def.Syndr.* 4: 987-999.

Lee HH, Chernesky MA, Schachter J, Burczak JD, Andrews WW, Muldoon S, Leckie G and Stamm WE (1995). Diagnosis of Chlamydia trachomatis genitourinary infection in women by ligase chain reaction assay of urine. *Lancet* 345(8944): 213-6.

Leslie WD and Brunham RC (1990). The dynamics of HIV spread: a computer simulation model. *Comput Biomed Res* 23(4): 380-401.

Levy JA (1993). The transmission of HIV and factors influencing progression to AIDS [review]. *Am.J.Med.* 95: 86-9100.

Lim KB, Thirumoorthy T, Lee CT, Sng EH and Tan T (1989). Endocervical chlamydial infection in female contacts of patients with non-gonococcal urethritis. *Sing.Med.J.* 30: 164-166.

Lindan CP, Allen S, Serufilira A *et al.* (1992). Predictors of mortality among HIV-infected women in Kigali, Rwanda. *Ann Intern Med* 116(4): 320-8.

Lodin A (1955). Has the incubation period of gonorrhoea undergone a change? *Acta Derm.Venereol.* 35: 457-462.

Low-Beer D and Stoneburner RL (1997). An age- and sex-structured HIV epidemiological model: features and applications. *Bull.WHO* 75(3): 213-221.

Low-Beer D, Barnett T, Whiteside A and Stoneburner R (2000). Knowledge diffusion and the personalisation of risk as key indicators of behaviour change in Uganda compared to Southern Africa. XIIIth International AIDS conference, Durban, South Africa.

Lycke E, Lowhagen GB, Hallhagen G, Johannisson G and Ramstedt K (1980). The risk of transmission of genital Chlamydia trachomatis infection is less than that of genital Neisseria gonorrhoeae infection. *Sex Transm Dis* 7(1): 6-10.

Mabey D, Bailey RC, Faal H, Mabey D, Vitale S and Schachter J (1998). Azithromycin in control of trachoma. 2. Community-based treatment of trachoma with oral azithromycin: a one year follow-up study in the Gambia. 9th International symposium on human chlamydial infection, San Franciso.

Madico G, Quinn TC, Rompalo A, McKee KT, Jr. and Gaydos CA (1998). Diagnosis of Trichomonas vaginalis infection by PCR using vaginal swab samples. *J Clin Microbiol* 36(11): 3205-10.

Magnuson H, Thomas E, Olansky S, Kaplan B, de Mello L and Cutler J (1956). Inoculation of syphilis in human volunteers. *Medicine* 35: 33-82.

Mahoney JF, Van Slyke J, Wolcott RR, Thayer JD and Nimelman A (1942). Culture studies in chronic gonorrhea of women. *Am.J.Syph.Gon.Ven.Dis.* **26**: 38-47.

Marlink R, Kanki P, Thior I *et al.* (1994). Reduced rate of disease development after HIV-2 infection as compared to HIV-1. *Science* **265**: 1587-1590.

Martin DH (1990). Chlamydial infections. *Med.Clin.North America* **74**(6): 1367-1387.

Martin HL, Richardson BA, Nyange PM *et al.* (1999). Vaginal lactobacilli, microbial flora, and risk of human immunodeficiency virus type 1 and sexually transmitted disease acquisition. *J Infect Dis* **180**(6): 1863-8.

Matondo P, Johnson I and Sivapalan S (1995). Morbidity and disease prevalence in male and female sexual contacts of patients with genital chlamydial infection. *Int J STD & AIDS* **6**: 367-368.

Mayaud P, Grosskurth H, Changalucha J *et al.* (1995). Risk assessment and other screening options for gonorrhoea and chlamydial infections in women attending rural Tanzanian antenatal clinics. *Bull WHO* **73**(5): 621-630.

Mayaud P, Mosha F, Todd J *et al.* (1997a). Improved treatment services significantly reduce the prevalence of STDs in rural Tanzania: results of a randomised controlled trial. *AIDS* **11**(15): 1873-1880.

Mayaud P, Msuya W, Todd J, Kaatano G, West B, Begkoyian G, Grosskurth H and Mabey D (1997b). STD rapid assessment in Rwandan refugee camps in Tanzania. *Genitourin.Med.* **73**: 33-38.

Mayer KH and Anderson DJ (1995). Heterosexual HIV transmission. *Infect.Agents Dis.* **4**: 273-284.

Mbizvo MT, Machekano R, McFarland W, Ray S, Bassett M, Latif A and Katzenstein D (1996). HIV seroincidence and correlates of seroconversion in a cohort of male factory workers in Harare, Zimbabwe. *Aids* **10**(8): 895-901.

Mbopi-Keou F-X, Grésenguet G, Mayaud P, Weiss HA, Gopal R, Brown DWG, Hayes RJ, Mabey DCW and Bélec L (1999). Genital HSV-2 shedding is increased in HIV-infected women in Africa. *AIDS* **13**(4): 536-537.

McCaughtry ML, Fleagle GS and Docherty JJ (1982). Inapparent genital herpes simplex virus infection in college women. *J Med Virol* **10**(4): 283-90.

McClelland RS, Wang CC, Mandaliya K *et al.* (2001). Treatment of cervicitis is associated with decreased cervical shedding of HIV-1. *Aids* **15**(1): 105-10.

McCormack WM, Stumacher RJ, Johnson K and Donner A (1977). Clinical spectrum of gonococcal infection in women. *Lancet* **1**(8023): 1182-5.

McCormack WM, Alpert S, McComb DE, Nichols RL, Semine DZ and Zinner SH (1979). Fifteen-month follow-up study of women infected with Chlamydia trachomatis. *NEJM* **300**(3): 123-125.

McCormack WM (1981). Clinical spectrum of infection with Neisseria gonorrhoeae. *Sex.Transm.Dis.* **8**(4): 305-37.

McCutchan JA (1984). Epidemiology of venereal urethritis: comparison of gonorrhea and nongonococcal urethritis. *Rev.Inf.Dis.* **6**(5): 669-688.

McLean KA, Evans BA, Lim JM and Azadin BS (1990). Postgonococcal urethritis: a double-blind study of doxycycline vs placebo [see comments]. *Genitourin Med* **66**(1): 20-3.

Meekers D (2000). Going underground and going after women: trends in sexual risk behaviour among gold miners in South Africa. *Int J STD AIDS* **11**(1): 21-6.

Meheus A and Antal GM (1992). The endemic treponematoses: not yet eradicated. *World Health Statist.Q.* **45**: 228-237.

Merson MH, Dayton JM and O'Reilly K (2000). Effectiveness of HIV prevention interventions in developing countries. *Aids* **14 Suppl 2**: S68-84.

Mertens TE, Hayes RJ and Smith PG (1990). Epidemiological methods to study the interaction between HIV infection and other sexually transmitted diseases. [Review]. *Aids* **4**(1): 57-65.

Mills S, Benjarattanaporn P, Bennet A, Pattalung RN, Sundhagul D, Trongsawad P, Gregorich SE, Hearst N and Mandel JS (1997). HIV risk behavioral surveillance in Bangkok, Thailand: sexual behavior trends among eight population groups. *AIDS* **11**(suppl 1): S43-S51.

Ministry of Health, Kaijuka EM, Kaija EZA, Cross AR and Loaiza E (1989). Uganda Demographic and Health Survey 1988/1989. Entebbe, Uganda, Ministry of Health, in collaboration with Ministry of Planning and Economic Development, Dept. of Geography and Institute of Statistics and Applied Economics, Makerere University, and Institute for Resource Development/Macro Systems Inc., Columbia, Maryland USA.

Mode CJ, Gollwitzer HE, Salsburg MA and Sleeman CK (1989). A methodological study of a nonlinear stochastic model of an AIDS epidemic with recruitment. *Ima J Math Appl Med Biol* 6(3): 179-203.

Molin L (1970). Gonorrhoea in 1968. *Acta Dermatovener. (Stockholm)* **50**: 157-160.

Morgan D, Malamba SS, Maude GH, Okongo MJ, Wagner H-U, Mulder DW and Whitworth JA (1997a). An HIV-1 natural history cohort and survival times in rural Uganda. *AIDS* **11**: 633-640.

Morgan D, Maude GH, Malamba SS, Okongo MJ, Wagner H-U, Mulder DW and Whitworth JA (1997b). HIV-1 disease progression and AIDS-defining disorders in rural Uganda. *The Lancet* **350**(245-250).

Morris M (1991). A log-linear modeling framework for selective mixing. *Math Biosci* **107**(2): 349-77.

Morris M (1993). Telling tails explain the discrepancy in sexual partner reports. *Nature* **365**(6445): 437-40.

Morris M and Kretzschmar M (1995). Concurrent partnerships and transmission dynamics in networks. *Social networks* **17**: 299-318.

Morris M, Sewankambo NK, Wawer MJ, Serwadda D and Lainjo B (1995). *Concurrent partnerships and HIV transmission in Rakai district, Uganda (Abstract TuC105)*. Kampala, IXth International Conference on AIDS and STD in Africa.

Morris M, Podhisita C, Wawer MJ and Handcock MS (1996). Bridge populations in the spread of HIV/AIDS in Thailand. *Aids* **10**(11): 1265-71.

Morris M (1997). Sexual networks and HIV. *AIDS* **11**(suppl A): S209-S216.

Morris M and Kretzschmar M (1997). Concurrent partnerships and the spread of HIV [see comments]. *Aids* **11**(5): 641-8.

Morris M and Kretzschmar M (1998). A microsimulation study of the effect of concurrent partnerships on the spread of HIV in Uganda. *IUSSP seminar on Measurement and modelling the spread of AIDS, Kopenhagen*.

Morse SA, Moreland AA and Thompson SE (1990). *Atlas of sexually transmitted diseases*. New York, Gower Medical Publishing.

Moses S, Plummer FA, Ngugi EN, Nagelkerke NJ, Anzala AO and Ndinya-Achola JO (1991). Controlling HIV in Africa: effectiveness and cost of an intervention in a high-frequency STD transmitter core group. *Aids* **5**(4): 407-11.

Moses S, Ngugi EN, Bradley JE, Njeru EK, Eldridge G, Muia E, Olenja J and Plummer FA (1994). Health care-seeking behavior related to the transmission of sexually transmitted diseases. *Am.J.Publ.Health* **84**(12): 1947-1951.

Moses S, Bailey RC and Ronald AR (1998). Male circumcision: assesment of health benefits and risks. *Sexually Transmitted Infections* **74**: 368-373.

Moses S, Ngugi EN, Costigan A, Kariuki C, Ronald AR, MacLean I and Plummer FA (2000). Declining STD and HIV prevalences among antenatal and family planning clinic attenders in Nairobi, Kenya, from 1992-1999. XIIIth International AIDS conference, Durban, South Africa.

Mosha F, Nicoll A, Barongo L *et al.* (1993). A population-based study of syphilis and sexually transmitted disease syndromes in north-western Tanzania. 1. Prevalence and incidence.

Genitourin Med 69(6): 415-20.

Moss GB and Kreiss JK (1990). The interrelationship between human immunodeficiency virus infection and other sexually transmitted diseases. [Review]. *Med Clin North Am* 74(6): 1647-60.

Moss GB, Overbaugh J, Welch M, Reilly M, Bwayo J, Plummer FA, Ndinya-Achola JO, Malisa MA and Kreiss JK (1995). HIV DNA in urethral secretions in men: association with gonococcal urethritis and CD4 cell depletion. *J.Inf.Dis.* **172**: 1469-1474.

Mostad SB and Kreiss JK (1996). Shedding of HIV-1 in the genital tract [Editorial review]. *AIDS* **10**: 1305-1315.

Mostad SB, Overbaugh J, DeVange DM *et al.* (1997). Hormonal contraception, vitamin A deficiency and other risk factors for shedding of HIV-1 infected cells from the cervix and vagina. *Lancet* **350**(350).

Mostad SB (1998). Prevalence and correlates of HIV-1 shedding in the female genital tract [review]. *AIDS Res.&Hum.Retrovir.* **14**(Suppl.1): S11-S15.

Mostad SB, Kreiss JK, Ryncarz AJ, Mandaliya K, Chohan B, Ndinya-Achola J, Bwayo JJ and Corey L (2000). Cervical shedding of HSV-2 in HIV-infected women: effects of hormonal contraception, pregnancy and vitamin A deficiency. *J.Inf.Dis.* **181**(1): 58-63.

Mulder DW, Nunn A, Kamali A and Kengeya-Kayondo J (1995). Decreasing HIV-1 seroprevalence in young adults in a rural Ugandan cohort. *BMJ* **311**: 833-836.

Munguti K, Grosskurth H, Newell J *et al.* (1997). Patterns of sexual behaviour in a rural population in North-Western Tanzania. *Soc.Sci.Med.* 44(10): 1553-1561.

Murray CJL and Lopez AD (1996). *The global burden of disease. A comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020*, Harvard School of Public Health, on behalf of the World Health Organization and the World Bank.

Mwabu GM (1986). Health care decisions at the household level: results of a rural health survey in Kenya. *Soc.Sci.Med.* 22(3): 315-319.

Mwijarubi E, Grosskurth H and Mayaud P (1993). Integration of STD control into a rural primary health care setting: experience from 25 health units in North-West Tanzania. VIIIth International Conference on AIDS in Africa, Marrakech.

Nagelkerke NJ, Plummer FA, Holton D, Anzala AO, Manji F, Ngugi EN and Moses S (1990). Transition dynamics of HIV disease in a cohort of African prostitutes: a Markov model approach. *Aids* 4(8): 743-7.

Nagelkerke NJD, Kimani J, Moses S and Plummer FA (1995). Exploring confounding in nested case-control studies [letter]. *AIDS* 9(10): 1202-1203.

Nahmias AJ, Lee FK and Beckman-Nahmias S (1990). Sero-epidemiological and -sociological patterns of herpes simplex virus infection in the world. *Scand J Infect Dis Suppl* 69: 19-36.

Nasio JM, Nagelkerke NJD, Mwatha A, Moses S, Ndinya-Achola JO and Plummer FA (1996). Genital ulcer disease among STD clinic attenders in Nairobi: association with HIV-1 and circumcision status. *Int J STD AIDS* 7: 410-414.

Nelson KE, Celentano DD, Eiumtrakol S, Hoover DR, Beyrer C, Suprasert S, Kuntolbutra S and Khamboonruang C (1996). Changes in sexual behavior and a decline in HIV infection among young men in Thailand [see comments]. *N Engl J Med* 335(5): 297-303.

Nelson KE, Eiumtrakul S, Celentano D, Maclean I, Ronald A, Suprasert S, Hoover DR, Kuntolbutra S and Zenilman JM (1997). The association of herpes simplex virus type 2 (HSV-2), Haemophilus ducreyi, and syphilis with HIV infection in young men in northern Thailand. *J Acquir Immune Defic Syndr Hum Retrovirol* 16(4): 293-300.

Newell J, Senkoro K, Mosha F *et al.* (1993). A population-based study of syphilis and sexually transmitted disease syndromes in north-western Tanzania. 2. Risk factors and health seeking behaviour. *Genitourin Med* 69(6): 421-6.

Ng'weshemi JZL, Boerma JT, Pool R *et al.* (1996). Changes in male sexual behaviour in

response to the AIDS epidemic: evidence from a cohort study in urban Tanzania. *AIDS* 10(12): 1415-1420.

Nopkesorn T, Mock PA, Mastro TD *et al.* (1998). HIV-1 subtype E incidence and STD in a cohort of military conscripts in northern Thailand. *J.Acq.Imm.Def.Syndr.Hum.Virol.* 18: 372-379.

Noren L, von Krogh G, Bondesson L, Nohlgard C and Grillner L (1998). Potential public health benefits from testing with Chlamydia trachomatis PCR technique on first void urine in men. *Acta Derm Venereol* 78(1): 63-6.

Nunn AJ, Wagner HU, Kamali A, Kengeya-Kayondo JF and Mulder DW (1995). Migration and HIV-1 seroprevalence in a rural Ugandan population. *AIDS* 9(5): 503-6.

Nzila N, Laga M, Thiam MA *et al.* (1991). HIV and other sexually transmitted diseases among female prostitutes in Kinshasa. *Aids* 5(6): 715-21.

Oakley A, Fullerton D and Holland J (1995). Behavioural interventions for HIV/AIDS prevention. [Review]. *Aids* 9(5): 479-86.

Oates JK and Csonka GW (1990). Gonorrhoea. In: *Sexually Transmitted Diseases; A Textbook of Genitourinary Medicine*. GW Csonka and JK Oates [Eds.]. London etc, Bailliere Tindall: 206-226.

Obasi A, Mosha F, Quigley M *et al.* (1999). Antibody to HSV-2 as a marker of sexual risk behaviour in rural Tanzania. *J.Inf.Dis.* 179(1): 16-24.

O'Farrell N (1999). Increasing prevalence of genital herpes in developing countries: implications for heterosexual HIV transmission and STI control programmes. *Sex.Transm.Inf.* 75: 377-384.

O'Hara HB, Voeten HACM, Kuperus AG, Otido JM, Kusimba J, Habbema JDF, Bwayo JJ and Ndinya-Achola JO (2001). Quality of health education during STD case management in Nairobi, Kenya. *Int.J.STD&AIDS* 12: 315-323.

Ohlemeyer CL, Hornberger LL, Lynch DA and Swierkosz EM (1998). Diagnosis of Trichomonas vaginalis in adolescent females: InPouch TV culture versus wet-mount microscopy. *J Adolesc Health* 22(3): 205-8.

Olsen GA (1973). Epidemiological measures against gonorrhoea. Experience in Greenland. *Brit.J.Vener.Dis.* 49: 130-133.

O'Reilly KR and Piot P (1996). International perspectives on individual and community approaches to the prevention of sexually transmitted disease and human immunodeficiency virus infection. [Review]. *J Infect Dis* 174(2): S214-22.

Oriel JD, Reeve P, Powis P, Miller A and Nicol CS (1972). Chlamydia infection. Isolation of chlamydia from patients with non-specific genital infection. *Brit.J.Vener.Dis.* 48: 429-236.

Oriel JD (1982). Epidemiology of genital Chlamydia infections. *Infection* 10(Suppl.1): S32-9.

Orroth KK, Gavyole A, Todd J, Mosha F, Ross D, Mwijarubi E, Grosskurth H and Hayes RJ (2000). Syndromic treatment of sexually transmitted diseases reduces the proportion of incident HIV infections attributable to these diseases in rural Tanzania. *Aids* 14(10): 1429-37.

Orroth KK, Korenromp EL, White RG *et al.* (2001). Higher risk behaviours and STD rates in Tanzania compared to Uganda - contribution to different outcomes of STD treatment trials? [poster presentation, abstract W006]. *14th Meeting of the International Society for Sexually Transmitted Diseases Research*, Berlin, Germany.

Otten Jr. MW, Zaidi AA, Peterman TA, Rolfs RT and Witte JJ (1994). High rate of HIV seroconversion among patients attending urban STD clinics. *AIDS* 8: 549-553.

Over M and Piot P (1992). HIV Infection and Sexually Transmitted Diseases. In: *Disease control priorities in developing countries*. DT Jamison, WH Mosley *et al.* [Eds.]. New York, Oxford University Press for the World Bank: 455-527.

Over M and Piot P (1996). Human immunodeficiency virus infection and other sexually

transmitted diseases in developing countries: public health importance and priorities for resource allocation. *J Infect Dis* **174**(2): S162-75.

Paavonen J, Kousa M, Saikku P, Vartiainen E, Kanerva L and Lassus A (1980). Treatment of nongonococcal urethritis with trimethoprim-sulphadiazine and with placebo. A double-blind partner-controlled study. *Br J Vener Dis* **56**(2): 101-4.

Palladino S, Pearman JW, Kay ID, Smith DW, Harnett GB, Woods M, Marshall L and McCloskey J (1999). Diagnosis of Chlamydia trachomatis and Neisseria gonorrhoeae. Genitourinary infections in males by the Amplicor PCR assay of urine. *Diagn Microbiol Infect Dis* **33**(3): 141-6.

Parks KS, Dixon PB, (ASCP) M, Richey CM and Hook EW (1997). Spontaneous clearance of chlamydia trachomatis infection in untreated patients. *Sex.Transm.Dis.* **24**(4): 229-235.

Paxton LA, Kiwanuka N, Nalugoda F, Gray R, Wawer MJ and Group RPS (1998a). Community-based study of treatment seeking among subjects with symptoms of sexually transmitted disease in rural Uganda. *Brit.Med.J.* **317**: 1630-1631.

Paxton LA, Sewankambo N, Gray R, Serwadda D, McNairn D and Wawer MJ (1998b). Asymptomatic non-ulcerative genital tract infections in a rural Ugandan population. *Sex.Transm.Inf.* **74**: 421-425.

Pepin J, Plummer FA, Brunham RC, Piot P, Cameron DW and Ronald AR (1989). The interaction of HIV infection and other sexually transmitted diseases: an opportunity for intervention. [Review]. *Aids* **3**(1): 3-9.

Peterman TA and Aral SO (1993). Evaluating behavioral interventions: need for randomized controlled trials. *JAMA* **269**(22): 2845.

Pettifor A, Walsh J, Wilkins V and Raghunathan P (2000). How effective is syndromic management of STDs?: A review of current studies. *Sex Transm Dis* **27**(7): 371-85.

Piot P and Tezzo R (1990). The epidemiology of HIV and other sexually transmitted infections in the developing world. [Review]. *Scand J Infect Dis Suppl* **69**: 89-97.

Piot P and Islam MQ (1994). Sexually transmitted diseases in the 1990ies. *Sex.Transm.Dis.* **21**(2(Suppl.)): S7-S13.

Plummer FA, D'Costa LJ, Nsanze H, Dylewski J, Karasira P and Ronald AR (1983). Epidemiology of chancroid and Haemophilus ducreyi in Nairobi, Kenya. *Lancet* **2**(8362): 1293-5.

Plummer FA, Simonsen JN, Cameron DW *et al.* (1991). Cofactors in male-female sexual transmission of human immunodeficiency virus type 1. *J Infect Dis* **163**(2): 233-9.

Plummer M, Todd J, Changalucha J *et al.* (2000). Triangulation of biological markers and quantitative and qualitative responses in sexual behaviour research with adolescents in rural Tanzania. XIIIth International AIDS conference, Durban, South Africa.

Prentice MJ, Taylor-Robinson D and Csonka GW (1976). Non-specific urethritis. A placebo-controlled trial of minocycline in conjunction with laboratory investigations. *Br J Vener Dis* **52**(4): 269-75.

Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, Meehan MO, Lutalo T and Gray RH (2000). Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group [see comments]. *N Engl J Med* **342**(13): 921-9.

Rahm VA, Belsheim J, Gleerup A, Gnarpe H and Rosén G (1986). Asymptomatic carriage of chlamydia trachomatis - a study of 109 teenage girls. *Eur.J.STD* **3**: 91-94.

Rakwar J, Lavreys L, Thompson ML, Jackson D, Bwayo J, Hassanali S, Mandaliya K, Ndinya-Achola J and Kreiss J (1999). Cofactors for the acquisition of HIV-1 among heterosexual men: prospective cohort study of trucking company workers in Kenya. *AIDS* **13**: 607-614.

Rees E, Tait IA, Hobson D, Byng RE and Johnson FWA (1977). Neonatal conjunctivitis caused by Neisseria gonorrhoeae and Chlamydia trachomatis. *Brit.J.Vener.Dis.* **53**(173-179).

Rees E (1980). The treatment of pelvic inflammatory disease. *Am J Obstet Gynecol* **138**(7

Pt 2): 1042-7.
Republic of Uganda MoP (1991). 1991 Population and Housing Census, Rakai district. *Entebbe: Statistical division, Ministry of Planning.*
Richey CM, Macaluso M and Hook EW (1999). Determinants of reinfection with Chlamydia trachomatis. *Sex Transm Dis* **26**(1): 4-11.
Ridgway GL, Mumtaz G, Robinson AJ, Franchini M, Carder C, Burczak J and Lee H (1996). Comparison of the ligase chain reaction with cell culture for the diagnosis of Chlamydia trachomatis infection in women. *J Clin Pathol* **49**(2): 116-9.
Robinson AJ and Ridgway GL (1996). Modern diagnosis and management of genital Chlamydia trachomatis infection. *Br J Hosp Med* **55**(7): 388-93.
Robinson JN, Mulder DW, Auvert B and Hayes RJ (1995). Modelling the impact of alternative HIV intervention strategies in rural Uganda. *AIDS* **9**(11): 1263-1270.
Robinson NJ (1994). The association of HIV-1 and other sexually transmitted diseases, and its relevance to intervention programmes in rural Uganda: a simulation modelling exercise [PhD thesis]. London, London School of Hygiene and Tropical Medicine.
Robinson NJ, Mulder DW, Auvert B and Hayes RJ (1997). Proportion of HIV infections attributable to other sexually transmitted diseases in a rural Ugandan population: simulation model estimates. *Int J Epidemiol.* **26**(1): 180-189.
Rotchford K, Sturm AW and Wilkinson D (2000). Effect of coinfection with STDs and of STD treatment on HIV shedding in genital-tract secretions: systematic review and data synthesis. *Sex Transm Dis* **27**(5): 243-8.
Rowley JT and Anderson RM (1994). Modeling the impact and cost-effectiveness of HIV prevention efforts. *Aids* **8**(4): 539-48.
Royce RA, Jackson TP, Thorp JM, Jr., Hillier SL, Rabe LK, Pastore LM and Savitz DA (1999). Race/ethnicity, vaginal flora patterns, and pH during pregnancy. *Sex Transm Dis* **26**(2): 96-102.
Saltz GR, Linnemann CC, Brookman RR and Rauh JL (1981). Chlamydia trachomatis cervical infections in female adolescents. *J Pediatr.* **98**(6): 981-985.
Sanchez-Martinez D, Schmid DS, Whittington W, Brown D, Reeves WC, Chatterjee S, Whitley RJ and Pellett PE (1991). Evaluation of a test based on baculovirus-expressed glycoprotein G for detection of herpes simplex virus type-specific antibodies. *J Infect Dis* **164**(6): 1196-9.
Schachter J, Hanna L, Hill EC, Massad S, Sheppard CW, Conte JE, Jr., Cohen SN and Meyer KF (1975). Are chlamydia infection the most prevalent venereal disease? *JAMA* **231**(12): 1252-5.
Schacker T, Zeh J, Hu HL, Hill E and Corey L (1998). Frequency of symptomatic and asymptomatic herpes simplex virus type 2 reactivations among human immunodeficiency virus-infected men. *J Infect Dis* **178**(6): 1616-22.
Schofield CBS (1982). Some factors affecting the incubation period and duration of symptoms of urethritis in men. *Br J Vener Dis.* **58**: 184-187.
Serwadda D, Sewankambo NK, Carswell JW *et al.* (1985). Slim disease: a new disease in Uganda and its association with HTLV-III infection. *The Lancet* **II**(8460): 849-852.
Serwadda D, Wawer MJ, Musgrave SD, Sewankambo NK, Kaplan JE and Gray RH (1992). HIV risk factors in three geographic strata of rural Rakai District, Uganda [see comments]. *AIDS* **6**(9): 983-9.
Sewankambo N, Gray RH, Wawer MJ *et al.* (1997). HIV-1 infection associated with abnormal vaginal flora morphology and bacterial vaginosis. *The Lancet* **350**: 546-550.
Sewankambo NK, Carswell JW, Mugerwa RD, Lloyd G, Kataaha P, Downing RG and Lucas S (1987). HIV infection through normal heterosexual contact in Uganda. *AIDS* **1**: 113-116.
Sewankambo NK, Wawer MJ, Gray RH, Serwadda D, Li C, Stallings RY, Musgrave SD and Konde-Lule J (1994). Demographic impact of HIV infection in rural Rakai district,

Uganda: results of a population-based cohort study. *Aids* 8(12): 1707-13.
Sherrard J and Barlow D (1993). Gonorrhoea in men [letter]. *Lancet* 341: 245.
Sherrard J and Barlow D (1996). Gonorrhoea in men: clinical and diagnostic aspects. *Genitourin.Med.* 72: 422-426.
Simonsen JN, Cameron DW, Gakinya MN *et al.* (1988). Human immunodeficiency virus infection among men with sexually transmitted diseases. Experience from a center in Africa. *N Engl J Med* 319(5): 274-8.
Simonsen JN, Plummer FA, Ngugi EN *et al.* (1990). HIV infection among lower socioeconomic strata prostitutes in Nairobi. *Aids* 4(2): 139-44.
Skulnick M, Chua R, Simor AE, Low DE, Khosid HE, Fraser S, Lyons E, Legere EA and Kitching DA (1994). Use of the polymerase chain reaction for the detection of Chlamydia trachomatis from endocervical and urine specimens in an asymptomatic low-prevalence population of women. *Diagn Microbiol Infect Dis* 20(4): 195-201.
Somse P, Mberyo-Yaah F, Morency P, Dubois MJ, Gresenguet G and Pepin J (2000). Quality of sexually transmitted disease treatments in the formal and informal sectors of Bangui, Central African Republic. *Sex Transm Dis* 27(8): 458-64.
Sorensen JL, Thranov I, Hoff G and Dirach J (1994). Early- and late-onset pelvic inflammatory disease among women with cervical Chlamydia trachomatis infection at the time of induced abortion - a follow-up study. *Infection* 22(4): 242-6.
Sparling PF (1990). Syphilis. In: *Sexually Transmitted Diseases*. KK Holmes, P Mardh *et al.* [Eds.]. New York, McGraw-Hill: 131-148, 161-180, 263-272.
Spiegel CA (1991). Bacterial Vaginosis. *Clin.Microbiol.Rev.* 4(4): 485-502.
Stall R, Ekstrand M, Pollack L, McKusick L and Coates TJ (1990). Relapse from safer sex: the next challenge for AIDS prevention efforts. *J.Acq.Imm.Def.Syndr.* 3: 1181-1187.
Stamm WE, Koutsky LA, Benedetti JK, Jourden JL, Brunham RC and Holmes KK (1984). Chlamydia trachomatis urethral infections in men. *Ann.Intern.Med.* 100: 47-51.
Stamm WE and Cole B (1986). Asymptomatic Chlamydia trachomatis urethritis in men. *Sex Transm Dis* 13(3): 163-5.
Stary A, Ching SF, Teodorowicz L and Lee H (1997). Comparison of ligase chain reaction and culture for detection of Neisseria gonorrhoeae in genital and extragenital specimens. *J Clin Microbiol* 35(1): 239-42.
Statistics Dept. Uganda MII (1996). Uganda Demographic and Health Survey, 1995. Calverton, Maryland, Statistics Dept. [Uganda], Macro International Inc.
Steen R and Dallabetta G (1999). The use of epidemiological mass treatment and syndrome management for sexually transmitted disease control. *Sex.Transm.Dis.* 26(4 (Suppl.)): S12-S20.
Steen R, Vuylsteke B, DeCoito T, Ralepeli S, Fehler G, Conley J, Bruckers L, Dallabetta G and Ballard R (2000). Evidence of declining STD prevalence in a South African mining community following a core-group intervention. *STD* 27(1): 1-8.
Stigum H, Falck W and Magnus P (1994). The core group revisited: the effect of partner mixing and migration on the spread of gonorrhea, chlamydia and HIV. *Math.Biosc.* 120: 1-23.
Stoneburner RL, Low-Beer D, Tembo GS, Mertens TE and Asiimwe-Okiror G (1996). Human immunodeficiency virus infection dynamics in east Africa deduced from surveillance data. *Am J Epidemiol* 144(7): 682-95.
Stott J and Hahn BH (1999). Vaccines and immunology - an overview. *AIDS* 13(Suppl.A): S103-S104.
Stover J and O'Way P (1995). Impact of interventions on reducing the spread of HIV in developing countries: computer simulation applications. *African J. of Medical Practice* 2(4): 110-120.
Stover J and Way P (1998). Projecting the impact of AIDS on mortality. *AIDS* 12(Suppl.1): S29-S39.

Stover J (2000). Influence of mathematical modeling of HIV and AIDS on policies and programs in the developing world. *Sex Transm Dis* 27(10): 572-8.

Sturm-Ramirez I, Gaye-Diallo A, Mboup S and Kanki P (2000). Bacterial vaginosis is associated with increased levels of proinflammatory cytokines in cervical secretions. XIIIth International AIDS conference, Durban, South Africa.

Sullivan AK, Atkins MC and Boag F (1997). Factors facilitating the sexual transmission of HIV-1 [review]. *Aids patient care and STDs* 11(3): 167-177.

Susser E, Desvarieux M and Wittkowski KM (1998). Reporting sexual risk behavior for HIV: a practical risk index and a method for improving risk indices. *Am.J.Publ.Health* 88(4): 671-674.

Sweat M, Gregorich S, Sangiwa G, Furlonge C, Balmer D, Kamenga C, Grinstead O and Coates T (2000). Cost-effectiveness of voluntary HIV-1 counselling and testing in reducing sexual transmission of HIV-1 in Kenya and Tanzania. *Lancet* 356: 113-121.

Sweat MD and Denison JA (1995). Reducing HIV incidence in developing countries with structural and environmental interventions. *AIDS* 9(Suppl.A): S251-S257.

Taha TE, Hoover DR, Dallabetta GA *et al.* (1998). Bacterial vaginosis and disturbances of vaginal flora: association with increased acquisition of HIV. *AIDS* 12: 1699-1706.

Taha TE, Gray RH, Kumwenda NI, Hoover DR, Mtimavalye LA, Liomba GN, Chiphangwi JD, Dallabetta GA and Miotti PG (1999). HIV infection and disturbances of vaginal flora during pregnancy. *J Acquir Immune Defic Syndr Hum Retrovirol* 20(1): 52-9.

Tait IA, Rees E, Hobson D, Byng RE and Tweedie MCK (1980). Chlamydia infection of the cervix in contacts of men with nongonococcal urethritis. *Brit.J.Vener.Dis.* 56: 37-45.

Telzak EE, Chiasson MA, Bevier PJ, Stoneburner RL, Castro KG and Jaffe HW (1993). HIV-1 seroconversion in patients with and without genital ulcer disease.A prospective study. *Ann.Intern.Med.* 119: 1181-1186.

Terho P (1978). Chlamydia trachomatis in non-specific urethritis. *Br.J.Vener.Dis.* 54: 251-256.

Theus SA, Harrich DA, Gaynor R, Radolf JD and Norgard MV (1998). Treponema pallidum, lipoproteins, and synthetic lipoprotein analogues induce human immunodeficiency virus type 1 gene expression in monocytes via NF-kappaB activation. *J Infect Dis* 177(4): 941-50.

Thomas JC, Schoenbach VJ, Weiner DH, Parker EA and Earp JA (1996). Rural gonorrhea in the southeastern United States: a neglected epidemic? *Am J Epidemiol* 143(3): 269-77.

Thompson SE and Washington E (1983). Epidemiology of sexually transmitted chlamydia trachomatis infections. *Epidemiologic Reviews* 5: 96-123.

Todd J, Balira R, Grosskurth H *et al.* (1997). HIV-associated adult mortality in a rural Tanzanian population. *AIDS* 11: 801-807.

Trollope-Kumar K (1999). Symptoms of reproductive-tract infection - not all that they seem to be. *Lancet* 354: 1745-1746.

UN (1993). Young women: silence, susceptibility and the HIV epidemic. New York, United Nations Development Programme.

UNAIDS (1997). Report on the global HIV/AIDS epidemic. Geneva, UNAIDS.

UNAIDS and WHO (2000). AIDS epidemic update: December 2000. Geneva.

Unicef (1995). *The state of the world's children 1995*. Oxford and New York, Oxford University Press for Unicef.

van de Wijgert JHHM, Mason PR, Gwanzura L, Mbizvo MT, Chirenje ZM, Iliff V, Shiboski S and Padian NS (2000). Intravaginal practices, vaginal flora disturbances, and acquisition of STD in Zimbabwean women. *J.Inf.Dis.* 181: 587-594.

Van der Ploeg CPB, Van Vliet C, De Vlas SJ, Ndinya-Achola JO, Fransen L, Van Oortmarssen GJ and Habbema JDF (1998). STDSIM: a microsimulation model for decision support on STD control. *Interfaces* 28: 84-100.

van Doornum GJ, Buimer M, Prins M, Henquet CJ, Coutinho RA, Plier PK, Tomazic-Allen S, Hu H and Lee H (1995). Detection of Chlamydia trachomatis infection in urine samples from men and women by ligase chain reaction. *J Clin Microbiol* **33**(8): 2042-7.

Van Vliet C, Holmes K, Singer B and Habbema J (1998). Effectiveness of HIV prevention strategies under alternative epidemiological scenarios: evaluation with the model STDSIM. In: *Confronting AIDS; public priorities in a global epidemic: background studies*. European Commission [Eds.]. Brussels, European Commission.

Verdon MS, Handsfield HH and Johnson RB (1994). Pilot study of azithromycin for treatment of primary and secondary syphilis. *Clin.Infect.Dis.* **19**: 486-488.

Vernazza PL, Eron JJ, Fiscus SA and Cohen MS (1999). Sexual transmission of HIV: infectiousness and prevention. *AIDS* **13**: 155-166.

Viravan C, Dance DA, Ariyarit C *et al.* (1996). A prospective clinical and bacteriologic study of inguinal buboes in Thai men. *Clin Infect Dis* **22**(2): 233-9.

Vittinghoff E and Padian NS (1996). Attributable risk of exposures associated with sexually transmitted disease. *J Infect Dis* **174 Suppl 2**: S182-7.

Voeten H, Otido J, O'Hara H, Kuperus A, Borsboom G, Ndinya-Achola J, Bwayo J and Habbema J (2001). Quality of STD case management in Nairobi, Kenya; a comparison of different types of health care facilities. *Sex.Transm.Dis.*: in press (July 2001).

Vuylsteke B, Bastos R, Barreto J, Crucitti T, Folgosa E, Mondlane J, Dusauchoit T, Piot P and Laga M (1993a). High prevalence of sexually transmitted diseases in a rural area in Mozambique. *Genitourin Med* **69**(6): 427-30.

Vuylsteke B, Laga M, Alary M, Gerniers MM, Lebughe JP, Nzila N, Behets F, Van Dyck E and Piot P (1993b). Clinical algorithms for the screening of women for gonococcal and chlamydial infection: evaluation of pregnant women and prostitutes in Zaire. *Clin Infect Dis* **17**(1): 82-8.

Wadsworth J, Johnson AM, Wellings K and Field J (1996). What's in a mean? - an examination of the inconsistency between men and women in reporting sexual partnerships. *J R Stat Soc A* **159**(Part 1): 111-123.

Wald A, Corey L, Handsfield HH and Holmes KK (1993). Influence of HIV infection on manifestations and natural history of other STDs. *Annu.Rev.Publ.Health* **14**: 19-42.

Wald A, Corey L, Cone R, Hobson A, Davis G and Zeh J (1997). Frequent genital herpes simplex virus 2 shedding in immunocompetent women. Effect of acyclovir treatment. *J Clin Invest* **99**(5): 1092-7.

Wald A, Zeh J, Selke S, Warren T, Ryncarz AJ, Ashley R, Krieger JN and Corey L (2000). Reactivation of genital herpes simplex virus type 2 infection in asymptomatic seropositive persons. *N Engl J Med* **342**(12): 844-50.

Walker D, Muyinda H, Foster S, Kengeya-Kayondo J and Whitworth J (2001). The quality of care by private practitioners for sexually transmitted diseases in Uganda. *Health Policy Plan* **16**(1): 35-40.

Wallin J (1974). Gonorrhoea in 1972. A 1-year study of patients attending the VD unit in Uppsala. *Br.J.Vener.Dis.* **51**: 41-47.

Ward H, Mertens TE and Thomas C (1997). Health seeking behaviour and the control of sexually transmitted disease. *Health Policy Planning* **12**(1): 19-28.

Wasserheit JN (1992). Epidemiological synergy. Interrelationships between human immunodeficiency virus infection and other sexually transmitted diseases. [Review]. *Sex Transm Dis* **19**(2): 61-77.

Waters JR and Roulston TM (1969). Gonococcal infection in a prenatal clinic. *Am.J.Obstet.Gynec.* **103**(4): 532-536.

Watson-Jones D, Mugeye K, Mayaud P *et al.* (2000). High prevalence of trichomoniasis in rural men in Mwanza, Tanzania: results from a population-based study. *Sex.Transm.Inf.* **76**: 355-362.

Watts CH and May RM (1992). The influence of concurrent partnerships on the dynamics

of HIV/AIDS. *Math Biosci* **108**: 89-104.
Wawer MJ, Serwadda D, Musgrave SD, Konde-Lule JK, Musagara M and Sewankambo NK (1991). Dynamics of spread of HIV-I infection in a rural district of Uganda. *B.M.J.* **303**(6813): 1303-6.
Wawer MJ, Sewankambo NK, Berkley S, Serwadda D, Musgrave SD, Gray RH, Musagara M, Stallings RY and Konde-Lule JK (1994). Incidence of HIV-1 infection in a rural region of Uganda [see comments]. *B.M.J.* **308**(6922): 171-3.
Wawer MJ, Serwadda D, Gray RH, Sewankambo NK, Li C, Nalugoda F, Lutalo T and Konde-Lule JK (1997). Trends in HIV-1 prevalence may not reflect trends in incidence in mature epidemics: data from the Rakai population-based cohort, Uganda. *AIDS* **11**: 1023-1030.
Wawer MJ, Gray RH, Sewankambo NK *et al.* (1998). A randomized community trial of intensive sexually transmitted disease control for AIDS prevention, Rakai, Uganda. *AIDS* **12**: 1211-1225.
Wawer MJ, Sewankambo NK, Serwadda D *et al.* (1999). Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomised community trial. *Lancet* **353**: 525-535.
Weir SS, Feldblum PJ, Roddy RE and Zekeng L (1994). Gonorrhea as a risk factor for HIV acquisition. *AIDS* **8**: 1605-1608.
WHO (1965). International work in endemic treponematoses and venereal infections, 1948-1963. WH Organization. Geneva.
WHO (1994). Management of Sexually Transmitted Diseases, WHO/GPA/TEM/94.1.
WHO (1999). An overview of selected curable sexually transmitted diseases. Geneva, World Health Organization, Global programme on AIDS/STDs.
WHO/UNAIDS (1998). Global report on AIDS / Epidemiological Fact Sheets, June 1998. http://www.who.ch/emc/diseases/hiv; http:/www.unaids.org, Working group on global HIV/AIDS and STD surveillance.
Wiesner PJ and Thompson SEI (1980). Gonococcal diseases. *Disease-a-month* **27**(5): 1-44.
Wiesner PJ (1981). Gonorrhea. *Cutis* **27**: 249-54.
Wilkinson D (1997). Syndromic management of STDs in developing countries: what role in the control of the STD and HIV epidemics? [Editorial]. *Genitourin.Med.* **73**: 427-428.
Wilkinson D, Connolly AM, Harrison A, Lurie M and Karim SS (1998). Sexually transmitted disease syndromes in rural South Africa. Results from health facility surveillance. *Sex Transm Dis* **25**(1): 20-3.
Wilkinson D, Abdool Karim SS, Harrison A, Lurie M, Colvin M, Connolly C and Sturm AW (1999). Unrecognized sexually transmitted infections in rural South African women: a hidden epidemic. *Bull.WHO* **77**(1): 22-28.
Willcox RR (1976). Single oral dose of 1.5g talampicillin in the treatment of gonorrhoea. *Brit.J.Vener.Dis.* **52**: 184-186.
Willcox RR (1985). Mass treatment campaigns against the endemic treponematoses. *Rev.Inf.Dis.* **7**(Suppl.2): S278-S283.
Willerford DM, Bwayo JJ, Hensel M, Emonyi W, Plummer FA, Ngugi EN, Nagelkerke N, Gallatin WM and Kreiss J (1993). Human immunodeficiency virus infection among high-risk seronegative prostitutes in Nairobi. *J Infect Dis* **167**(6): 1414-7.
Winfield J and Latif AS (1985). Tracing contacts of persons with sexually transmitted diseases in a developing country. *Sex Transm Dis* **12**(1): 5-7.
Workowski KA, Stevens CE, Suchland RJ, Holmes KK, Eschenbach DA, Pettinger MB and Stamm WE (1994). Clinical manifestations of genital infection due to Chlamydia trachomatis in women: differences related to serovar. *Clin Infect Dis* **19**(4): 756-60.
Worldbank, Ed. (1993). *World Development Report 1993: investing in health*. New York, Oxford University Press, Inc.
Worldbank (1997). *Confronting AIDS: public priorities in a global epidemic (A World*

Bank Policy Research Report). New York, Oxford University Press, Inc.

Wu CH, Lee MF, Yin SC, Yang DM and Cheng SF (1992). Comparison of polymerase chain reaction, monoclonal antibody based enzyme immunoassay, and cell culture for detection of Chlamydia trachomatis in genital specimens. *Sex Transm Dis* **19**(4): 193-7.

Xu F, Schillinger JA, Markowitz LE, Sternberg MR, Aubin MR and St. Louis ME (2000). Repeat Chlamydia trachomatis infection in women: analysis through a surveillance case registry in Washington State, 1993-1998. *Am J Epidemiol* **152**(12): 1164-70.

Yorke JA, Hethcote HW and Nold A (1978). Dynamics and control of the transmission of gonorrhea. *Sex Transm Dis* **5**(2): 51-6.

Zenilman JM, Fresia A, Berger B and McCormack WM (1999). Bacterial vaginosis is not associated with circumcision status of the current male partner. *Sex.Transm.Inf.* **75**: 347-348.

Summary

The epidemic of the acquired immunodeficiency syndrome (AIDS) is among the most pressing global issues in public health. By the year 2000, 36 million people were infected with the human immunodeficiency virus (HIV), the underlying cause of AIDS; more than 80% of them were living in sub-Saharan Africa. There is no vaccine against HIV infection, and in most developing countries the price of treatment puts it beyond the reach of most AIDS patients. For this reason, the prevention of infection is the primary mode of control. In sub-Saharan Africa, most HIV infections are acquired by heterosexual intercourse, and prevention programmes focus on reducing its sexual spread.

This thesis studies the extent to which the treatment of sexually transmitted diseases (STD) can help to prevent HIV spread in sub-Saharan Africa, where both STD and HIV are common. People with STD are often infected with HIV and vice versa, and STD seem to be a risk or 'co-'factor in the transmission of HIV. STD damage the skin barrier to the entrance and dissemination of viruses, and allow HIV-susceptible white blood cells to accumulate in the genital tract. Yet it is unclear *to what extent* treatment of STD can contribute to HIV prevention. Knowing this is important, as it determines the proportion of HIV control efforts and money that should be spent on STD treatment, relative to other prevention strategies.

To answer this question, numerous studies have been conducted over the past two decades on STD/HIV associations. These include two intervention trials that assessed the impact of improved STD treatment on HIV incidence in rural African populations. In a trial in Mwanza, Tanzania, improved syndromic management of symptomatic STD in clinic attendees was associated with a 38% reduction in HIV incidence (with a 95% confidence interval of 15% to 55%), but with limited reductions in STD rates. In contrast, a trial of home-based mass STD treatment of the whole population in Rakai, Uganda, found reductions in STD rates without a reduction in HIV incidence (3%, with a 95% confidence interval of -16% to +19%). As a result of these contrasting outcomes, it remained unclear whether STD treatment is an effective HIV prevention strategy. In this thesis, I have therefore re-examined, quantitatively, these and other data on the role of STD cofactors in HIV spread and control.

The magnitude of STD cofactor effects on HIV transmission

Previous estimations of the magnitude of STD cofactor effects derived from observational studies were reconsidered. **Chapter 2** reviews the multiple reasons underlying the fact that STD and HIV occur in the same individuals. Most importantly, STD and HIV share a common primary risk factor, i.e. (frequent) unprotected sexual intercourse with many different partners. Since data are

often incomplete, it is difficult to statistically adjust for all relevant factors when estimating cofactor magnitudes from observational studies. Notably, STD and HIV cluster not only in study subjects and their direct partners, but also in the partners of their partners. Of the latter, little is usually known, but their risk profile will certainly enhance the HIV/STD association in study subjects. On the other hand, HIV/STD associations are sometimes diluted by factors such as the misclassification of exposure status due to unrecognised symptoms or imperfect STD diagnostic tests. As an illustration of the way in which these factors affect cofactor estimations, we recalculated the cofactor effect for genital ulcers on HIV acquisition in prostitutes in Nairobi. If several plausible non-cofactor determinants of the HIV/ulcer association were taken into account, they would reduce the cofactor estimate from 23-fold to 3-fold (per sexual contact), suggesting a strong confounding in the original estimate. We conclude that observational studies such as those done so far have mostly overestimated STD cofactor magnitudes.

Another conclusion of this re-analysis is that STD are an important indicator of an individual's risk of HIV infection - irrespective of how much of the HIV/STD association is due to STD cofactor effects. This implies that care for STD patients, if it includes counselling on behavioural risk reduction and perhaps condom provision, can be an important means of targeting HIV prevention to the group most in need.

STD symptom probabilities and treatment seeking

Chapters 3 and 4 focus on a determinant of the efficacy of clinical, syndromic STD treatment (the intervention evaluated in the Mwanza trial): i.e. the proportion of STD episodes in which recognised symptoms occur - which may prompt the patient to seek treatment.

Chapter 3 documents a meta-analysis of cross-sectional surveys on the proportion of gonorrhoea and chlamydia infections in which the patient has symptoms. This proportion was generally low, between 6% and 40%. Symptom prevalence varied very little between a number of (developed and developing) countries and populations. This was not expected, as, logically, symptom prevalence should decrease with the proportion of symptomatic STD infections that gets timely treatment, and treatment patterns do vary considerably between these populations. No correlations were found between symptom prevalence and indicators of treatment rates in the respective populations. We infer that, setting-specific reporting behaviour co-determine the prevalence of reported symptoms, together with treatment patterns. Symptom recognition and reporting is probably better in countries with good treatment facilities, thus counterbalancing the effect of treatment on symptom prevalence.

Chapter 4 estimated the probability with which gonorrhoea and chlamydia

episodes become symptomatic. We used symptom prevalences derived from a cross-sectional survey in Rakai, which were combined in a natural history model with data on the duration of symptomatic and asymptomatic disease phases, and with data both on the proportion of patients seeking treatment and on patient delay in treatment seeking. Symptom probabilities for the Rakai population were estimated at 45% for gonorrhoea in males, 14% for gonorrhoea in females, 11% for chlamydia in males and 6% for chlamydia in females. These fractions proved to be much lower than estimates for men in the United States. This outcome thus corroborates the conclusions of Chapter 3, that symptom reporting varies between populations, and is very poor in underserviced and uneducated populations such as that in rural Uganda.

Explaining the discrepant outcomes of the Mwanza and Rakai STD treatment trials

We explored possible reasons for the seeming discrepancy in outcomes between the STD treatment trials in Mwanza and Rakai. Several hypotheses centred around the apparently lower prevalence of curable STD in Rakai as compared to Mwanza. Where curable STD are less prevalent, their importance in HIV transmission is less and the impact of STD treatment will also be less.

In **Chapter 5**, STD prevalences were systematically compared between the two trials, taking into account differences in the population (e.g. age) groups sampled, and the sensitivities and specificities of the different diagnostic tests used. After standardisation, the prevalences of gonorrhoea, chlamydia and trichomoniasis proved to be considerably higher in Mwanza than in Rakai. Active (recently acquired) syphilis was also more prevalent in Mwanza, but overall (i.e. if also including late stages of infection), syphilis was equally prevalent in both sites. In contrast, for the incurable STD herpes simplex virus type 2 (HSV-2), no site differences in seroprevalence were found.

To further study the role of differences in the types of STD intervention and in the study populations between Rakai and Mwanza, we made use of an epidemiological model that simulates the spread of HIV and STD through populations, and specifically the trial populations. The model, *STDSIM*, was first 'fitted' to reproduce the trial outcomes, using data collected during the trials and from related surveys on demography, sexual behaviour and epidemiology. The model was then used to predict the impact of intervention scenarios not actually performed, such as mass treatment in Mwanza. **Chapter 6** describes *STDSIM* in detail. Particular reference is given to the model representation of sexual behaviour, one of its most complex features. This chapter also demonstrates that behavioural interventions of seemingly moderate scope (e.g. which induce small decreases in numbers of partners) can have a startling influence on the spread of HIV.

Chapter 7 describes *STDSIM* simulations of STD interventions in Mwanza.

We first fitted the model to the actual Mwanza trial outcomes. The model best fitted the observed impact of syndromic treatment on HIV incidence (a 38% reduction) if we assumed high cofactors (as compared to the outcomes of **Chapter 2**). Even with high assumed cofactors (resulting in a simulated impact on HIV of syndromic treatment of 30%), reductions in STD prevalence had to be specified as larger than they appeared to be in the actual trial. In all scenarios, a hypothetical single-round of mass treatment (resembling the Rakai intervention) was predicted to be about effective as syndromic treatment over the first two years (e.g. 36% and. 30% HIV incidence reduction, respectively).

As a complementary approach to assessing the role of the type of intervention in determining the trial outcomes, we simulated the effect of syndromic STD management in Rakai. **Chapter 8** shows that, if it had been implemented in the late 1990s, i.e. at the time of the Rakai trial, this intervention would hardly have been any more effective against HIV than was mass treatment in the actual trial (8% HIV incidence reduction in the best model scenario, vs. 3% in the actual trial). These outcomes argue against the hypothesis that the difference in impact between the trials was due to differential impact of the respective interventions on curable STD.

Chapter 8 also shows that, had STD interventions been implemented earlier in the HIV epidemic in Rakai (e.g. around 1988), they might have been more effective (for example achieving a 11% reduction in HIV incidence, rather than one of 8% in 1998). This trend over time was due in part to a behaviour change that occurred in the late 1980s, after the end of Uganda's civil war. The consequent fall in STD prevalences and in the occurrence of short, casual partnerships in which STD cofactors are most important, reduced the importance of STD in HIV spread in the 1990s. Simulations of a hypothetical Rakai-like population without behaviour change revealed that, even without behaviour change, the impact of STD treatment on HIV spread would have fallen somewhat over the HIV epidemic (e.g. from 19% in 1988 to 15% in 1998). This is due firstly to selective AIDS-related mortality among high-risk groups where STD are highly prevalent, which reduces the prevalence of STD in the population. In addition, the types of relationships in which most HIV transmissions occur shifts during the epidemic, from casual short relationships to long-term relationships, in which STD cofactors are less important. Contrary to what has been hypothesised, an increase in ulcers due to the incurable cofactor HSV-2 during the HIV epidemic, due to AIDS patients suffering more frequent herpetic recurrences, make little difference to the impact of STD treatment at different timepoints in the Rakai epidemic.

In summary, the results of **Chapters 5 to 8** indicate that the behaviour change in Uganda preceding the Rakai trial and the relatively late stage of the HIV epidemic in Rakai, both contributed to the relatively low impact of the STD intervention on HIV incidence there. What remains to be explained is the outcomes of the Mwanza trial - which were difficult to reproduce in simulations: how could

such a large reduction in HIV incidence occur with so little reduction in STD prevalences? Studies not documented in this thesis suggest two possible explanations:

- The coincidentally low starting prevalence of HIV and STD, and their main risk factors in the Mwanza intervention arm as compared to the comparison arm. This phenomenon may have caused residual confounding in the statistical analysis of trial outcomes, and was shown in simulations to be potentially influential;
- Alternative, non-cofactor mediated mechanisms of the Mwanza intervention on HIV incidence. For example, participants' risk behaviour may have been reduced by counselling provided during the clinic visit, and by the population-based STD health education offered to increase clinic attendance, thus reducing the transmission of HIV directly (and, initially, probably more than the transmission of STD).

Interactions between HIV and HSV-2

Chapter 9 elaborates on the interactions in epidemiology between HIV and HSV-2. In several developing countries, the proportion of genital ulcers that are due to HSV-2 is increasing, at the expense of the curable causes, syphilis and chancroid. This is commonly thought to be due to the enhancing effect of HIV disease on herpetic ulceration, as well as to the consequent increase in the transmission of HSV-2 from HIV patients to their partners. However, by simulating the interactions between HIV and HSV-2 during a severe African HIV epidemic, we demonstrated that, at the population level, the increase in genital herpes is likely to be limited. This is because only a minority of HSV-2 patients have (symptomatic) HIV, and because the putative increase in HSV-2 transmission is limited by the existing high prevalence of HSV-2 among partners of HIV patients. By contrast, behavioural risk reduction (as occurred in Rakai) was shown to bring about a large increase in the proportion of ulcers that are of herpetic nature (although not an absolute increase in herpes incidence), as it decreases syphilis and especially chancroid much more than genital herpes.

Implications

The combined results suggest that we should temper our expectations of the role of STD treatment in HIV prevention. For a better quantitative understanding of the role of STD care in HIV prevention, new trials of syndromic management that allow a distinction between cofactor-mediated and behavioural effects, would be needed. Further trials would also help to delineate the cost-effectiveness of syndromic STD management as compared, for example, to behavioural

interventions. For several reasons, it is unclear whether such new trials will be conducted. In the meantime, four main conclusions can be drawn with regard to HIV control:

- It is essential that greater attention is paid to the behavioural components of STD management, such as counselling on the prevention of reinfection and partner infection, and the provision of condoms;
- To improve the use of STD management services, parallel population-based STD health education is indicated;
- The promotion of behavioural risk reduction remains the first priority in any setting (for example, via education and condom distribution);
- With regard to the future, the greatest potential lies in the development of effective vaccines against HIV.

SAMENVATTING

Dit proefschrift gaat over de preventie van de verspreiding van AIDS in Afrika. Deze dodelijke ziekte is het gevolg van infectie met HIV (het humaan immunodeficiëntie-virus). HIV wordt overgedragen van mens tot mens via seksueel contact, via bloed en van moeder op kind rondom de geboorte.

De AIDS-epidemie, die rond 1980 begon met de verspreiding van HIV, is één van de belangrijkste ziekte- en doodsoorzaken geworden, met name in ontwikkelingslanden. In het jaar 2000 waren er wereldwijd 36 miljoen mensen geïnfecteerd met HIV; meer dan 80% hiervan woonde in Afrika beneden de Sahara. Er bestaat geen geneesmiddel tegen AIDS. Sinds de jaren 1990 zijn er wel medicijnen tegen het HIV-virus, die de levensverwachting en levenskwaliteit van patiënten aanzienlijk verhogen. Deze medicijnen zijn echter slechts beschikbaar voor een klein deel van de geïnfecteerden, nl. diegenen in de rijkste landen waar geavanceerde medische zorg voorhanden is. Bovendien hebben de antivirale middelen moeilijk te tolereren bijwerkingen, en wordt hun effectiviteit verminderd door virusresistentie die na verloop van tijd optreedt in een meerderheid van de gebruikers. Er wordt gewerkt aan vaccins die HIV-besmetting kunnen verhinderen, maar tot op heden bestaan die niet.

In Afrika wordt HIV voornamelijk overgebracht via heteroseksueel contact. De bestrijding van AIDS concentreert zich op het voorkómen van HIV-besmetting. Behalve op het vermijden van onveilig seksueel contact, richt men zich op het verminderen van het risico van transmissie (overdracht) tijdens onbeschermd contact. Dit risico varieert tussen mensen en bevolkingsgroepen, en hangt onder meer af van het ziektestadium van de HIV-geïnfecteerde, de algehele gezondheidstoestand van beide partners en het type geslachtsverkeer.

Als één van beide partners tegelijkertijd een andere seksueel overdraagbare aandoening (SOA) heeft, kan het transmissierisico aanzienlijk oplopen (het zgn. SOA-cofactor-effect). Voorbeelden hiervan zijn genitale zweren (door syfilis, weke sjanker en genitale herpes) of infecties die ontsteking van de huid of het slijmvlies veroorzaken (zoals gonorroe en chlamydia). Deze aandoeningen vergemakkelijken het binnendringen van het HIV-virus doordat zij de huid lokaal beschadigen en meer doorlaatbaar maken. Op vergelijkbare wijze vergroot een SOA in de HIV-geïnfecteerde partner het risico van besmetting van de partner, omdat deze leidt tot verhoogde genitale uitscheiding van het HIV-virus. In de landen waar de HIV-epidemie het ergst is, komen SOA's veel voor. Daarom wordt verondersteld dat het bestrijden van SOA's - de meeste kunnen worden genezen met antibiotica - een belangrijke bijdrage kan leveren aan het verminderen van HIV-verspreiding.

In dit proefschrift heb ik bestudeerd hoe groot de rol van SOA's als 'cofactoren' in HIV-transmissie is en hoeveel SOA-behandeling kan bijdragen aan HIV-preventie in Afrika. Kennis hierover is belangrijk omdat dit mede bepaalt hoeveel geld er

aan SOA-behandeling moet worden besteed in vergelijking met andere typen bestrijdingsprogramma's. Met name in ontwikkelingslanden, waar budgetten voor gezondheidszorg klein zijn, is een goede prioritering tussen (kosten-)effectieve en minder (kosten-)effectieve activiteiten essentieel.

Over dit onderwerp zijn al eerder veel studies gedaan, maar deze leverden geen eenduidig antwoord op. Met name zijn er twee experimentele onderzoeken (*trials*) in Uganda en Tanzania uitgevoerd, waarin werd bekeken hoeveel minder nieuwe HIV-infecties optraden in dorpen waar SOA-behandeling verbeterd werd ten opzichte van dorpen met het normale, beperkte niveau van zorg. In de trial in Tanzania verminderde HIV-incidentie met naar schatting 38% door verbeterde zorg voor SOA-patiënten die naar algemene klinieken kwamen. Tegen de verwachting in reduceerde deze interventie het aantal SOA's zelf echter nauwelijks. In Uganda, daarentegen, had een herhaalde 10-maandelijkse behandeling van de hele bevolking met antibiotica tegen SOA's geen noemenswaardig effect op HIV-incidentie (3% reductie over 2 jaar), hoewel deze interventie aantallen SOA's wél verminderde. Dit boek bevat een aantal nadere analyses van deze twee eerdere onderzoeken, alsook van andere typen gerelateerde studies.

Als eerste (**hoofdstuk 2**) bekeek ik schattingen van de grootte van het SOA-cofactoreffect, die waren gebaseerd op correlaties tussen het voorkomen van beide infecties. Mensen met HIV hebben vaker SOA's, en omgekeerd. Dit verband bestaat onder andere doordat SOA's cofactoren voor HIV-infectie zijn. Een belangrijker reden is echter dat SOA en HIV samenhangen met dezelfde onderliggende factoren, zoals onbeschermde seks met verschillende partners of met partners met een verhoogd risico op zowel SOA als HIV door wisselende contacten. Schattingen van cofactorgroottes uit zulke correlaties, moeten gecorrigeerd worden voor deze samenhang. Een heranalyse toont echter aan dat de meeste studies niet voldoende (kunnen) corrigeren, omdat de benodigde gegevens - bijvoorbeeld over de eigenschappen van partners - niet compleet zijn. Als illustratie berekenden we de cofactorgrootte van genitale zweren op het krijgen van HIV voor vrouwen in Nairobi. Onder plausibele aannamen, zoals dat vrouwen met zweren vaker risicovolle partners hebben, vergrootte het hebben van zweren de kans op HIV-overdracht met een factor 3 per seksueel contact. Oorspronkelijk was de cofactorgrootte echter - zonder correctie voor deze verstorende factoren - door andere onderzoekers op een factor 23 geschat. Dit voorbeeld toont aan dat correlatiestudies de rol van SOA-cofactoren in HIV-verspreiding aanzienlijk kunnen overschatten.

Hoofdstukken 3 en 4 behandelen de kans dat SOA herkenbare symptomen geven. Deze kans bepaalt hoeveel SOA-patiënten vanwege symptomen naar klinieken komen, en daarmee het totale effect van SOA-zorg. Sommige SOA's, waaronder syfilis en weke sjanker, geven bijna altijd symptomen die de patiënt makkelijk voelt of ziet, zoals genitale zweren. Ziektes zoals gonorroe en chlamy-

dia leiden echter niet altijd tot symptomen, of het symptoom (bijv. jeuk) is te mild om de patiënt aan te sporen hulp te zoeken. Herbeschouwingen van de proporties van SOA-patiënten met symptomen in verschillende landen, toonden het volgende aan. In alle landen heeft slechts een klein deel van de SOA-patiënten symptomen op het moment van ondervraging. In geïndustrialiseerde, Westerse landen komt dit omdat de meeste patiënten met symptomen onmiddellijk behandeld worden, zodat alleen de patiënten zonder symptomen met de infectie blijven rondlopen. In ontwikkelingslanden krijgen daarentegen weinig SOA-patiënten behandeling, zelfs wanneer ze symptomen hebben. De proportie met symptomen is niettemin laag, omdat symptoomherkenning slecht is in de vaak slecht opgeleide bevolking. Volgens een schatting voor het platteland van Uganda, leidt chlamydia hier slechts in 6-11% van de gevallen tot herkende symptomen, en gonorroe in 14% tot 45%. Deze analyses maken duidelijk dat in onderontwikkelde regio's het effect van verbetering van behandeling van symptomatische patiënten in de bestrijding van SOA (en HIV) slechts beperkt is. In zulke gebieden moeten programma's van verbeterde klinische zorg gepaard gaan met voorlichting aan een breed publiek over symptoomherkenning en het belang van vroegtijdige behandeling.

Ik onderzocht verder waarom SOA-behandeling in de trials in Uganda en Tanzania zo'n verschillend effect op HIV liet zien. Een deel van dit onderzoek (**hoofdstukken 6-9**) werd gedaan met behulp van een epidemiologisch computermodel dat de verspreiding van SOA en HIV nabootst (**hoofdstuk 6**). Met dit model kunnen ook de effecten van bestrijdingsprogramma's worden doorgerekend en voorspeld. We pasten dit model toe door eerst de werkelijke uitkomsten van de twee trials te simuleren, en daarna te bekijken wat zou zijn gebeurd als steeds één factor anders dan in werkelijkheid zou zijn geweest.

Een belangrijke verklaring voor het grotere effect van SOA-behandeling op HIV-verspreiding in Tanzania bleek te zijn dat ten tijde van de trials SOA's veel meer voorkwamen in Tanzania dan in Uganda (**hoofdstuk 5**). Daarom was de rol van SOA's in HIV-verspreiding het grootst in Tanzania. De lagere SOA-prevalentie in Uganda had twee redenen. Ten eerste was de HIV-epidemie in Uganda in een later stadium, waarin HIV zich al had verspreid buiten de hoog-risicogroepen die de meeste SOA hebben, en waarin bovendien veel SOA-patiënten door AIDS gestorven waren. Ten tweede, maar waarschijnlijk belangrijker, had in Uganda al een aantal jaren vóór de trial een vermindering van seksueel risicogedrag plaatsgevonden, in de vorm van minder prostitutie en minder wisselende partners. Als gevolg hiervan kwam het geteste SOA-bestrijdingsprogramma in Uganda op een moment dat SOA al niet meer zo belangrijk waren. Schattingen met behulp van het model tonen aan dat, als de interventie in Uganda eerder in de epidemie zou zijn uitgevoerd, de vermindering in HIV-infecties waarschijnlijk geen 3% maar ongeveer 19% zou zijn geweest (**hoofdstukken 8 en 9**).

Verder suggereerden simulaties van de Uganda-interventie in de Tanzaniaanse

bevolking en vice versa, dat het verschil in type SOA-behandeling (klinische behandeling voor symptomatische patiënten danwel periodieke massabehandeling) tussen de twee trials weinig bijdroeg aan het verschil in hun uitkomsten (**hoofdstukken 7 en 8**).

Mijn studies konden niet volledig verklaren waarom in Tanzania zo'n groot effect op HIV werd gevonden terwijl de aantallen SOA-infecties weinig verminderden. Voor deze uitkomst bestaan wel twee mogelijke redenen. Ten eerste kan de grote HIV-reductie deels een toevalsbevinding zijn. Deze verklaring wordt ondersteund door het feit dat in de trial, bij toeval de dorpen mét interventie al begonnen met een lagere prevalentie van HIV, SOA en andere HIV-risicofactoren (oftewel in een bij voorbaat gunstigere uitgangssituatie) in vergelijking tot de dorpen zonder interventie. Simulatiestudies die we elders beschreven, lieten zien dat zulke toevalligheden de trialuitkomst aanzienlijk kunnen beïnvloeden. Ten tweede wordt wel geopperd dat de Tanzania-interventie HIV-verspreiding vermindere via andere wegen dan SOA-behandeling. Dit zou kunnen zijn omdat - naast antibiotica en in tegenstelling tot in Uganda - ook voorlichting aan SOA-patiënten over het voorkomen van herinfectie werd gegeven, alsook voorlichting over SOA aan een breder publiek buiten de klinieken. De hypothese is dan dat deze voorlichting de bevolking bewoog tot veiliger gedrag, wat de incidentie van HIV rechtsreeks zou hebben verminderd. (Weliswaar zou gedragsverandering SOA-aantallen óók verminderen, maar minder, vanwege verschillende eigenschappen van deze typen infecties.)

Samenvattend betekenen de resultaten dat de verwachtingen over de rol van SOA-behandeling in HIV-preventie naar beneden bijgesteld moeten worden - totdat eventueel uit verder onderzoek meer zekerheid over (grote) effectiviteit is verkregen. Concreet impliceert dit voor de HIV-bestrijding in Afrika in de komende jaren:

- Binnen de zorg voor SOA-patiënten verdienen de componenten gericht op preventie van herinfectie, zoals voorlichting en verspreiding van condooms, meer aandacht;
- Bij verbetering van zorg voor SOA-patiënten hoort altijd voorlichting onder een breder publiek buiten de klinieken, om het gebruik van deze diensten te optimaliseren;
- De eerste prioriteit blijft vermindering van risicogedrag, hetzij via voorlichting van de bevolking hetzij door meer structurele (bijv. sociaal-economische) veranderingen;
- Voor de verdere toekomst ligt de hoop vooral bij de ontwikkeling van vaccins tegen HIV.

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The project *'The impact and cost-effectiveness of HIV prevention strategies in sub-Saharan Africa: a comparative analysis of four strategies evaluated in three randomized trials'* involved the model-aided analysis of not only the Rakai trial but also the Mwanza trial and another ongoing trial of STD treatment in combination with interventions promoting behavioural change in Masaka, Uganda. This project was a collaboration between the groups mentioned above, those involved in the Mwanza trial (AMREF Tanzania, Drs. Awene Gavyole and Jim Todd; London School of Hygiene and Tropical Medicine, Prof. Richard Hayes, Dr. Heiner Grosskurth, Mrs. Kate Karter-Orroth, Mr. Richard White), and in the Masaka trial (Medical Research Council UK/Entebbe, Prof. Jim Whitworth, Dr. Anatoli Kamale). The project ran between December 1998 and December 2001, and was sponsored by the Department for International Development, UK. Further support was provided by GlaxoSmithKline, UK, specifically for the addition of HSV-2 to the *STDSIM* model and for the study described in Chapter 9.

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Eline
augustus 2001

Curriculum vitae

Eline Korenromp werd op 9 augustus 1972 geboren te Den Haag. Zij behaalde daar in 1990 het gymnasium-beta diploma aan het Christelijk Gymnasium Sorghvliet. Tussen 1990 en 1996 studeerde zij medische biologie aan de Rijksuniversiteit Utrecht (tegenwoordig Universiteit Utrecht), waar zij bovendien een propaedeuse in de wijsbegeerte deed. Onderzoeksstages voerde zij uit bij het Rudolf Magnus Instituut voor Neurowetenschappen, het Rijksinstituut voor Volksgezondheid en Milieuhygiëne (RIVM), en het Clarke Institute of Psychiatry, University of Toronto.

Sinds maart 1997 is zij als wetenschappelijk medewerker verbonden aan het instituut Maatschappelijke Gezondheidszorg van de Erasmus Universiteit Rotterdam. Haar onderzoek betrof de bestrijding van HIV/AIDS en seksueel-overdraagbare aandoeningen in Afrika. Dit had plaats in de vorm van een aantal internationale projecten in samenwerking met onder meer de London School of Hygiene and Tropical Medicine, UK; Johns Hopkins University School of Public Health, Maryland, USA; Makerere Universiteit, Kampala, Uganda; en Uganda Virus Research Institute, Entebbe, Uganda. In februari 2000 behaalde zij een registratie als epidemioloog-A.

Sinds augustus 2001 werkt zij bij de Wereldgezondheidsorganisatie (WHO) te Genève, Communicable Diseases cluster, in de evaluatie van infectieziektebestrijding.

Publicatielijst

Steerenberg PA, Korenromp EL, Van Loveren H, Mol DQ, Geerse L and De Gruijl FR **1997** Natural killer cell activity during UV radiation-induced skin tumor formation in the Skh hairless mouse. *J.Photochem.Photobiol.*, 65(1): 150-154.

Gray RH, Wawer MJ, Sewankambo NK, Serwadda D, Li C, Moulton LH, Lutalo T, Wabwire-Mangen F, Meehan MP, Ahmed S, Paxton LA, Kiwanuka N, Nalugoda F, Korenromp EL, Quinn TC and the Rakai Project Team **1999** Relative risks and population attributable fraction of incident HIV associated with STD symptoms and treatable STDs in Rakai District, Uganda. *AIDS* 13: 2113-2123.

Korenromp EL, Van Vliet C, Bakker R, Habbema JDF **2000** HIV spread and partner reduction for different patterns of sexual behaviour - a study with the microsimulation model *STDSIM. Math Pop Studies*, 8(2): 135-173.

Korenromp EL, Van Vliet C, Grosskurth H, Gavyole A, Van der Ploeg CPB, Fransen L, Hayes RJ, Habbema JDF **2000** Model-based evaluation of single-round mass STD treatment for HIV control in a rural African population. *AIDS*, 14(5): 573-593.

Van Vliet C, Meester EI, Korenromp EL, Singer B, Bakker R, Habbema JDF **2001** Focusing strategies of condom use against HIV in different behavioural settings: an evaluation based on a simulation model *Bull.WHO*, 79(5): 442-454.

Korenromp EL, De Vlas SJ, Nagelkerke NJD, Habbema JDF **2001** Estimating the magnitude of STD cofactor effects on HIV transmission - how well can it be done? *Sex.Trans.Dis.*, in press.

Korenromp EL, Bakker R, Gray RH, Wawer MJ, Serwadda D, Habbema JDF **2001** The effect of HIV, behavioural change and STD syndromic management on STD epidemiology in sub-Saharan Africa: simulations of Uganda. *Sex.Transm.Inf.*, in press.

Korenromp EL, Bakker R, De Vlas SJ, Robinson NJ, Hayes R, Habbema JDF. Can behaviour change explain increases in the proportion of genital ulcers attributable to herpes in sub-Saharan Africa? A simulation modelling study. *Sex.Transm.Dis.*, in press.

Korenromp EL, Sudaryo MK, De Vlas SJ, Gray R, Sewankambo NK, Serwadda D, Wawer MJ, Habbema JDF. What proportion of episodes of gonorrhoea and chlamydia become symptomatic? *Int.J.STD&AIDS*, in press.

Sudaryo MK, Korenromp EL, Arends, LR, Habbema JDF. The prevalence of discharge and dysuria in *Neisseria gonorrhoea* and *Chlamydia trachomatis* infection: a systematic review. *Submitted.*

Korenromp EL, Bakker R, De Vlas SJ, Gray RH, Wawer MJ, Serwadda D, Sewankambo NK, Habbema JDF. HIV/STD dynamics and behaviour change as determinants of the changing impact of STD treatment on HIV spread - implications for the interpretation of the Rakai trial. *Submitted.*

Orroth KK, Korenromp EL, White RP, De Vlas SJ, Hayes R, Grosskurth H. Comparison of STD prevalences among general populations in sub-Sahara Africa: the role of selection bias and test diagnostics. *Manuscript in preparation.*