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**The interaction between HIV and other
sexually transmitted infections in South Africa:
a model-based evaluation**

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Abstract

The interaction between HIV and other sexually transmitted infections in South Africa: a model-based evaluation

By Leigh F. Johnson

Sexually transmitted infections (STIs) have been shown to increase the probability of HIV transmission, but there remains much uncertainty regarding the role of STI treatment in HIV prevention. This thesis aims to develop a mathematical model to estimate the prevalence of STIs in South Africa, the contribution of STIs to the spread of HIV, and the effects of changes in sexual behaviour and changes in STI treatment.

A deterministic model is developed to simulate the transmission of HIV and six other STIs (syphilis, genital herpes, chancroid, gonorrhoea, chlamydial infection and trichomoniasis), as well as the incidence of bacterial vaginosis and vaginal candidiasis in women. The model is fitted to national HIV prevalence survey data, STI prevalence data from sentinel surveys and data from sexual behaviour surveys, using Bayesian techniques.

Model results suggest that South Africa has some of the highest STI prevalence levels in the world, but that certain STIs – notably syphilis, chancroid, gonorrhoea and trichomoniasis – have declined in prevalence since the mid-1990s, following the introduction of syndromic management programmes and increases in condom use. STIs account for more than half of new HIV infections, and genital herpes is the most significant STI promoting the transmission of HIV. Syndromic management programmes reduced HIV incidence in South Africa by 3-10% over the decade following their introduction (1994-2004). Further reductions in HIV incidence could be achieved by promoting patient-initiated treatment of genital herpes, by addressing rising levels of drug resistance in gonococcal isolates, and by encouraging prompt health seeking for STIs. Concurrent partnerships are a major factor driving HIV transmission, accounting for 74-87% of new HIV infections over the 1990-2000 period. Halving unprotected sex in non-spousal relationships would reduce HIV incidence over the 2010-2020 period by 32-43%.

This thesis contributes to the understanding of HIV/AIDS epidemiology in South Africa by quantifying the contribution of various behavioural and biological factors to HIV transmission. This thesis also highlights several opportunities for reducing the future incidence of HIV. In addition, this thesis advances the assessment of uncertainty in STI models by proposing a Bayesian approach to incorporating sexual behaviour data and STI prevalence data into the parameter estimation process.

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Glossary

Many of the definitions given below are adapted from the *Oxford Concise Medical Dictionary* (E.A. Martin (ed.), 5th edition, 2000, Oxford University Press, Oxford UK).

Acyclovir: an antiviral drug used in the treatment of genital herpes

Amsel's criteria: a method for diagnosing bacterial vaginosis, based on a constellation of clinical signs (abnormal discharge, amine test, presence of clue cells on microscopy and high vaginal pH)

Antigen: any substance/organism which the body regards as foreign, and against which the body produces antibodies

Assortative mixing: a pattern of sexual mixing in which individuals in a particular risk group tend to form partnerships with individuals in the same risk group

Asymptomatic: not experiencing symptoms of infection. A person who is asymptomatic may nevertheless have signs of infection.

Bacterial vaginosis: a condition brought about by changes in the vaginal flora, which may lead to symptoms of vaginal discharge

Basic reproductive number (R_0): the number of secondary infections that the average infected individual would be expected to generate before they die or cease to be infectious, if all of their contacts were susceptible

Bayesian statistics: a branch of statistics concerned with combining experts' prior knowledge about particular parameters and data concerning those parameters

Calibration: the process of setting model parameters so that they are consistent with empirical evidence, and so that the resulting model outputs are consistent with observations

Candidiasis: the presence of *Candida* yeasts in moist areas of the body. The presence of these yeasts in the vagina may lead to vaginitis.

CD4+ count: a measure of the strength of the immune system. A healthy adult would usually have a CD4+ count of $>800/\mu\text{l}$, while an adult sick with AIDS would typically have a CD4+ count of $<200/\mu\text{l}$.

CD4+ T-lymphocytes: T-lymphocytes with CD4 receptors, also known as 'helper T cells' due to their role in directing either the cellular or humoral immune response. HIV infects these cells and other immune cells with CD4 receptors.

Cellular immunity: the immune response in which cytotoxic T-lymphocytes (CTLs) play a crucial role (also known as cell-mediated immunity)

Cervical ectopy: the presence of columnar epithelial cells (which normally line the endocervix) in the ectocervix. Unlike the squamous epithelium, the columnar epithelium comprises a single layer of cells and is therefore easier for HIV to penetrate.

Cervicitis: inflammation of the cervix, usually as a result of chlamydial infection or gonorrhoea

Challenge: experimental injection of infectious material into a subject

Chancroid: an STI associated with genital ulcers, caused by the bacteria *Haemophilus ducreyi*. Also known as 'soft sore'.

Chlamydial infection: an STI associated with cervical discharges in women and urethritis in men, caused by the bacteria *Chlamydia trachomatis*

Ciprofloxacin: an antibiotic commonly used in the treatment of gonorrhoea

Commensal: an organism that neither harms nor benefits its host

Core group: a small sub-population with a high risk of infection, which is usually regarded as being significant in both the initial spread and long-term persistence of infection in the general population

Concurrency: (in the context of STI epidemiology) the state of having more than one current sexual partner

Contact tracing: identifying sexual partners of individuals seeking treatment, and providing treatment to them

Cross-sectional study: a study that measures the prevalence of disease in a sample of individuals, at a point in time (compare with 'longitudinal study')

Culture: a population of microorganisms grown in a solid or liquid laboratory medium. Growth of cultures in laboratory media is one method for diagnosing infection.

Cytokines: protein molecules released by cells when activated by an antigen, which play an important role in directing the immune response to the antigen

Cytomegalovirus (CMV): a chronic viral infection that can be transmitted sexually, although commonly acquired in childhood. Symptoms are usually mild, but in immuno-compromised individuals symptoms can be severe.

Deterministic: (in the context of disease modelling) calculating expected outcomes in cohorts of individuals who share the same characteristics, without allowing for random variation

Diagnostic technique: technique used to diagnose infection or disease, e.g. culture, microscopy, serology, antigen detection, genome detection

Direct immunofluorescence (DIF): an antigen detection method used to diagnose chlamydial infection

Discharge: pus or mucus exuded from the urethra, cervix or vagina, often indicating infection of the reproductive tract

Donovanosis: a rare bacterial STI that is associated with symptoms of genital ulceration. Also known as granuloma inguinale.

Dose-response effect: an effect of a particular exposure ('dose') on an outcome ('response'); the greater the level of exposure, the greater the effect on the outcome.

Dysuria: painful urination

Enzyme immunoassay (EIA): an antigen detection method

Enzyme-linked immunosorbent assay (ELISA): a method used to detect antibodies to a particular infection

Epithelium: tissue covering the external surface of the body and hollow surfaces such as the vagina and anus

Fixed effects model: (in the context of meta-analysis) a method for pooling the results from several studies, which is based on the assumption that the variable being estimated is the same across populations, and that differences between study estimates are due only to sampling variation (compare with 'random effects model')

Frequency-dependent model: a model in which the probability of acquiring infection over a short period of time depends on the prevalence ('frequency') of the

infection in the pool of potential contacts and is independent of the prevalence among existing contacts

Genital ulcer disease (GUD): presence of ulcers, blisters or lesions on the genitals. This is often due to infection with chancroid, syphilis or herpes, though in rare instances it may be due to other STIs such as lymphogranuloma venereum or donovanosis.

Gonorrhoea: an STI associated with cervical discharges in women and urethritis in men, caused by the bacteria *Neisseria gonorrhoeae*. Also known as ‘clap’ or ‘drop’.

Granuloma inguinale: See donovanosis.

Hepatitis B virus: a virus that can be transmitted sexually or through injections with contaminated needles. In developing countries, the virus is commonly acquired in childhood. Some chronically infected individuals develop liver disease.

Herpes simplex virus (HSV): a chronic viral infection that causes intermittent ulcers/blisters. There are two types: type 1, which usually causes blisters on the lips (‘cold sores’), and type 2, which is usually transmitted sexually, causing blisters in the genital area.

High power field: microscopic examination at a 1000× magnification

Human papillomavirus (HPV): a chronic viral STI. There are many different types, some of which cause genital warts and some of which can cause cancer of the cervix, penis and anus.

Humoral immunity: the immune response in which B-lymphocytes play a crucial role, by producing antibodies (compare with ‘cellular immunity’)

Incubation period: the time between infection and the appearance of symptoms

Inoculation: the introduction of a small quantity of infectious material into the body (usually in the context of immunization or challenge experiments)

Lactobacilli: bacteria that occur naturally in the vagina, which protect against infection

Lattice model: See ‘percolation model’

Lavage: washing out of a body cavity with water or a solution

Leucocyte (also known as ‘white blood cell’): any blood cell with a nucleus, involved in protecting the body against infection. There are three main types of leucocyte: granulocytes (also known as polymorphonuclear leucocytes), lymphocytes and monocytes.

Ligase chain reaction (LCR): a genome detection method, highly sensitive in detecting most infections

Likelihood function: the probability of observing a particular set of values, if it is assumed that observations follow a specified distributional form

Longitudinal study: a study that follows a cohort of individuals over a period of time and measures the incidence of death or disease in that cohort (compare with ‘cross-sectional study’)

Lower abdominal pain (LAP): a symptom of pelvic inflammatory disease

Lymphocyte: a type of white blood cell. There are broadly two types of lymphocyte: B lymphocytes (involved in the humoral immune response) and T lymphocytes (involved mainly in the cellular immune response). T lymphocytes can be classified as cytotoxic T lymphocytes (CTLs), helper T lymphocytes or suppressor T lymphocytes.

Lymphogranuloma venereum (LGV): a bacterial STI that causes genital ulcers. It is caused by a strain of *Chlamydia trachomatis* that differs from that which causes discharges (chlamydial infection).

Macrophages: large cells that engulf and digest bacteria, protozoa, cells and cell debris. They have CD4 receptors, which make them potential targets for HIV.

Male circumcision (MC): removal of the foreskin of the penis

Markov Chain Monte Carlo (MCMC): a method for simulating the posterior distribution in a Bayesian analysis, when it is not possible to calculate the posterior distribution analytically. Each sequence of sampled parameter combinations is a Markov chain, i.e. the probability that the next parameter combination in a sequence takes on a particular set of values depends only on the last parameter combination and not previous ones.

Mass treatment: a once-off campaign to treat all individuals in a particular population or sub-population, with the objective of eliminating asymptomatic infection

Meta-analysis: a technique to estimate the ‘average’ value of a particular quantity by pooling results from different studies

Meta-regression: a meta-analysis that attempts to account for variation in estimates of a quantity between studies by performing a regression, with study characteristics as explanatory variables

Metronidazole: antibiotic commonly used to treat trichomoniasis and bacterial vaginosis

Metropolis algorithm: a Markov Chain Monte Carlo technique in which the jumping distribution (the distribution used to sample the next parameter combination in the sequence) is symmetric. The method can be extended to allow for asymmetric jumping distributions (the Metropolis-Hastings algorithm).

Microscopy: identification of microorganisms by microscopic examination

Mucopurulent: containing mucus and pus

Mucosa/mucous membrane: the moist membrane lining many cavities, e.g. the vagina

Murine models: experiments in mice

Mycoplasma genitalium: a bacterial infection of the genital tract that is often associated with urethritis and cervicitis

Network model: a model of STI transmission that can be represented graphically. In graph theory terms, each node (‘vertex’) of the graph represents an individual, and each connection between nodes (‘edge’) represents a sexual partnership.

Non-gonococcal urethritis (NGU): urethritis in which no gonococcal infection is apparent

Non-specific urethritis (NSU): urethritis in which neither gonococcal nor chlamydial infection is apparent

Non-syngium-inducing (NSI) HIV: the HIV phenotype most frequently involved in the sexual transmission of HIV. The NSI phenotype infects mainly macrophages, whereas the syngium-inducing (SI) phenotype infects mainly CD4+ T lymphocytes.

Non-treponemal test: a test that detects antibodies to syphilis (the test usually ceases to produce positive results a few months after the individual is cured of syphilis)

Nugent’s score: a method for diagnosing bacterial vaginosis, based on a scoring system that takes into account the relative levels of *Lactobacillus*, *Bacteroides*, *Mobiluncus* and *Gardnerella vaginalis* in the vagina

Pair formation model: an STI model in which pairs of partnered individuals are modelled separately from single individuals, and pairs are classified according to the infection statuses of both partners

Pelvic inflammatory disease (PID): inflammation of the uterus, fallopian tubes and ovaries, often due to gonococcal or chlamydial infection ascending into the upper reproductive tract

Percolation model: a model for examining how an infection spreads ('percolates') through a population from a single infected individual, assuming all individuals have the same number of susceptible contacts, and assuming a constant probability of transmission per contact

Periodic presumptive treatment (PPT): provision of treatment to all individuals in a particular group at regular intervals, regardless of their disease status. Treatment is provided presumptively because of the high risk of infection in the particular group.

Phenotype: the characteristics of an organism that result from interactions between its genes and its environment

Placebo: a pharmacologically inactive substance often given to subjects in the control arm of a randomized control trial

Polymerase chain reaction (PCR): a genome detection method, highly sensitive in detecting most infections

Polymorphonuclear leucocyte (PMNL): a type of white blood cell (leucocyte) having a nucleus that is divided into lobes. Also known as a granulocyte.

Population attributable fraction (PAF) or risk (PAR): the proportion of new cases of a particular disease that can be attributed to a particular risk factor, in a given population

Posterior: (in the context of Bayesian analysis) a probability density function representing the range of likely parameter values or model outputs, after integrating expert prior knowledge about the parameter(s) and data concerning the parameter(s) or model outputs

Prior: (in the context of Bayesian analysis) a probability density function representing experts' *a priori* beliefs about the range of likely parameter values, specified prior to the data in the current analysis being known

Prospective study: See 'longitudinal study'.

Prostatitis: inflammation of the prostate gland, often due to infection

Protozoa: a group of single-cell microorganisms, many of which exist in humans as parasites

Random effects model: (in the context of meta-analysis) a method for pooling the results from several studies, which is based on the assumption that the variable being estimated varies between populations. The mean produced from a random effects model represents the average value of the variable across populations, and the confidence interval around this mean is wider than that produced using a fixed effects model.

Randomized controlled trial (RCT): a study in which the effect of a particular treatment or intervention on a particular outcome is assessed by randomly allocating subjects to either receive the intervention (the 'intervention arm') or not receive the intervention (the 'control arm')

Rapid plasma reagin (RPR): a non-treponemal antibody test commonly used to test for syphilis

Sampling Importance Resampling (SIR): a method for simulating the posterior distribution in a Bayesian analysis, when it is not possible to calculate the posterior distribution exactly. Parameter combinations are sampled from the prior, the likelihood function is calculated for each parameter combination, and then a 'resample' of parameter combinations is drawn from the original sample, using the likelihood values as weights.

Screening: actively testing and treating individuals for infection even when they do not have symptoms

Sensitivity: the probability that a diagnostic method detects infection in an infected individual

Seroconversion: the time at which an individual begins to produce antibodies to a particular pathogen, detectable on antibody tests

Serodiscordant couple: a couple in which one partner (the 'index partner') has a particular infection (usually determined serologically) and the other partner does not have the infection

Serology: the study of blood serum, or the detection of antibodies to pathogens in blood serum

Seroprevalence: the prevalence of an infection based on serological tests

Sexually transmitted infection (STI) or disease (STD): an infection or disease that is sexually transmitted. The term 'STD' is usually used more specifically to refer to symptomatic infection. In the past, the term 'venereal disease' (VD) was used.

Shedding: See 'viral shedding'

Specificity: the probability that an uninfected individual tests negative on a particular diagnostic test

Social desirability bias: the tendency to report behaviour that is considered socially desirable, rather than actual behaviour

Spontaneous resolution: the disappearance of infection in the absence of treatment, often due to the host immune response

STI cofactor effect: the factor by which the HIV transmission probability is multiplied in the presence of an STI

Stochastic: (in the context of disease modelling) calculating numbers of events for each individual separately, allowing for random variation in outcomes (compare with 'deterministic')

Super-infection: the acquisition of an infection when one is already infected with another strain of the same infection

Symptomatic: experiencing symptoms

Syndromic management: a set of treatment protocols that recommend treatment according to the particular signs and symptoms (syndrome) with which the patient presents, rather than according to microbiological assessment of the infectious agent

Syphilis: an STI associated with genital ulcers in its primary stage, skin lesions in its secondary stage and potentially fatal complications of the neurological and cardiovascular systems in its tertiary stage. The disease is caused by the bacteria *Treponema pallidum*.

Titre: a measure of the amount of antibody present in a serum sample (the reciprocal of the weakest dilution at which the antibody can be detected)

Treponemal test: a test that detects antibodies to syphilis (the test usually continues to produce positive results even after the individual is cured of syphilis)

Trichomoniasis: an STI associated with vaginal discharges in women and urethritis in men, caused by the protozoan *Trichomonas vaginalis*

Urethritis: inflammation of the urethra, often defined in clinical terms as five or more polymorphonuclear leucocytes per high power field (in men). Symptoms include urethral discharge, though urethritis can be asymptomatic.

Vaginal candidiasis: See ‘vulvovaginal candidiasis’

Vaginal flora: organisms occurring in the vagina

Vaginitis: inflammation of the vagina, often associated with increased vaginal discharge, dysuria and itching

Validation: the process of checking that model outputs are consistent with observations, after having set the model parameters on the basis of other data sources (compare with ‘calibration’)

Viral load: concentration of virus, in either blood plasma or other specimens (e.g. semen)

Viral shedding: the detectable presence of virus, usually (in the case of STIs) in specimens collected from the reproductive tract

Vulvovaginal candidiasis (VVC): infection of the vulva/vagina by *Candida* yeasts, which can cause symptoms of itching and discharge

Western blot: a diagnostic technique based on the detection of proteins associated with a particular pathogen

White blood cell (WBC): See ‘leucocyte’.

Yeasts: a class of fungi. Yeasts that cause disease in humans include *Candida* and *Cryptococcus*.

Chapter 1: Introduction

In the year 2000, unsafe sex was responsible for approximately 6.3% of the global burden of disease, making it the second-most significant risk factor after childhood and maternal undernutrition (Ezzati *et al*, 2002). The significance of this risk factor was particularly profound in the African region, accounting for 19.4% of the total burden of disease in Africa. In South Africa, the contribution of unsafe sex to the burden of disease is even larger; a recent comparative risk assessment study estimates that in the year 2000, 31.5% of the burden of disease was attributable to unsafe sex, making unsafe sex by far the most significant risk factor in South Africa (Norman *et al*, 2007). Most of this burden is directly attributable to HIV/AIDS, though other sexually transmitted infections (STIs) also comprise an important element. Interventions to limit the spread of HIV and other STIs are therefore urgently needed in South Africa.

Prior to the emergence of HIV/AIDS, the public health significance of STIs lay largely in their effect on infertility, adverse pregnancy outcomes and mortality and morbidity of infants born to infected women. The morbidity associated with most STIs is generally of short duration in adults, though there are notable exceptions, such as syphilis and human papillomavirus (the cause of cervical cancer). With the emergence of HIV/AIDS, there has been renewed interest in other STIs, due to a growing body of evidence showing that the probability of HIV transmission is enhanced in the presence of other STIs. This interaction between HIV and other STIs was first hypothesized in the late 1980s, when it was noted that HIV was present in high concentrations in the genital ulcers of individuals who were co-infected with HIV and ulcerative STIs (Kreiss *et al*, 1989; Plummer *et al*, 1990) and that individuals experiencing genital ulcers were at a significantly increased risk of acquiring HIV, even after controlling for behavioural factors (Cameron *et al*, 1989; Plummer *et al*, 1991). Subsequent studies showed that non-ulcerative STIs and asymptomatic STIs also played a role in HIV transmission, and a series of systematic reviews have documented the growing evidence of the effect of STIs on HIV transmission (Wasserheit 1992; Fleming and Wasserheit 1999; Rotchford *et al*, 2000; Røttingen *et al*, 2001; Sexton *et al*, 2005).

In recognition of the importance of untreated STIs in the transmission of HIV, and the difficulties associated with treating STIs in many developing countries, the World Health Organization (WHO) developed a new strategy for treating STIs, referred to as syndromic management (World Health Organization 1991). This strategy aims to treat all patients presenting with STIs according to the symptoms (or syndrome) with which they present, at their first point of contact with the health system, rather than deferring treatment until the results of laboratory tests are available. Apart from the obvious benefit to the patient of receiving immediate treatment, this strategy circumvents problems that may be experienced with limited laboratory facilities and coordination of test results (major problems in many developing countries), the high cost of laboratory tests and the limited sensitivity of laboratory tests. However, it requires that patients be treated for all possible infections that may be causing a particular syndrome, and this often implies “over-treatment”.

Trials that have examined the effect of improved STI treatment on HIV incidence have produced mixed results. The first such trial, which assessed the effect of syndromic management in Mwanza (Tanzania), showed a roughly 40% reduction in HIV incidence as a result of syndromic management (Grosskurth *et al*, 1995; Hayes *et al*, 1995a). However, a later trial of syndromic management combined with information and education campaigns, in the Masaka district of Uganda, failed to show any effect of the intervention on HIV incidence (Kamali *et al*, 2003). Another trial of mass antibiotic treatment provided to all adults in Rakai (Uganda) at ten-monthly intervals also did not reduce significantly the incidence of HIV (Wawer *et al*, 1999). Trials of monthly STI treatment among commercial sex workers in Côte d’Ivoire (Ghys *et al*, 2001) and Kenya (Kaul *et al*, 2004) have also failed to detect any significant reduction in HIV incidence. The optimism that followed the Mwanza trial has thus been gradually replaced by growing scepticism regarding the role of STI treatment in HIV prevention, and there remains much confusion regarding the reasons for the discrepant trial outcomes.

South Africa has historically had very high STI prevalence levels (Kark 1949), but HIV/AIDS emerged later in South Africa than in most other African countries. In 1990, the prevalence of HIV in pregnant South African women was less than 1%, but

by 2005, prevalence had risen to 30.2% (Department of Health 2006), coinciding with a dramatic rise in mortality levels (Dorrington *et al*, 2001; Bradshaw *et al*, 2004a). A number of factors account for the severity of the South African HIV/AIDS epidemic. The migrant labour system, which became entrenched under colonial administration and apartheid, disrupted stable sexual relationships, thus creating social conditions that would foster the transmission of HIV and other STIs (Lurie 2000; Jochelson *et al*, 1991). Sexual behaviour patterns in South Africa are characterized by a high degree of concurrency (Parker *et al*, 2007), a high frequency of transactional and commercial sex (Dunkle *et al*, 2004), and entry into marriage at a relatively late age (Bongaarts 2007) – all of which are thought to be significant risk factors for HIV. The low socio-economic position of women and the high levels of urbanization in South Africa are other social factors that may be responsible for the high level of HIV prevalence in South Africa. Biological factors have also been an important determinant of the spread of HIV; in addition to the role of STIs, already described, male circumcision has been shown to be protective against HIV and other STIs (Weiss *et al*, 2008; Weiss *et al*, 2006). The relatively low prevalence of male circumcision in South Africa therefore also partially explains the relatively high HIV prevalence (Williams *et al*, 2006a).

Recognizing that untreated STIs were a significant factor driving the spread of HIV in South Africa, the South African Department of Health introduced syndromic management protocols in the public health sector in the mid-1990s, at the same time that it started increasing the distribution and promotion of male condoms. Unfortunately, however, there was no mechanism in place to monitor whether the syndromic management programme was having any impact. South African STI prevalence data have been – and continue to be – obtained from independently conducted studies in different communities, based on different sampling strategies and different diagnostic procedures. This makes it difficult to compare STI prevalence estimates from different studies, and it is even more challenging to establish whether there has been any change in STI prevalence levels over time. With the exception of the national antenatal clinic survey estimates of syphilis prevalence (Department of Health 2006), there are no nationally representative estimates of the prevalence of STIs other than HIV. In spite of the importance of STIs in HIV transmission, there

has been no attempt to integrate the available STI prevalence data in South Africa to form a clear picture of the state of STIs and HIV-STI interactions in South Africa.

Data problems have also bedevilled the assessment of the role of sexual behaviour in the spread of HIV in South Africa. Although many studies have gathered data on sexual behaviour (Eaton *et al*, 2003), these studies have generally been specific to particular communities or particular risk groups, and prior to the 1998 Demographic and Health Survey (Department of Health 1999), no surveys provided nationally representative sexual behaviour data. In the last decade, however, there have been several nationally representative surveys of sexual behaviour in South Africa, and over the same period a substantial body of international literature has emerged, which has aimed to quantify bias in self-reported sexual behaviour. Given these significant advances in our knowledge of sexual behaviour, it should now be possible to assess which aspects of sexual behaviour are contributing most to the spread of HIV in South Africa, and which changes in sexual behaviour would achieve the greatest reduction in HIV and STI prevalence.

This thesis aims to address four questions. Firstly, what is the prevalence of various STIs in South Africa and how are STI prevalence levels changing over time? Secondly, to what extent have STIs promoted the spread of HIV in South Africa, and which STIs are currently the most significant drivers of HIV transmission? Thirdly, how effective have past improvements in STI treatment been in limiting the spread of HIV, and how can changes to current STI treatment practices limit the further spread of HIV? Lastly, which sexual risk behaviours are contributing most significantly to the transmission of HIV and other STIs in South Africa?

To answer these questions, it is necessary to develop a mathematical model to simulate the spread of HIV and other STIs in South Africa. Mathematical models have been used extensively to gain insights into the transmission of infectious diseases and their impact. They have been used to formulate and test hypotheses about disease transmission and progression, to interpret epidemiological data, to make predictions about the future spread of infectious diseases, and to assess the appropriateness of different prevention and treatment strategies (Hethcote 2000; Anderson and May 1992). The results of these models are heavily dependent on the

assumptions that are made about the behavioural and biological processes affecting the transmission and progression of disease, and it is therefore important that assumptions be based on the best available evidence. It is also important that model outputs be validated against epidemiological data, to ensure that the model produces reasonably realistic results. This thesis therefore aims to develop a mathematical model of HIV and other STIs in South Africa, that incorporates the best available data on STI epidemiology, and that can be used to answer the questions outlined above.

In modelling STIs other than HIV, the focus of this thesis is limited to those STIs that are most frequently associated with genital ulcers (syphilis, genital herpes and chancroid) and with genital discharges or dysuria (gonorrhoea, chlamydial infection and trichomoniasis). In addition, bacterial vaginosis and vaginal candidiasis, which cause vaginal discharges, are modelled. These last two infections, which occur only in women, are usually not considered sexually transmissible, but are often considered together with the listed non-ulcerative STIs because of the similarity of the symptoms they produce. These eight genital tract infections have all been shown to increase significantly the risk of HIV acquisition (Röttingen *et al*, 2001), and are the primary targets of the syndromic management protocols. Other STIs are excluded from this analysis either because they are relatively rare (e.g. donovanosis, lymphogranuloma venereum), because there is little evidence to suggest that they increase the risk of HIV transmission (e.g. human papillomavirus, *Mycoplasma genitalium*) or because they are not usually associated with genital symptoms (e.g. hepatitis B, cytomegalovirus). As the focus of this thesis is on the role of STIs in the sexual transmission of HIV, the effects of certain STIs on the risk of infertility and adverse pregnancy outcomes, and mother-to-child transmission of STIs are also beyond the scope of this thesis.

This thesis begins with a brief review of mathematical models of STIs and the modelling of interactions between HIV and other STIs. Chapter 3 is then devoted to describing the basic structure of the model developed to address the four questions listed previously, and the default parameter values are described and motivated. In chapter 4, the model is fitted, firstly just to the available sexual behaviour and HIV prevalence data (ignoring STIs) and then to the available STI prevalence data (ignoring the effect of STIs on HIV transmission), thus producing estimates of trends

in STI and HIV prevalence. In chapter 5, the analysis is extended to allow for the effect of STIs on the probability of HIV transmission, and proportions of HIV infections attributable to other STIs are calculated. The potential effects of interventions – improvements in STI treatment and changes in sexual behaviour – are then evaluated in chapter 6. Finally, key results, policy implications, strengths, limitations and scope for further research are discussed in chapter 7.

University of Cape Town

Chapter 2: Literature review: Mathematical models of STIs, HIV and STI-HIV interactions

2.1 Introduction

Mathematical modelling of infectious diseases began in the 1760s with Daniel Bernoulli's modelling of smallpox (Linder 1936). Since then, mathematical models have been developed to simulate the spread of a wide range of other infectious diseases, such as bubonic plague, measles, tuberculosis, malaria and influenza – to name but a few examples. These mathematical models have been developed to address a range of questions that cannot be answered through the use of traditional epidemiological methods. For example, what proportion of the population needs to be vaccinated in order to avoid outbreaks of a particular infectious disease? What is the predicted future incidence of a disease, considering possible changes to factors that may favour or inhibit its transmission? How rapidly can an infection be expected to spread when it is introduced into a population for the first time? Central to answering these questions is an appreciation of the non-linearity of infectious disease dynamics; because the rate at which new infections occurs depends on the prevalence of the infection, the percentage reduction in incidence that follows a particular intervention is not proportional to the percentage reduction in susceptibility, except in the very short term.

Models of infectious disease transmission can be distinguished from models that calculate disease incidence independently of transmission parameters. The latter body of modelling work is typically concerned with fitting functional forms to time series data – usually reported numbers of cases or estimated levels of prevalence – in order to characterize changes in disease incidence over time and age differences in disease incidence. Such models require no assumptions about the transmission process, and indeed are often used in the modelling of non-infectious diseases such as cancer (Robertson *et al*, 1999). Applications of these 'curve fitting' models to epidemiological data predate the development of models of infectious disease

transmission (Anderson and May 1992), and they continue to be a popular tool for analysing epidemiological data because they require relatively few assumptions.

Mathematical models of infectious diseases vary greatly, and can be classified in a number of ways. In their classic text on infectious disease modelling, Anderson and May (1992) start by classifying modelling work according to the type of infection that is modelled, distinguishing between models of microparasites (viruses, bacteria and protozoa) and models of macroparasites (helminth and arthropod infections), and distinguishing between directly transmitted infections and indirectly transmitted infections (transmitted between humans by 'vectors' such as mosquitoes and fleas). In Hethcote's review of infectious disease modelling (Hethcote 2000), the primary distinction that is made is the distinction between epidemic models (models of disease outbreaks that typically persist in a population for less than a year) and endemic models (models of diseases that can be expected to persist in a population for longer than a year). A distinction is also made between the 'standard incidence model', in which the incidence of infection is assumed to be proportional to the prevalence of infection; and the 'mass action model', in which the incidence of infection is assumed to be proportional to the number of infected individuals, so that incidence rates will tend to be higher in large populations than in small populations. Disease models are also sometimes classified as compartmental or distributional (Garnett 2002); a compartmental model, for example, might split the population into infected and uninfected individuals, while a distributional model might model the distribution of parasite loads within the infected individuals.

Mathematical models of STI transmission were first developed in the 1970s (Cooke and Yorke 1973; Hethcote and Yorke 1984), in response to concern over the dramatic increases in the number of reported gonorrhoea cases in the USA during the 1960s and 1970s. Although earlier 'curve fitting' models had been applied to trichomoniasis prevalence data (Ipsen and Feigl 1970), these did not make assumptions about the STI transmission process. Models of STI transmission are based on the standard incidence model rather than the mass action model. However, unlike most other models of infectious disease, STI models usually make separate assumptions about rates of contact between individuals and the probability of transmission per contact; models of other infectious diseases usually specify a rate of 'adequate contact' (Hethcote 2000),

which is the product of the rate of contact and the probability of transmission per contact. The separation of the rate of contact and the probability of transmission is probably due to contacts being easier to define and measure in the context of STIs than in the context of other infectious diseases. STI models are usually endemic models, and because they are projected for relatively long periods, they usually allow for demographic processes (birth and death) and loss of immunity over time.

Since the emergence of HIV as a new STI in the early 1980s, interest in STI modelling has grown considerably. While models of other STIs have generally been quite simple, due to the lack of information on the transmission and natural history of these infections, the large amount of empirical research into the epidemiology of HIV has permitted a degree of sophistication and complexity in HIV models that is unmatched by models of other infections. The volume of literature relating to STI modelling is now enormous, and several reviews have been published on various aspects of HIV and STI modelling (Garnett and Anderson 1996; Anderson and Garnett 2000; Cassels *et al*, 2008).

The purpose of this chapter is to provide an overview of the themes that have been most commonly tackled in the STI modelling literature and a commentary on the approaches that have most frequently been adopted. Section 2.2 outlines the types of STI models and critically examines the assumptions about sexual behaviour and STI transmission implicit in these different classes of models. Section 2.3 then describes the approaches that are most commonly adopted in modelling the natural history of sexually transmitted infection. In section 2.4, approaches to modelling interactions between HIV and other STIs are discussed, and in section 2.5, models of STI treatment are reviewed, with a focus on the important conclusions relating to HIV and STI control. Finally, in section 2.6, limitations of existing STI models are summarized.

2.2 Approaches to modelling sexual behaviour and STI transmission

Models of sexual behaviour and STI transmission can be classified as either stochastic individual-based models ('micro-simulation' models) or deterministic 'macro-simulation' models. The former assign distinct characteristics to each individual in the modelled population and generate events such as partnership formation and transmission of infection randomly, at the individual level. The latter group of models divide the population into cohorts of individuals, on the basis of factors such as disease status, sexual behaviour and age, and simulate the *expected* numbers of events in each cohort. In cases in which it is possible to construct deterministic and stochastic versions of the same STI model, deterministic models have generally been found to produce results consistent with the average results produced by their stochastic analogues (Chick *et al*, 2000; Kretzschmar and Morris 1996; Eames and Keeling 2002; Mode 1991; Koopman *et al*, 2000). However, when an STI is very close to the threshold of persistence in a population, deterministic models can over-estimate the average STI prevalence that would be expected, because they typically do not allow for the possibility of the STI becoming extinct (Gallop *et al*, 2002).

Although deterministic models have the advantage of being easier to calibrate and parameterize than stochastic models, they are more limited in their ability to handle the complexities of sexual behaviour and STI transmission, and all rely on approximations of some sort in order to represent these dynamics. Figure 2.1 is a schematic representation of the various types of deterministic models, which differ according to the nature of the approximations made. In static network models (which include lattice models and percolation models), the network of sexual relationships remains fixed over the course of the simulation, i.e. partnership formation and dissolution are not modelled explicitly (Wu and Bradley 1991; Eames and Keeling 2002). The focus of these models is therefore the dynamics of STI transmission and resolution over relatively short time intervals, rather than the longer term spread of STIs in a population.

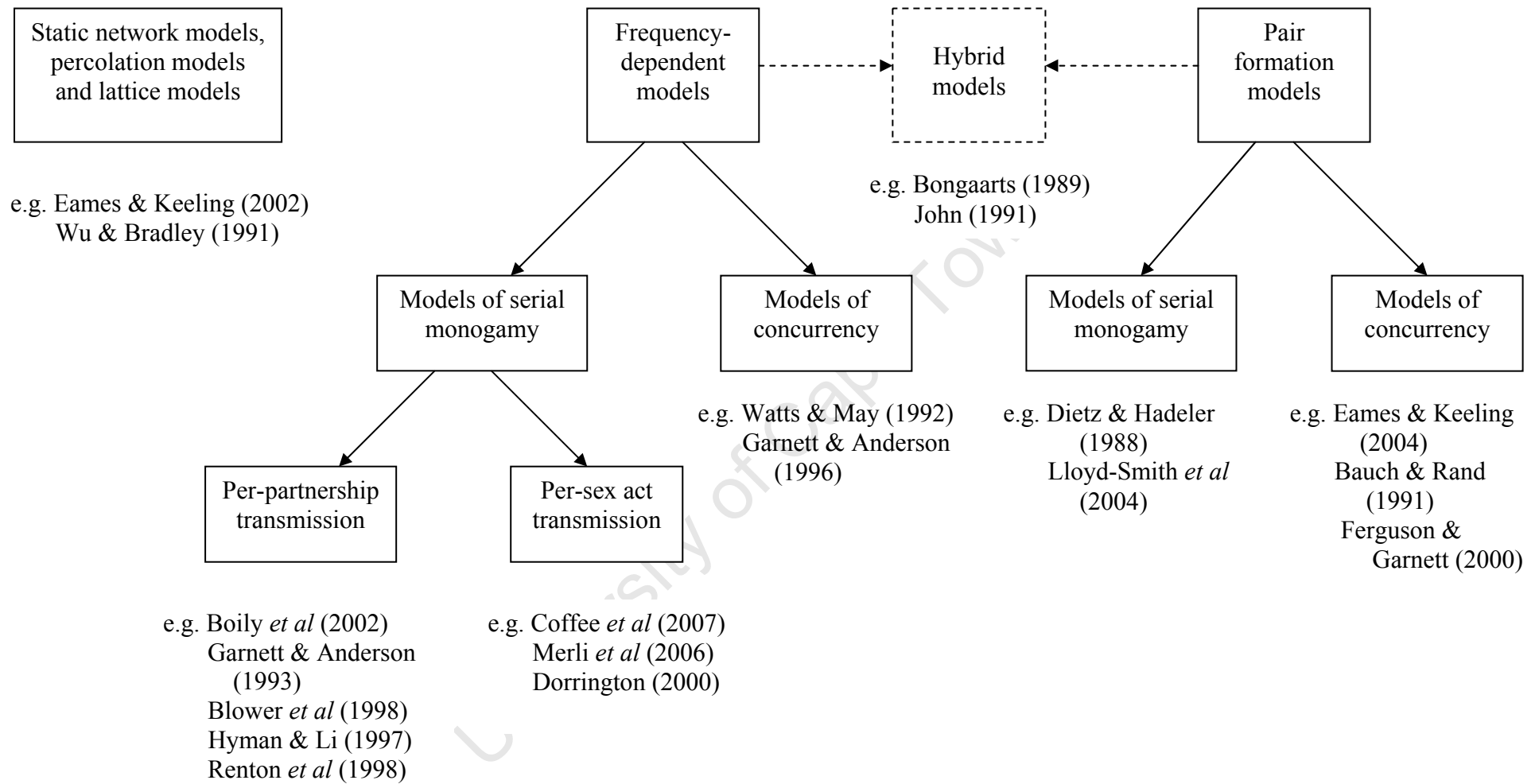


Figure 2.1: Deterministic models of sexual behaviour and STI transmission

Frequency-dependent models¹ are models in which the probability of acquiring infection over a small time step is proportional to the prevalence of infection in the pool of potential partners. Individuals are not grouped according to the infection status of their partner(s), so that in each cohort, the probability of acquiring infection over a short time step is effectively independent of the infection status of the individual's current partner(s). It has been argued that this is unrealistic, particularly in the case of STIs with high transmission probabilities (e.g. gonorrhoea), for which one would expect a high degree of correlation between the infection statuses of individuals and their partners (Lloyd-Smith *et al*, 2004). Pair formation models provide an alternative way of modelling STI transmission dynamics, by defining cohorts according to the infection status of partner(s), so that there are effectively cohorts of couples (stratified according to the infection status of both partners) in addition to cohorts of single individuals. It has been shown that under certain conditions pair formation models can produce significantly lower estimates of STI prevalence than frequency-dependent models (Eames and Keeling 2002; Lloyd-Smith *et al*, 2004). This is a cause for concern, as the majority of STI models follow the frequency-dependent approach.

However, pair formation models also have limitations, and are not necessarily the 'gold standard' in comparisons with frequency-dependent models. Most pair formation models are models of serial monogamy, which do not allow for the possibility that some individuals may have more than one current partner (Dietz and Haderler 1988; Lloyd-Smith *et al*, 2004). This is a significant limitation, as several studies have shown that even after controlling for average rates of partnership formation or average infectivity, high levels of concurrency in a sexual network are associated with significantly higher STI prevalence levels (Morris and Kretzschmar 1997; Ghani *et al*, 1997; Eames and Keeling 2004; Koopman *et al*, 2000). In recent years there have been several attempts to extend pair formation models to allow for concurrency. These models estimate changes in the numbers of coinfecting or singly infected pairs from 'triples' (groups of three individuals comprising a 'polygamous' individual and their two sexual partners). In order to estimate the change in the

¹ The term 'frequency-dependent model' is used in some papers (Thrall and Antonvics 1997; Lloyd-Smith *et al*, 2004), and although the term is not widely used, we use it here in the absence of a better term. The term 'mean-field model' is used in some texts to describe the same concept (Eames and Keeling 2002).

numbers of triples, it is necessary to estimate the number of ‘quadruples’, and so the system can expand to include quintuples etc. To prevent the system of differential equations becoming unmanageable, ‘moment closure approximations’ have been proposed, which limit the analysis to triples (Ferguson and Garnett 2000; Bauch and Rand 2000; Eames and Keeling 2004). These approximations are based on the assumption that in any given triple, the infection statuses of the two partners of the polygamous individual are independent, conditional upon the infection status of the polygamous individual. Bauch and Rand (2000) have shown that this approximation works reasonably well for STIs with low transmission probabilities and long average durations, but that it can significantly exaggerate the prevalence of STIs with high transmission probabilities and short average durations.

Most frequency-dependent models are models of serial monogamy. Usually this is implicit in the assumption that the probability of acquiring infection from a partner depends only on the partner’s infection status at the *start* of the relationship; it is also implicit in the absence of any assumptions about the average duration of partnerships, which would determine the extent of overlap between partnerships. Very few attempts have been made to allow for concurrency within the frequency-dependent approach (Watts and May 1992; Garnett and Anderson 1996). Some modellers have avoided the serial monogamy vs concurrency question by working with a rate of sexual contact rather than a rate of partnership formation, effectively assuming that sex acts occur at random between members of certain sub-populations (Bongaarts 1989; De Gruttola and Mayer 1988). This is the standard approach used in modelling the incidence of other infectious diseases (Hethcote 2000). De Gruttola and Mayer (1988) have argued that this approach is reasonable when the probability of transmission per sex act is substantially lower than the inverse of the average number of sex acts per partnership. This condition would generally hold for HIV, but not necessarily for other STIs.

Deterministic frequency-dependent models of serial monogamy can be distinguished according to whether they model STI transmission using per-partnership probabilities (the traditional approach) or probabilities of transmission per sex act. Since coital frequency is not always positively correlated with the number of partners (Nordvik and Liljeros 2006; Blower and Boe 1993), the latter approach might be considered

more realistic in some settings. However, Garnett and Anderson (1993) observe that in the case of HIV, the cumulative HIV infection probability is *not* linearly related to the cumulative number of sexual encounters with the infected partner, and argue that it is therefore reasonable to assume a per-partnership transmission probability, without reference to the coital frequency in the partnership. Limited evidence suggests that similar non-linearities exist in the case of herpes (Wald *et al*, 2001; Corey *et al*, 2004), chlamydial infection and gonorrhoea (Lin *et al*, 1998; Hooper *et al*, 1978), which might justify the use of per-partnership transmission probabilities in modelling these STIs.

Although many STI models assume homogeneity in sexual behaviour patterns, it is well recognized that models should allow for heterogeneity in sexual behaviour in order to model STI spread realistically. Garnett and Anderson (1993), for example, have shown that a model with heterogeneous sexual behaviour produces a more rapid growth in HIV prevalence but a lower endemic HIV prevalence than a model of homogeneous sexual behaviour with the same average rate of partner acquisition, and the HIV prevalence trend predicted by the former model is much more typical of the prevalence trends observed in sub-Saharan African countries. Much STI modelling work has focused on the significant role of ‘core groups’ of individuals with high rates of partner change (typically sex workers and their clients), in spreading and sustaining STI epidemics (Hethcote and Yorke 1984; Ghani and Aral 2005; Auvert *et al*, 2000; Stigum *et al*, 1994; Brunham and Plummer 1990). Although this has been a popular avenue of research, some critics have argued that this focus on high risk groups rather than high risk behaviours is stigmatizing and unhelpful (Wojcicki and Malala 2001; Varga 1997a), and others have argued that sexual behaviour patterns in the broader population may play a more important role in STI transmission dynamics (Helleringer and Kohler 2007). Korenromp *et al* (2000a) have used the STDSIM model to show that HIV prevalence may rise to very high levels in some populations in the absence of a ‘core group’ of sex workers and clients, while in other populations HIV prevalence may remain at relatively low levels in spite of high levels of commercial sex activity.

A few deterministic STI models allow for heterogeneity in sexual behaviour by assigning continuous distributions to individuals’ desired rates of partner acquisition

(Kault 1992; Engen 1992; Anderson and May 1992), but most allow for heterogeneity by dividing the population into discrete 'risk groups', with each risk group being characterized by different rates of partner acquisition. In such cases it is important to specify the extent to which different risk groups interact with one another, and several approaches have been proposed (Gupta *et al*, 1989; Hyman and Li 1997; Tan and Xiang 1996). Sexual mixing patterns are usually characterized as being 'assortative' (individuals tend to form partnerships with individuals in the same risk group), 'disassortative' (individuals tend to choose their partners from other risk groups) or random (individuals have no preference regarding the risk group of their partner) (Garnett and Anderson 1996). Trends in STI prevalence have been shown to be very sensitive to both the form of sexual mixing (Doherty *et al*, 2006; Kretzschmar and Morris 1996; Merli *et al*, 2006; Garnett and Anderson 1996; Stigum *et al*, 1994) and the 'balancing rule' that is used to adjust desired rates of partnership formation when there are imbalances in demand for relationships between risk groups. As an example of the latter, Garnett and Anderson (1993) predict that if women's rates of entry into partnership were determined entirely by male demand for partnerships, the differences in HIV prevalence between males and females are likely to be much greater than they would be if men's rates of partner acquisition were determined entirely by female demand for partnerships. Most models allow for this balancing process to be dynamically updated; this can be particularly important in HIV/AIDS models, since AIDS mortality is likely to change the population structure and the relative numbers of individuals in different risk groups. Significant reductions in rates of partner acquisition can occur as a result of the imbalances in demand for relationships that develop over the course of an HIV/AIDS epidemic (Gupta *et al*, 1989; Garnett and Anderson 1993), and observed reductions in rates of partner acquisition are therefore not always attributable to the success of interventions.

Although most deterministic STI models do not allow for stratification of the population by age, there have been some attempts to explore the significance of age variation in sexual behaviour and age mixing patterns. For example, Anderson *et al* (1992) have shown that the demographic impact of HIV/AIDS is likely to be greater when sexual activity is more heavily concentrated at younger ages. Anderson *et al* also show that the demographic impact of HIV/AIDS is likely to be much greater if all age groups interact sexually with one another than if individuals only form

partnerships with individuals of the same age. However, other analyses have suggested that HIV prevalence is not very sensitive to assumed levels of mixing between age groups (Hallett *et al*, 2007; Garnett and Anderson 1993).

In addition to stratification by age and risk group, several other stratifications of sexually active populations have been proposed. A number of modellers have considered stratification by geographic location (Coffee *et al*, 2007; Eames and Keeling 2004; Dorrington 2000), ethnic group (Turner *et al*, 2004; Dorrington 2000; Morris 1991; Tan and Xiang 1996) and genetic characteristics (Sullivan *et al*, 2001). There have also been some attempts to stratify populations on the basis of marital status. Both Bongaarts (1989) and John (1991) introduce this stratification by adopting a pair formation approach to modelling HIV in marital unions (effectively assuming that there are no concurrent partnerships among married individuals), while using a frequency-dependent approach to model HIV transmission in pre-marital sexual relationships. Most stochastic models distinguish between spousal relationships, non-spousal relationships and once-off encounters (including contacts between sex workers and clients) (Robinson *et al*, 1997; Korenromp *et al*, 2000a; Bracher *et al*, 2004). Deterministic models of STI transmission, on the other hand, tend to model only one type of sexual relationship. This is a significant limitation, as patterns of sexual behaviour are likely to differ substantially between married and unmarried individuals, with important implications for STI transmission dynamics.

It is worth noting that a number of STI models avoid assumptions about sexual behaviour and STI transmission altogether, by using data on STI prevalence or STI cases to 'back-calculate' the STI incidence rate. Examples are the Spectrum model, which projects the impact of HIV/AIDS by calculating rates of HIV incidence from estimated HIV prevalence levels (Stover 2004), models that are fitted to HIV prevalence data by assuming that trends in HIV incidence follow a particular functional form (Low-Beer and Stoneburner 1997; Salomon and Murray 2001), and numerous models that 'back-calculate' rates of HIV incidence from reported numbers of AIDS cases (Brookmeyer and Liao 1990; Gilks *et al*, 1999; Tan and Ye 2000). Because of the substantial delay between HIV infection and AIDS, and because of under-reporting of AIDS, the latter method does not provide very reliable estimates of

recent HIV incidence, and models parameterized in this way can only be used to make short-term projections of trends in AIDS mortality and HIV prevalence.

In summary, a wide variety of different approaches have been adopted in modelling STI transmission. Individual-based stochastic models have the advantage of being more flexible and are capable of achieving greater realism than deterministic models, but the large number of parameters required in order to achieve this can be a problem, particularly since stochastic models are difficult to calibrate to observed data. Deterministic models rely on various simplifying assumptions and/or approximations in order to estimate average rates of STI incidence in cohorts of individuals. While these simplifying assumptions are reasonable in many scenarios, they can lead to unrealistic results for certain STIs in certain populations. Despite these limitations, both stochastic and deterministic models are capable of yielding important insights into the relationship between sexual behaviour and STIs, particularly with respect to the role of heterogeneity in sexual contact patterns and the role of patterns of mixing between different sub-populations in sustaining the spread of STIs.

2.3 Modelling the natural history of STIs

Models of infectious diseases in humans tend to follow a similar format in their presentation of the course of infection and resolution of infection. This common format, often referred to as the MSEIR model (Hethcote 2000), is illustrated in Figure 2.2. The population is divided into groups of individuals who are susceptible to infection (S), individuals who are infected and infectious (I), individuals who are infected but not yet infectious (E), and individuals who are uninfected but not susceptible, either because they are immune to reinfection following a previous infection (R), or because they acquired antibodies from their mothers at birth (M). Infants are assumed to lose their maternally acquired antibodies rapidly, at rate ϕ . Susceptible individuals are assumed to become infected at rate λ , progress from infected to infectious at rate θ and then recover at rate γ . Individuals are assumed to be withdrawn from the population at rate μ .

STI models do not consider the ‘maternally acquired immunity’ state, since any maternally acquired antibodies would wane many years before the initiation of sexual activity, and would therefore not be significant in the overall STI transmission dynamics. Although most STIs can be transmitted from women to their newborn at birth, with potentially fatal or disabling consequences for the infant, STI models usually do not allow for mother-to-child transmission of infection, except in the case of models designed to assess the demographic impact of HIV/AIDS (John 1991; Bongaarts 1989; Dorrington 2000; Garnett and Anderson 1993; Leclerc and Garenne 2007).

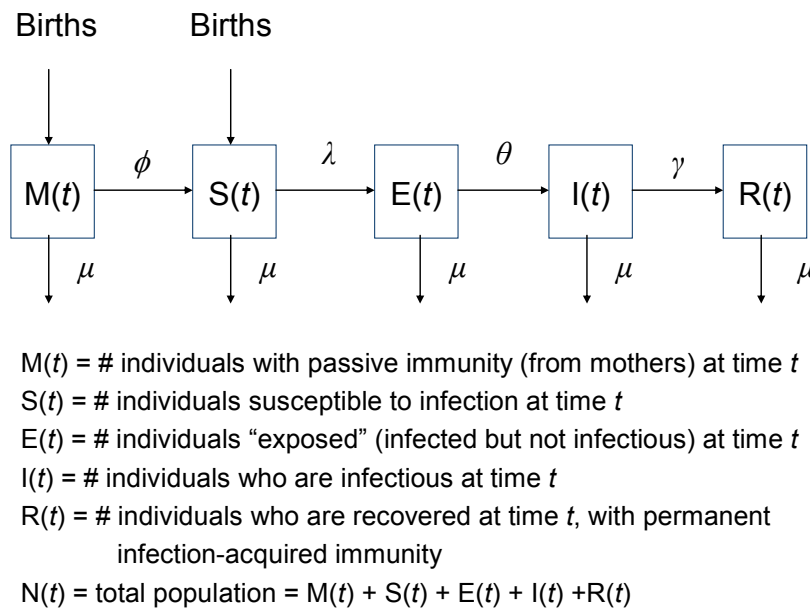


Figure 2.2: The MSEIR model

Source: Hethcote (2000)

STI models also generally omit the ‘E’ state, representing individuals who have acquired infection but are not yet infectious. This is probably because most STIs have an incubation phase that is very short relative to the overall duration of untreated infection, and the incubation phase is therefore not important. A possible exception is syphilis, which has an average incubation period of roughly one month (Garnett *et al*, 1997). Some models of syphilis have therefore allowed for an incubation period

(Pourbohloul *et al*, 2003; Garnett *et al*, 1997). In the early years of HIV research, several modellers speculated that there might be a similar non-infectious incubation phase in the case of HIV infection, and this is reflected in a number of the early HIV/AIDS models (De Gruttola and Mayer 1988; Watts and May 1992; Tan and Xiang 1996). Subsequent research demonstrated that in fact levels of infectiousness in the first few months of HIV infection are extremely high (Wawer *et al*, 2005; Pilcher *et al*, 2004), and any delay between the acquisition of HIV infection and HIV infectiousness would therefore be negligible.

Unlike many other diseases, STIs are generally believed to confer little (if any) immunity against reinfection, and hence virtually all STI models assume that individuals return to the 'susceptible' state immediately after recovering from the STI (Lena *et al*, 2005). Two exceptions are syphilis and chlamydial infection. A number of models allow for temporary immunity against reinfection after recovery from syphilis, and these models show that the average duration of this protection can significantly affect the prevalence of syphilis in the population (Korenromp *et al*, 2000b; Garnett *et al*, 1997; Pourbohloul *et al*, 2003). A few models also allow for reduced susceptibility to reinfection after recovery from chlamydial infection (White *et al*, 2004; Garnett and Anderson 1996; Brunham *et al*, 2005). These assumptions are supported by empirical evidence (Magnuson *et al*, 1956; Brunham *et al*, 1996; Arno *et al*, 1994), but as there is little evidence of immunity after recovery in the case of other STIs, models of other STIs generally omit the 'R' state.

Although STI models generally simplify the MSEIR model by omitting the 'M', 'E' and 'R' states, most STI models also extend the MSEIR model by allowing for heterogeneity within the 'I' state. The early modelling work of Hethcote and Yorke (1984) has been particularly influential. In their modelling of gonorrhoea, Hethcote and Yorke split the infectious state into a symptomatic state (short average duration as a result of treatment) and an asymptomatic state (long average duration), assuming that symptomatic and asymptomatic infections are equally infectious, and assuming no movement occurs between the asymptomatic and symptomatic states. This became the standard approach for much subsequent modelling of gonorrhoea, chancroid and chlamydial infection, with almost all modellers making the same assumptions about the absence of switching between symptomatic and asymptomatic states and the

absence of any difference in infectiousness between symptomatic and asymptomatic infection (Rowley and Berkley 1998; Korenromp *et al*, 2000b; Kretzschmar *et al*, 1996; Garnett *et al*, 1999; Bracher *et al*, 2004). It is possible that switches between symptomatic and asymptomatic infection states may occur (Grosskurth *et al*, 1996; McCutchan 1984; Schachter 1978; Rahm *et al*, 1988) and that symptomatic and asymptomatic infections may differ in their transmissibility, but these assumptions have never been sensitivity-tested in models of short-term acute STIs.

In the cases of herpes, syphilis and HIV, a number of more sophisticated models of infection and infectiousness have been developed. Several models of genital herpes reflect the periodic nature of HSV-2 infection by allowing for frequent switches between symptomatic and asymptomatic states (Newton and Kuder 2000; Korenromp *et al*, 2002b) or between infectious and non-infectious states (Gershengorn and Blower 2000; Blower *et al*, 1998; Blower *et al*, 2004). Models of syphilis tend to track progression of infected individuals through the primary, secondary and latent stages of infection, in most cases assuming that infectiousness is limited to the primary and secondary disease stages (Garnett *et al*, 1997; Pourbohloul *et al*, 2003; Rowley and Berkley 1998; Korenromp *et al*, 2000b). Models of HIV/AIDS typically allow for a very high level of infectiousness in the first few months of infection, followed by a long asymptomatic phase in which infectiousness is low, followed by a 'pre-AIDS' symptomatic phase in which HIV infectiousness is increased, and finally an AIDS phase in which sexual activity is assumed to cease (Robinson *et al*, 1997; Boily *et al*, 2002; Hallett *et al*, 2007; Coffee *et al*, 2007). The relative significance of the high HIV infectiousness in the early and late stages of infection has been assessed in a number of studies, and has been found to be a highly significant factor affecting the pattern of HIV spread (Koopman *et al*, 1997; Rapatski *et al*, 2005; Anderson 1996).

It is well recognized that the natural history and infectiousness of various STIs may be changing over time, in response to selection pressures brought about by treatment, changes in sexual behaviour and demographic changes. Several modellers have attempted to predict these evolutionary changes, usually by comparing two different strains of the same infection and applying the principle of "competitive exclusion" (i.e. assuming that hosts cannot be co-infected with both strains). It has been shown

that if there is perfect homogeneity in sexual behaviour, competing strains of the same STI cannot coexist in the long-term equilibrium with constant population size unless both strains have the same basic reproductive number (Castillo-Chavez *et al*, 1996; Lipsitch and Nowak 1995). However, if there is heterogeneity in sexual behaviour, it is possible for strains with different R_0 values to coexist by selecting different ‘niches’ (Li *et al*, 2003). In addition, Lipsitch and Nowak (1995) show that if fertility rates are constant and the population is growing exponentially, coexistence of competing strains is possible in the equilibrium, with less virulent strains being favoured the higher the rate of partner change and the lower the fertility rate. Paradoxically, though, higher rates of partner change favour the *more* virulent strains in the early phases of the epidemic, when the competing strains are introduced into the population for the first time, and it is therefore possible that the strain that spreads most rapidly at first may ultimately be competitively excluded by the less virulent strain (Lipsitch and Nowak 1995). Other studies have modelled the effects of competition between strains with different symptom severity (Turner and Garnett 2002) and between strains with different modes of transmission (Thrall and Antonovics 1997).

Most of the modelling of the evolution of STIs is limited by the assumptions of homogeneous sexual behaviour and competitive exclusion. It is likely that protection against super-infection by competing strains would not be absolute (Turner and Garnett 2002). In fact, different strains could operate synergistically if prior infection with one strain increases susceptibility to a different strain – a phenomenon referred to as “original antigenic sin” (Lena *et al*, 2005). Another limitation of models of competitive exclusion is that most do not dynamically model the processes by which new strains arise, i.e. through genetic mutations of existing strains (Lipsitch and Nowak 1995). The extent to which different strains actually compete is therefore probably exaggerated by the existing models, but these models nevertheless provide a useful framework for understanding evolutionary pressures.

2.4 Modelling HIV-STI interactions

Numerous studies have shown that HIV transmission probabilities are significantly increased in the presence of other STIs (Røttingen *et al*, 2001). At the most basic

level, this effect can be allowed for in HIV models by assuming higher HIV transmission probabilities in those risk groups in which STI prevalence is likely to be highest (Nagelkerke *et al*, 2002; Dorrington 2000), or by assuming a constant STI prevalence and an increased rate of HIV incidence associated with it (Rehle *et al*, 1998; Brown and Peerapatanapokin 2004; Merli *et al*, 2006). However, since STI prevalence levels are likely to change over time, a better approach is to model the transmission and resolution of other STIs explicitly, linking them to the transmission of HIV through an assumed ‘STI cofactor’. Most models of HIV-STI interactions adopt this approach, with the STI cofactor taking the form of a multiple by which the probability of HIV transmission is increased in the presence of the STI.

There is great diversity in the range of cofactor assumptions that have been made in different models, and Table 2.3.1 summarizes the assumptions made in a selection of HIV-STI interaction models. In much of the early modelling work, which was strongly influenced by the cofactor estimates of Hayes *et al* (1995b), it was assumed that the HIV transmission probability per act of sex was increased dramatically in the presence of other STIs – by as much as 100-fold (Robinson *et al*, 1997; Rehle *et al*, 1998; Bernstein *et al*, 1998; Korenromp *et al*, 2000b). However, since the publication of a systematic review of STI cofactors by Røttingen *et al* (2001) and an analysis of the biases affecting STI cofactor estimation (Korenromp *et al*, 2001), most modellers have used more conservative assumptions about the extent to which the HIV transmission probability per sex act is increased in the presence of other STIs (Bracher *et al*, 2003; Korenromp *et al*, 2002c; Williams *et al*, 2006b; Coffee *et al*, 2007). In some cases the cofactor multiples are relatively low because they are assumed to apply to the probability of HIV transmission per partnership, not per sex act (Over and Piot 1996; Renton *et al*, 1998; Boily *et al*, 2002; Blower and Ma 2004). Since HIV transmission can occur at any point in a relationship, while an acute STI is likely to be present for a relatively short period of time, it makes sense to assume STIs would have a smaller effect on the probability of HIV transmission per partnership than on the probability of HIV transmission per sex act.

In most models, the STI cofactor is assumed to be larger in the case of STIs causing ulcerative symptoms than in the case of non-ulcerative STIs. Although genital ulcer disease is indeed associated with greater susceptibility to HIV than other STI

symptoms (Sexton *et al*, 2005; Røttingen *et al*, 2001), the STIs that cause ulcerative symptoms are – with the exception of chancroid – mostly asymptomatic. Korenromp *et al* (2002c) and Bracher *et al* (2003) assume that syphilis and herpes increase HIV transmission probabilities only when they are symptomatic/infectious, but other models effectively assume that the STI cofactor is the same in all stages of infection. This latter assumption is probably unrealistic, as there is no disruption of epithelial barriers or increased immune activation in the genital tract for most of the asymptomatic stages of syphilis and herpes, and it therefore seems likely that any STI cofactor would be lower than in the symptomatic disease stages.

Although most models assume STIs have the same effect on the probability of HIV transmission whether they are present in the HIV-positive or the HIV-negative partner, a number of modellers assume that STIs have more of an effect on HIV susceptibility than on HIV infectiousness, or ignore the effect of STIs on HIV infectiousness completely (Bracher *et al*, 2003; Coffee *et al*, 2007; Rehle *et al*, 1998; Brown and Peerapatanapokin 2004). This reflects the greater uncertainty regarding the effects of STIs on HIV infectiousness; while meta-analyses have shown convincingly that STIs increase HIV susceptibility (Sexton *et al*, 2005; Røttingen *et al*, 2001), only gonorrhoea has been found to increase HIV infectiousness significantly in meta-analytic reviews (Rotchford *et al*, 2000). However, the effect of STIs on HIV infectiousness may well be more important than the effect of HIV susceptibility. The STDSIM model, for example, suggests that the proportion of HIV infections attributable to curable STIs in HIV-infected individuals exceeds the proportion attributable to curable STIs in HIV-negative individuals (Orroth *et al*, 2006). This is probably because curable STIs tend to cluster in high-risk individuals, and are thus more prevalent in HIV-infectious individuals than in HIV-susceptible individuals.

Table 2.3.1: Multiples by which HIV transmission probabilities are increased in the presence of different STIs: assumptions from different studies

Study	STI/STI type	STI cofactor if STI present in		Per sex act/ partnership
		HIV- partner	HIV+ partner	
Over & Piot (1996)	Chancroid	5	5	Per partnership
	Syphilis	5	5	
	Chlamydia	2	2	
	Gonorrhoea	3	3	
Robinson <i>et al</i> (1997)	Ulcerative	10-100	10-100	Per sex act
	Non-ulcerative	2-5	2-5	
Rehle <i>et al</i> (1998)	Ulcerative	30 (f), 60 (m)	-	Per sex act
	Non-ulcerative	10	-	
Korenromp <i>et al</i> (2000b)	Chancroid	100	100	Per sex act
	Syphilis	100*	100*	
	Chlamydia	10	10	
	Gonorrhoea	10	10	
Korenromp <i>et al</i> (2002c)	Chancroid	25	25	Per sex act
	Herpes	10 [†]	10 [†]	
	Syphilis	10*	10*	
	Chlamydia	5	5	
	Gonorrhoea	5	5	
Bracher <i>et al</i> (2003)	Chancroid	2*	-	Per sex act
	Herpes	2.75*	-	
	Syphilis	2.5*	-	
	Chlamydia	2.25*	-	
	Gonorrhoea	2*	2*	
	BV	1.5*	-	
Williams <i>et al</i> (2006b)	Herpes	3.3	3.3	Per sex act
	Gonorrhoea	2	2	
Coffee <i>et al</i> (2007)	Herpes	4	2	Per sex act
	Gonorrhoea	3	2	

* Applies only when the STI-infected partner is infectious. † Applies only during the symptomatic disease stages. f = female, m = male.

Simulations suggest that a high proportion of HIV infections can be attributed to the effect of other STIs on HIV transmission probabilities. Over the course of the HIV/AIDS epidemic, the proportion of incident HIV infections attributable to curable STIs usually declines (Robinson *et al*, 1997; Orroth *et al*, 2006; Freeman *et al*, 2007), in part because the individuals acquiring HIV in the nascent phase of the HIV/AIDS epidemic are likely to be 'high risk' individuals who have a high prevalence of other STIs, and in part because the prevalence of curable STIs can be expected to decline over the course of the HIV/AIDS epidemic in response to interventions and behaviour change. Genital herpes, on the other hand, is expected to account for an increasingly high proportion of incident HIV cases as the HIV/AIDS epidemic matures (Freeman *et al*, 2007; Orroth *et al*, 2006), as the HIV and HSV-2 viruses are mutually enhancing, HSV-2 becoming more symptomatic and more transmissible in the presence of HIV coinfection.

Although much attention has focused on the effect of STIs on the probability of HIV transmission, there has been little analysis of the effect of HIV on other STIs. It might be expected that increases in mortality due to AIDS would disproportionately affect 'high risk' groups, and thus bring about a reduction in the prevalence of other STIs, even in the absence of interventions (Kault 1992; Chesson *et al*, 2003). Conversely, reductions in AIDS mortality due to antiretroviral treatment might be expected to lead to increases in STI prevalence, even in the absence of any 'behavioural disinhibition' (Boily *et al*, 2004).

There is little clarity regarding the effect of HIV infection on susceptibility to other STIs, duration of STIs, severity of STI symptoms or effectiveness of STI treatment, and consequently most modellers assume STI parameters are unaltered by HIV infection. Korenromp *et al* (2002b) allow for an effect of HIV on HSV-2, assuming that the HSV-2 recurrences are twice as frequent and persist twice as long during the symptomatic stages of HIV infection. On the basis of these assumptions they predict that the incidence of herpetic ulcers would increase by 25% over the first 20 years of the HIV/AIDS epidemic in a typical African setting, while the overall seroprevalence of HSV-2 would remain roughly unchanged. A greater effect might be predicted if it were assumed that the principle effect of HIV was to increase HSV-2 shedding (and

hence HSV-2 infectiousness), as some have argued (Paz-Bailey *et al*, 2007a). The effects of HIV on HSV-2 can therefore be particularly significant.

2.5 Modelling the effect of STI treatment

Many STI modelling studies have examined the potential effects of improvements in STI treatment on the incidence of STIs. The STI treatment strategies that are most commonly modelled are:

- Improvements in the quality and availability of treatment for symptomatic individuals who seek treatment (e.g. syndromic management)
- Contact tracing (treating sexual partners of individuals seeking treatment)
- Screening and presumptive treatment (actively testing and treating individuals beyond the STI clinic setting, even if they do not have STI symptoms)
- Suppressive/episodic treatment of chronic STIs to reduce their transmissibility.

Each of these strategies is considered in turn, and finally their relative effects on HIV incidence are discussed.

Models suggest that improvements in the quality and availability of treatment for individuals attending STI clinics are likely to be most effective in reducing the prevalence of STIs that are highly symptomatic, such as chancroid, but would have relatively modest effects on STIs that are mostly asymptomatic, such as chlamydial infection (Korenromp *et al*, 2002c; Kretzschmar *et al*, 1996). In many models, the effects of these improvements in symptomatic STI treatment are modelled by assuming a reduction in the average duration of infection (Robinson *et al*, 1995; Turner *et al*, 2004; Garnett *et al*, 1999), while in others it is assumed that treatment is sought at a particular rate (Kretzschmar *et al*, 1996; Garnett *et al*, 1997; Gershengorn and Blower 2000). There are also models in which an assumed fraction of STI cases get correctly treated (Bernstein *et al*, 1998; Korenromp *et al*, 2000b), which is mathematically equivalent to assuming a rate of treatment seeking if it is assumed that this rate is constant with respect to the duration of infection (Bowden and Garnett 2000). Most models implicitly assume that if treatment is sought, the STI is correctly treated and treatment is 100% effective. In general, models of symptomatic STI

treatment do not include parameters to determine the probability that the infected individual recognizes signs of infection, the rate at which the symptomatic individual seeks treatment, the source from which the individual seeks treatment, the probability that the visited source provides the correct treatment, and the probability that treatment is effective. Breaking down the probability of cure into these components would make models of STI treatment more useful to policymakers, particularly in developing countries in which STI treatment is sub-optimal.

Relatively few models have assessed the effects of contact tracing, probably because it is difficult to represent the effects of contact tracing in frequency-dependent deterministic models, which do not link the infection statuses of individuals and their partners. Kretzschmar *et al* (1996) found, when modelling a Dutch heterosexual population, that treating all sexual partners of symptomatic individuals would be the most effective treatment strategy for reducing the incidence of chlamydial infection and gonorrhoea. A greater reduction may be gained from treating the source from which the symptomatic individual acquired their infection than from treating the partner to whom the symptomatic individual has transmitted their infection (Hethcote and Yorke 1984), as the former would be expected to have the higher level of sexual activity.

Two types of screening are typically modelled: periodic screening (mass treatment) and continuous screening. Models suggest that mass treatment can significantly reduce the prevalence of acute STIs in the short term, although STI prevalence levels usually return to baseline levels in the absence of repeated mass treatment at regular intervals (Bowden and Garnett 2000; Pourbohloul *et al*, 2003; Korenromp *et al*, 2000b). This 'rebound' in STI prevalence is most rapid when the STI has a high transmission probability, when migration of infected individuals into the intervention community is high, and when there is little or no immunity against reinfection after recovery (Pourbohloul *et al*, 2003; Boily *et al*, 2000; Korenromp *et al*, 2000b). Repeating mass treatment at regular intervals would lead to a more sustained reduction in STI prevalence, particularly when targeted at those sub-populations with the highest levels of asymptomatic infection. For example, it has been shown in the cases of gonorrhoea, trichomoniasis and chlamydial infection, that periodic screening in men would be far less effective than periodic screening in women (Kretzschmar *et*

al, 1996; Bowden and Garnett 2000), and this is probably because the prevalence of asymptomatic infection in women is substantially higher than that in men, for all three STIs. Continuous screening is usually modelled by assuming a constant rate at which all individuals get treated, regardless of whether they are symptomatic or asymptomatic.

In the case of HIV and HSV-2, which are treatable but not curable, modelling work has focused on the likely effect of long-term treatment on the transmissibility of these infections. Models suggest that highly active antiretroviral treatment (HAART) could substantially reduce the incidence of HIV and possibly even lead to its eradication over the long term (Law *et al*, 2001; Velasco-Hernandez *et al*, 2002; Blower *et al*, 2000). However, these models typically assume a very high level of HAART coverage and assume that HAART is initiated in the relatively early stages of disease. In developing countries, where access to HAART is poor and most individuals only start treatment in the very late stages of disease, the impact of HAART on HIV incidence is likely to be relatively modest (Johnson and Dorrington 2006). The impact of antiviral treatment on the incidence of genital herpes is also likely to be modest, unless very high levels of coverage are achieved (White and Garnett 1999; Gershengorn and Blower 2000; Williams *et al*, 2007) or treatment is limited to those infected individuals who have high frequencies of viral shedding (Blower *et al*, 2004). The impact of treatment on the incidence of HSV-2 and HIV is also likely to be curbed by the development of drug-resistant strains of these viruses (Nagelkerke *et al*, 2002; Gershengorn and Blower 2000; Velasco-Hernandez *et al*, 2002), and could potentially be negated by adoption of riskier sexual practices in response to reduced fear of infection (Blower *et al*, 2000; Law *et al*, 2001).

Because of the significant effect of STIs on HIV transmission probabilities, much modelling work has examined the potential effect of improved STI treatment on HIV incidence. A large body of work by the STDSIM group has attempted to explain the contradictory findings of the STI treatment trials conducted in Mwanza, Rakai and Masaka: while the Mwanza study showed that syndromic management could achieve a roughly 40% reduction in HIV incidence (Grosskurth *et al*, 1995), the mass treatment trial conducted in Rakai was found to have no effect on HIV incidence (Wawer *et al*, 1999), and the study conducted in Masaka showed no significant

reduction in HIV incidence in communities in which syndromic management was introduced (Kamali *et al*, 2003). Analyses conducted using the STDSIM model suggest that most of the differences between these trials can be attributed to differences between study populations rather than differences between interventions (White *et al*, 2004). The Mwanza trial was conducted at a relatively early stage in the HIV/AIDS epidemic, when there was still a high prevalence of curable STIs, while the Rakai and Masaka studies were conducted in Uganda, at a relatively advanced stage in its HIV/AIDS epidemic, when the prevalence of curable STIs had already reduced significantly as a result of behaviour change (Orroth *et al*, 2003a; Orroth *et al*, 2003b). STDSIM and other models suggest that the effect of STI treatment on HIV incidence reduces as the HIV/AIDS epidemic matures and as behaviour change reduces the prevalence of other STIs (Korenromp *et al*, 2002a; Korenromp *et al*, 2005; Boily *et al*, 2002). The disappointing results from the Rakai trial are not evidence that mass treatment is less effective than syndromic management in reducing HIV incidence; in fact, mass treatment is likely to be *more* effective than syndromic management in reducing HIV incidence over the short term (Korenromp *et al*, 2000b; White *et al*, 2004; Korenromp *et al*, 2005), and mass treatment would have been significantly more effective in the earlier stages of the Rakai epidemic and in the absence of preceding behaviour change (Korenromp *et al*, 2002a; Korenromp *et al*, 2005). This is an important example of the utility of simulation models in explaining observations that traditional epidemiological techniques would be incapable of explaining.

Recent work by Brunham and colleagues has explored the potential treatment implications of “arrested immunity” (Brunham and Rekart 2008). It has been observed in many STI inoculation experiments that immune responses tend to be weaker if treatment is received soon after infection than if treatment is received long after infection has occurred (Magnuson *et al*, 1956; Schmidt *et al*, 2001; Su *et al*, 1999), and on the basis of this it has been hypothesized that STI treatment programmes may ultimately fail to have a substantial impact on STI prevalence because they weaken the immune responses that would have developed in the absence of treatment. Brunham *et al* (2005) demonstrate this using a model of a chlamydial treatment intervention; their model suggests that improving treatment of chlamydial infection in its early stages may lead to a short-term reduction in prevalence, but

ultimately prevalence is likely to return to a level close to baseline once population levels of chlamydial immunity have reduced substantially. The potential implications of the arrested immunity phenomenon still need to be explored for STIs that are usually associated with weaker immune responses.

In summary, most models of STI treatment interventions have focused on the potential effects of improved treatment of symptomatic STIs, and the potential effects of screening or mass treatment programmes. The general consensus is that improvement in treatment of symptomatic STIs is likely to be most effective in the elimination of STIs that are mostly symptomatic, while screening and mass treatment would be substantially more effective control strategies for STIs that are mostly asymptomatic. If the objective of the STI treatment intervention is to reduce HIV incidence, the effectiveness of the intervention is also likely to depend on the stage of the HIV/AIDS epidemic at the time that the intervention is introduced and the extent of behaviour change preceding the STI treatment programme.

2.6 Limitations of existing models

This review has identified three broad areas in which STI modelling could be further refined. Firstly, deterministic models of sexual behaviour could be extended to gain a more nuanced understanding of the behavioural factors driving STI transmission. Traditionally, deterministic STI models have divided the population into risk groups that represent different average levels of sexual risk behaviour. Although this is a useful means of modelling heterogeneity in sexual behaviour, there is much heterogeneity that is not captured within this model structure. Most importantly, risk groups are not differentiated on the basis of marital status. It is also usually assumed that individuals do not move between risk groups over time, and there is thus no allowance for temporary increases in sexual risk behaviour (for example, following the dissolution of a long-term partnership). In addition, relatively few deterministic models have allowed for concurrent partnerships explicitly. Deterministic models have therefore allowed only a limited understanding of the role of sexual behaviour in the transmission of HIV and other STIs. These models have usually emphasized the role of “core groups” in spreading and sustaining HIV and other STIs at the

population level, but there has been little consideration of the role of sexual risk behaviours in the broader population. There is clearly a need for deterministic models that more accurately represent the changing levels of sexual risk behaviour over the life course, to provide a better understanding of the role of factors such as concurrent partnerships, late marriage, early sexual debut and commercial sex.

There is also potential for further research into the progression of sexually transmitted infection. Early models of gonorrhoea classified individuals as being either symptomatic or asymptomatic, with no allowance for movements between these states and no allowance for immunity upon recovery (Hethcote and Yorke 1984). This has become the standard model for the natural history of acute short-term STIs, but there has been little examination of whether alternative assumptions about the natural history of infection and immunity may yield greater consistency with empirical observations. Such analysis is important, as assumptions about these variables can influence significantly the modelled impact of improvements in STI treatment and changes in sexual behaviour, and thus the policy implications of mathematical model results.

Another potential area for further STI modelling work is in the understanding of obstacles to prompt and effective STI treatment in developing countries. STI models have usually assumed either that a particular proportion of STIs are effectively cured, or that infections resolve at a particular rate as a result of treatment. There has been little attempt to model in more detail the factors that contribute to low rates of effective treatment: delays in health seeking, health seeking from unqualified providers of treatment, low adoption of syndromic management protocols, drug shortages and antibiotic failure. Modelling of each of these factors would significantly improve the utility of mathematical models to policymakers.

Chapter 3: Method for modelling HIV and STIs in South Africa

The objective of this thesis is to develop a mathematical model that can be used to estimate the prevalence of STIs in South Africa, their contribution to the spread of HIV, and the likely effects of changes in STI treatment and changes in sexual behaviour. In order to achieve this, it is necessary to make several refinements to the standard deterministic model of STI transmission that has traditionally been used. As discussed in Chapter 2, these refinements include more detailed modelling of changes in sexual risk behaviour over time, more detailed modelling of the determinants of effective STI treatment, and consideration of alternative models of STI natural history. The purpose of this chapter is to describe the mathematical model used to simulate the spread of HIV and other STIs in South Africa and discuss the literature upon which the various assumptions are based. This includes a description of the demographic assumptions, sexual behaviour assumptions and assumptions regarding HIV and other STIs.

3.1 Demographic assumptions and model structure

The demographic component of the model is based on the ASSA2003 AIDS and Demographic model (Dorrington *et al*, 2006), a combined cohort component projection and HIV/AIDS model of the South African population. The demographic parameters in the ASSA2003 model have been determined using data from the 1970, 1996 and 2001 censuses, vital registration data from 1985 onwards and the 1998 Demographic and Health Survey (DHS). The 'lite' version of the ASSA2003 model, which is based on the summing of the estimates obtained for each of the four population groups in South Africa, is used in all analyses. As the purpose of the current model is not to predict the demographic impact of HIV/AIDS, but rather to understand the factors driving the transmission of HIV and other STIs in South Africa, a number of demographic simplifications are made.

The population is divided into separate age and sex cohorts. Individuals over the age of 10 are grouped into five-year age cohorts (10-14, 15-19, ..., 80-84, 85+), while

individuals below the age of 10 are grouped by individual age, to allow for the more accurate modelling of paediatric AIDS and non-AIDS mortality (both of which are strongly age-dependent). As in the ASSA2003 model, the projection begins at the middle of 1985, a few years ahead of the first reported heterosexual AIDS cases in South Africa (Schoub *et al*, 1988). The profile of the population at the middle of 1985 is obtained directly from the ASSA2003 model, which estimates the 1985 population to be 32.3 million.

Within each of the five-year age cohorts, the cohort is further split by current sexual activity status, and each of these sexual activity cohorts is split by HIV status and stage of HIV infection. Finally, within each HIV status/stage sub-cohort, proportions in each STI state are calculated separately for each STI. These calculations are performed independently for each STI, i.e. it is assumed that for an individual of a particular age and sex, within a particular sexual activity state and a particular HIV infection state, the risk of infection with one STI is independent of the risk of infection with other STIs. The frequency with which individuals move between these various cohorts can be altered by the user of the model, but in the analyses considered here, the following frequencies apply:

- Movements between STI states are calculated at ‘weekly’ intervals (four times per month).
- Movements between HIV states are calculated at monthly intervals in the initial analysis presented in section 4.1, but at weekly intervals in the analysis presented in section 4.2.
- Movements between sexual activity states, including mortality and widowhood, are calculated at monthly intervals.
- Births and movements between age cohorts are calculated at annual intervals.

Non-AIDS mortality rates vary by age, sex and year, and are obtained from the ASSA2003 model, which produces demographic output by individual age. For each year, the mortality rate in each age five-year band is calculated as the number of non-AIDS deaths in that age band divided by the number of individuals in that age band at the start of the year, as estimated by the ASSA2003 model. This annual probability of death is then converted into a non-AIDS mortality hazard, added to the AIDS

mortality hazard (for the relevant HIV states), and applied at monthly intervals. The life expectancy at birth, in 1985, is estimated by the ASSA2003 model to be 62.4 years, with relatively little change up to 1995.

Fertility rates in HIV-negative women vary by age and year, and are also calculated from the ASSA2003 model, which predicts a total fertility rate of 4.2 in 1985, reducing to 3.3 by 1995. For each year, the fertility rate in HIV-negative women in a particular five-year age band is calculated as the weighted average ASSA2003 fertility rate in HIV-negative women, where the weights are the numbers of women at each individual age. The fertility rates in HIV-positive women are calculated by applying a reduction factor to the corresponding fertility rates in HIV-negative women of the same age. These reduction factors have been set to vary by HIV stage, based on estimates of the annual reduction in the rate of fertility per year of HIV infection (Johnson *et al*, 2007) and the observed effects of antiretroviral treatment on fertility (Blair *et al*, 2004). The reduction factor is 1.00 for women in the acute stage of HIV infection, 0.92 for women in the asymptomatic phase of infection, 0.80 in the pre-AIDS symptomatic phase, 0.73 in the AIDS phase and 0.94 in women receiving antiretroviral treatment. The proportion of births that are male is set at 50.39%, as in the ASSA2003 model.

No allowance is made for migration into or out of South Africa. As the net number of migrants into South Africa over the 1985-2000 period is estimated by the ASSA2003 model to be some 1.1 million, this will lead to under-estimation of the rate of population growth and the total population size and a slight distortion in the distribution of the population by age.

The proportion of each age group moving into the next age group, at the end of each year, varies by sex, age band, sexual experience and HIV stage. These probabilities are also calculated using the ASSA2003 model. In most cases, the proportion of a particular five-year age group that moves into the next age group in the following year is calculated from the ASSA2003 model for five different years (1985, 1995, 2005, 2015 and 2025), and the assumed probability of movement into the next age group is the average of these five values.

3.2 Sexual behaviour assumptions

This section begins with a brief description of the structure of the sexual behaviour model, which includes an explanation of the different sexual activity states defined in the model, and the methods used to calculate the rates of transition between these states. This is followed by an explanation of the sexual behaviour parameter values. Although the parameter values are based on empirical data as far as possible, many of these parameter values cannot be determined precisely, and it is therefore necessary to perform a Bayesian analysis in order to assess the range of parameter values that are consistent with sexual behaviour data and HIV prevalence data. Where there is significant uncertainty around the value of a particular parameter, a prior distribution is assigned, and the plausible values for this parameter are then assessed in the Bayesian analysis described in section 4.1.

3.2.1 Sexual activity states and types of sexual relationship

Sexual behaviour is modelled by dividing the population into two sexual activity classes: individuals who have a propensity to engage in commercial sex and/or concurrent partnerships ('high risk'), and individuals who never engage in such relationships ('low risk'). The proportions of the population in each class are set separately for males and females, based on data collected in sexual behaviour surveys. In the 2005 HSRC household survey, the proportions of sexually experienced unmarried men who reported more than one current partner varied between 12% and 18% over the 15 to 59 age range, and the corresponding proportions in unmarried women varied between 1% and 3% (Shisana *et al*, 2005). These are likely to be underestimates of the proportions of individuals with a propensity for concurrent partnerships, as individuals tend to under-report multiple partnerships in face-to-face interviews (Gregson *et al*, 2004; Gregson *et al*, 2002b; Rogers *et al*, 2005; Mensch *et al*, 2003), and not all individuals who have a propensity for concurrent partnerships would currently have multiple partners (Carter *et al*, 2007). The 'high risk proportion' has therefore been set at 35% in males and 25% in females. Some studies in Gauteng province suggest that the true proportions may be closer to 40% (Dunkle *et al*, 2004;

Jewkes *et al*, 2002), but when these higher proportions were used in the model, the resulting HIV prevalence trends were found to be unrealistic.

Three types of sexual relationship are modelled: short-term relationships, long-term (spousal) relationships and contacts between sex workers and their clients. It is assumed that all spousal relationships start off as short-term relationships, i.e. it is only possible to enter the married state from the short-term relationship state. It follows from the definitions of the sex activity classes above that individuals in the 'low risk' group only enter short-term and spousal relationships, and never have more than one current relationship. For the sake of simplicity, it is assumed that individuals in the 'high risk' group never have more than two concurrent spousal or short-term relationships, though 'high risk' men can continue to have contact with sex workers, even when they already have two sexual partners. Women in the 'high risk' group can also enter a 'sex worker' class, and it is assumed (again in the interests of simplicity) that none of these women are in short-term or spousal relationships. No allowance is made for polygyny, as it is uncommon in South Africa (Budlender *et al*, 2004). There is also no allowance made for homosexual relationships, as there is hardly any research on these relationships in the South African setting.

A multi-state approach is adopted in modelling sexual behaviour. Each sexual activity state is defined in terms of the nature of the relationship(s) the individual is currently in. Figure 3.2.1 shows the states that are defined for women in the 'high risk' group and the possible movements between these states. The multi-state model used for men in the 'high risk' group is identical to that shown in Figure 3.2.1, except that there is no 'Sex worker' state. The model that is used to model sexual behaviour in the male and female 'low risk' groups is the same as that shown in Figure 3.2.1, but with the shaded cells omitted.

Individuals move between these states over time, based on a transition probability matrix, the elements of which are set age-specifically and updated on a monthly basis. The rates at which partnerships are formed by men and women are adjusted so that the numbers of partnerships of each type are consistent between men and women. For example, the rate at which men in the high risk group form short-term partnerships with women in the low risk group is determined to be consistent with the rate at which

women in the low risk group form short-term partnerships with men in the high risk group. The weight given to male and female rates of partnership formation are determined by a 'gender equality factor', which can take on any value between 0 and 1 (0 implying that rates of partnership formation are determined only by male desires, and 1 implying that rates are determined solely by female desires). The default value of this gender equality factor is set at 0.5. A more detailed mathematical explanation of the model is given in Appendix A.

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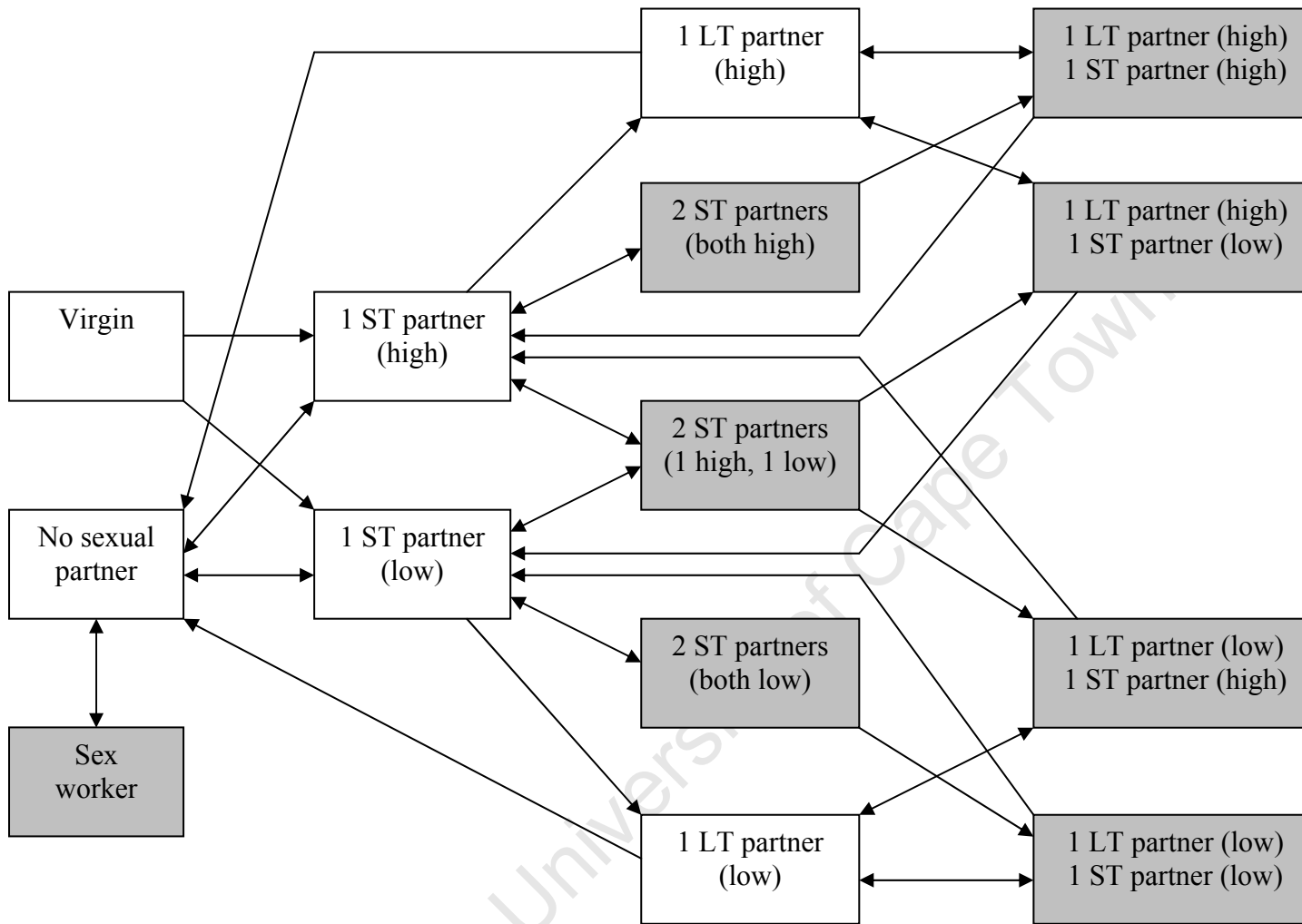


Figure 3.2.1: Multi-state model of sexual behaviour of 'high risk' females

LT = long-term. ST = short-term. Shaded cells are relevant only to the 'high risk' group.

3.2.2 Rates of short-term partnership formation

Rates of short-term partnership formation are assumed to vary according to age, sex, HIV disease stage, propensity for concurrent partners, and the characteristics of the individual's existing partnership(s). Suppose $c_{g,i,j,l}^s(x)$ is the rate at which an individual of sex g wishes to form new short-term partnerships if they are in risk group i , aged x , in HIV disease state s , and in relationship type l with a partner in group j (if the individual is currently single, $j = 0$ and the l subscript is omitted). The approach adopted is to specify this parameter for a 'baseline' group (single HIV-negative individuals in the high risk group, who are aged 15 to 19), and then to assume a series of multiplicative adjustments to allow for the effects of age, risk group, HIV disease stage, and nature of current relationship(s).

The desired rate of partner acquisition in the baseline female group can be estimated from data collected by Jewkes *et al* (2001) among pregnant and non-pregnant adolescent females in a South African community with a high prevalence of HIV. Women who had ended their first sexual relationship and subsequently entered a second relationship were asked about the time interval between the two relationships. The cumulative proportion entering new relationships at different durations since break-up is shown in Figure 3.2.2, together with predictions of the cumulative proportions forming new partnerships when the time to a new partnership is exponentially distributed with a mean of 25 or 40 days. It is assumed that the desired rate of partner acquisition in the 15-19-year old female high risk group is 14.6 per annum, which is equivalent to a mean interval between partnerships of 25 days – this is consistent with the intervals reported by pregnant adolescent females, who can probably be considered mostly 'high risk'.

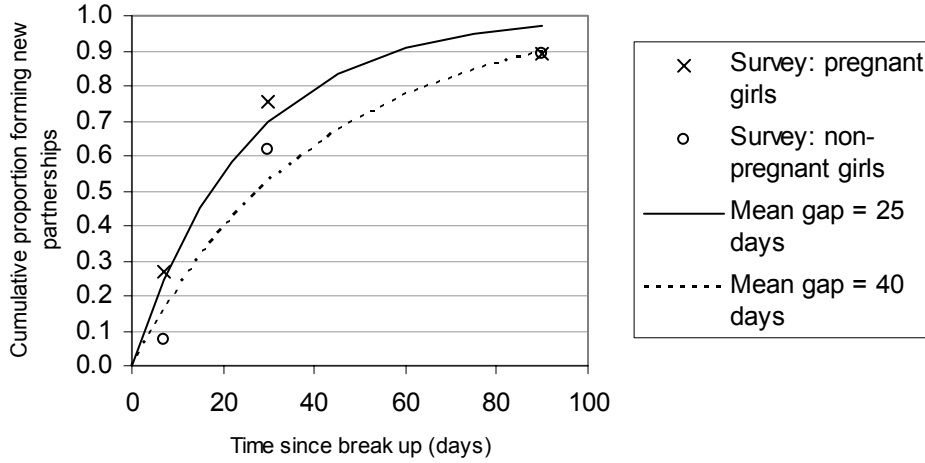


Figure 3.2.2: Cumulative proportions of young females entering new partnerships

Similar data for South African men are not readily available, but it would be expected that the mean intervals between partnerships would be greater in the case of male adolescents than female adolescents, considering that rates of secondary abstinence are higher in young males than in young females (Shisana *et al*, 2005; Reproductive Health Research Unit 2004; Human Sciences Research Council 2002). It is assumed that the desired rate of partner acquisition in the 15-19-year old male high risk group is 7.3 per annum, half of the rate in females. Although the choice of parameter is to some extent arbitrary, the model is only sensitive to this parameter if the assumed effects of risk group and existing partnerships on rates of partnership formation are held constant. Since these parameters are allowed to vary in the uncertainty analysis (as discussed below), it is acceptable to fix the baseline parameter at 7.3.

To allow for the effect of age on the rate of partner acquisition, the relative rates of partner acquisition at different ages are determined using a scaled gamma density:

$$c_{g,i,j,l}^s(x) = c_{g,i,j,l}^s(17.5) \frac{\lambda_g^{\alpha_g} (x-10)^{\alpha_g-1} \exp(-\lambda_g(x-10))}{\lambda_g^{\alpha_g} 7.5^{\alpha_g-1} \exp(-7.5\lambda_g)}, \quad (3.1)$$

where λ_g and α_g are the parameters for the gamma density, and x is the mid-point of the age range. Initial maximum likelihood fits of the model to HIV prevalence data and sexual behaviour data revealed that the fitted gamma means and variances were

reasonably stable across a range of scenarios. The averages of these gamma means and variances were therefore used in setting λ_g and α_g : values of 0.1486 and 3.98 were assumed for males and values of 0.2272 and 4.14 were assumed for females².

The rate at which individuals wish to acquire new partners if they have no propensity for concurrent partnerships is assumed to be a constant multiple of the corresponding rate at which single individuals with a propensity for concurrent partnerships wish to acquire new partners. This multiple, $c_{g,2,0}^s(x)/c_{g,1,0}^s(x)$, differs for males and females but is assumed to be constant with respect to age and HIV disease stage. Although there are no published data indicating plausible values for this multiple, it would be expected that the multiple would be less than 1, and a uniform (0, 1) prior has therefore been assigned to this parameter, for both males and females.

Individuals with a propensity for concurrent partnerships are assumed to acquire new partners at a lower rate if they already have one partner than if they are single. The multiple $c_{g,1,j,l}^s(x)/c_{g,1,0}^s(x)$ is specified separately for males and females in non-spousal ($l = 1$) and spousal ($l = 2$) relationships, but is assumed to be constant with respect to the individual's age, HIV disease stage and the risk group of the partner. As there are no published data indicating the likely magnitudes of these parameters, uniform (0, 1) priors have been assigned to each of the four parameters.

The rates of partner acquisition discussed thus far relate only to individuals who are already sexually experienced. For virgins, separate parameters are specified to determine the rates at which first sexual contact occurs. Studies conducted in South Africa and Zimbabwe suggest that the rate at which 'low risk' individuals (however they may be defined) initiate their first sexual contact is typically between 0.24 and 0.59 times that in 'high risk' individuals, with an average of 0.5 (Dunkle *et al*, 2004; Mpofu *et al*, 2006; Pettifor *et al*, 2004b). It is therefore assumed that virgins with no propensity for multiple partnerships acquire their first sexual contact at a rate equal to half of that in virgins who subsequently enter the high risk group. The desired rates of first sexual contact in the high risk group are shown in Table 3.2.1; these have been

² The corresponding means and standard deviations are 26.8 and 13.45 respectively for males, and 18.2 and 8.95 for females. The means 26.8 and 18.2 correspond to ages 36.8 and 28.2 respectively.

determined to be consistent with the reported rates of sexual experience in the 2005 HSRC household survey, on the assumption that young women under-report sexual experience and young men slightly exaggerate their sexual experience (Mensch *et al*, 2003; Hewett *et al*, 2004; Turner *et al*, 1998). All individuals are assumed to be sexually experienced by age 30.

Table 3.2.1: Desired annual rates of first sexual contact in the high risk group

Age group	10-14	15-19	20-24	25-29
Male	0.01	0.25	0.78	1.00
Female	0.05	0.47	0.95	1.00

3.2.3 Rates of marriage

Several authors have noted that marriage in South Africa occurs at a later age than is typically the case in most other African countries (Bongaarts 2006; Garenne 2004; Bakilana 2005). In the model, rates of marriage are assumed for each five-year age group, for males and females separately, with these rates being chosen in such a way that the modelled proportions of individuals who are married at each age are roughly consistent with the corresponding proportions from the 1996 Census, 2001 Census and 2007 Community Survey. Following the convention in the Demographic and Health Surveys, ‘marriage’ refers to both formal marriages and cohabiting relationships. The resulting assumed rates of marriage at each age are shown in Figure 3.2.3.

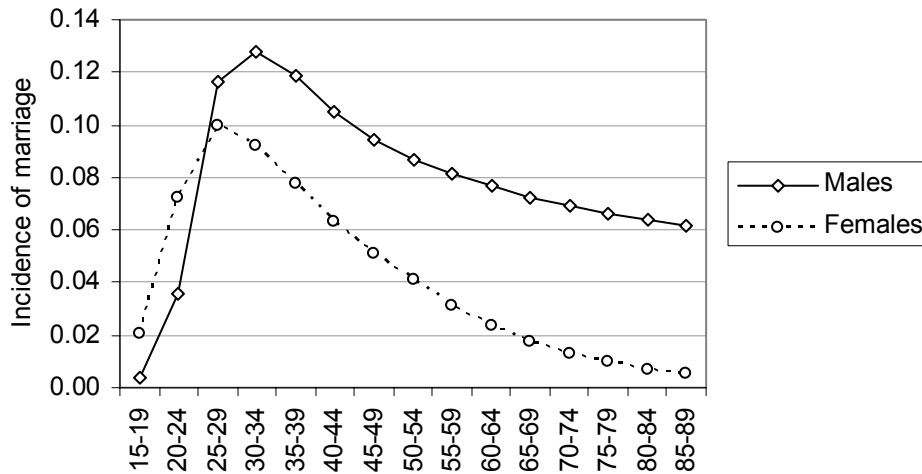


Figure 3.2.3: Assumed annual rates of marriage by age and sex

Although average rates of marriage at each age are constrained to remain constant at the levels shown in Figure 3.2.3, rates of marriage also vary in relation to the current number of non-spousal partners and the individual's risk group. As noted previously, individuals can only enter the married state from the short-term partnership state, and thus the rate of marriage is assumed to be proportional to the number of current short-term partnerships, after controlling for age, sex, risk group and risk group of partner(s). The relationship between risk group and rate of marriage is more difficult to determine; although there are some African studies suggesting that propensity for concurrent partnerships and transactional sex are associated with lower rates of marriage (White *et al*, 2000; Dunkle *et al*, 2004), there are also some studies showing the risk of HIV to be elevated in married individuals after controlling for age (Zuma *et al*, 2003; Auvert *et al*, 2001b; Clark 2004), and it is thus unclear whether 'high risk' individuals do indeed take longer to marry. It is therefore assumed that average age-specific rates of marriage (not controlling for number of short-term partners or risk group of partners) are the same in individuals in the high and low risk groups.

In order to ensure that the average rates of marriage in the high risk and low risk groups are the same at each age, it is necessary to vary the rates of marriage in relation to the risk group of the partner. The rate at which a man in risk group i marries a female partner of risk group j at time t is assumed to be proportional to the ratio

$$\frac{\sum_y N_{1,i,j,2}(y,0) / \sum_{u=1}^2 \sum_y N_{1,i,u,2}(y,0)}{\sum_y N_{1,i,j,1}(y,t) / \sum_{u=1}^2 \sum_y N_{1,i,u,1}(y,t)}, \quad (3.2)$$

where $N_{g,i,j,l}(y,t)$ is the number of relationships of type l ($1 = \text{short-term}$, $2 = \text{long-term}$) between individuals of sex g and age y in group i , and individuals of the opposite sex in group j , at time t . The numbers of long-term relationships at time 0 (1985) are set on the assumption that the rate of marriage is the same in high and low risk groups and the degree of assortative mixing is the same in long-term and short-term relationships (see section 3.2.6). This adjustment ensures that the proportions of married partners in the high and low risk groups remain consistent with the initial proportions, and prevents the higher rates of short-term partner acquisition in the high risk group from leading to higher rates of marriage in the high risk group.

3.2.4 Average durations of partnerships

The average length of non-marital relationships is difficult to estimate reliably from surveys, as individuals who are asked questions about their “most recent partner” are likely to report on their main current partner rather than on current or recent casual partners. The most reliable estimates are obtained from surveys in which individuals are asked about the duration of *all* partnerships over a particular period, or a specific partnership (e.g. the respondent’s first sexual partnership). African surveys in which such questions have been asked have estimated the median duration of non-marital relationships to be between 3 and 12 months (Ferry *et al*, 2001; Jewkes *et al*, 2001; Nnko *et al*, 2004), with the mean durations of current relationships substantially exceeding the mean durations of recently ended relationships (Nnko *et al*, 2004). It is assumed that the average duration of non-marital relationships is 6 months, and that the rate of relationship termination is constant with respect to the relationship duration.

The rates at which spousal relationships are terminated are also difficult to estimate, and there is little demographic literature on rates of union dissolution in Africa (Porter

et al, 2004; Reniers 2003). Registered divorce statistics can be used to approximate rates of divorce in South Africa, although these are likely to understate the true rate at which spousal relationships are terminated. This is partly because reporting of divorces is incomplete (Bah 1999), and partly because our definition of spousal relationships includes unmarried cohabiting partners, who might be expected to have a higher rate of separation than that in formal marriages (Porter *et al*, 2004). In addition, many formal marriages end in separation, which may precede divorce by several years (van Tonder 1985), and union dissolution is therefore often not reflected in published divorce statistics. In the model it is therefore assumed that rates of spousal union dissolution are two times the age-specific rates of divorce estimated from published divorce statistics in 2004 (Statistics South Africa 2006). Although this chosen multiple of two is somewhat arbitrary, the model results are not sensitive to this parameter if the married proportion of the population is held constant. Figure 3.2.4 shows the assumed annual rates of union dissolution by age and sex, for spousal relationships.

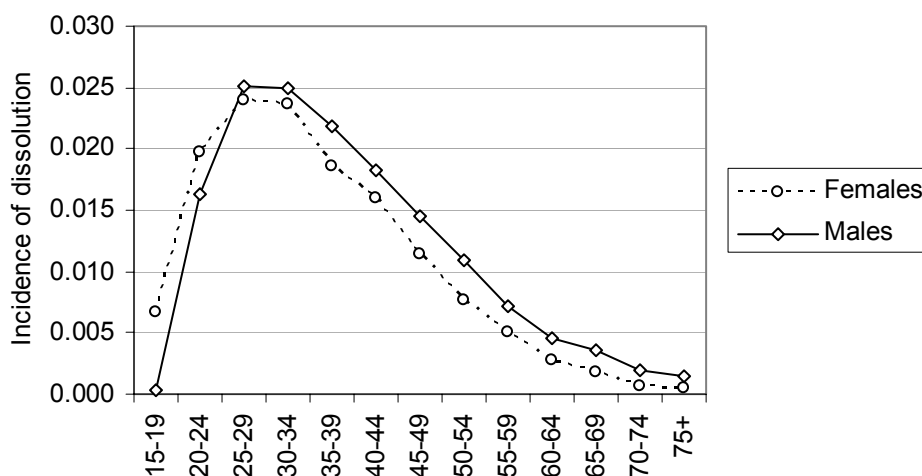


Figure 3.2.4: Assumed annual rates of dissolution of spousal relationships, by age and sex

3.2.5 Commercial sex

Rates of male contact with commercial sex workers are assumed to depend on male risk group, age and current partnership status. No South African survey has measured

the proportion of the general male population engaging in commercial sex, but the average proportion of men reporting sex with sex workers in the last 12 months has been estimated at 6.3% in other southern African countries (Caraël *et al*, 2006). This is probably an under-estimate of the true proportion of men having sex with sex workers, as men appear to under-report such sexual contacts in face-to-face interviews (Des Jarlais *et al*, 1999; Lau *et al*, 2003; Morison *et al*, 2001). Taking into account the levels of social desirability bias measured in various studies, it is assumed that men aged 15 to 49 have on average 0.126 acts of sex with sex workers per annum (twice the average proportion reporting sex worker contact). In the high-risk group, the frequency of sex with sex workers at age x is assumed to be proportional to a gamma density of the form

$$6.05^{-3.31}(x-10)^{(3.31-1)}\exp(-(x-10)/6.05), \quad (3.3)$$

where the parameters 6.05 and 3.31 were determined in such a way that the relative frequencies of sex worker contact by age were consistent with those estimated by Caraël *et al* (2006) for other southern African countries. The frequency of sex worker contact, relative to that in men who currently have no sexual partner, is assumed to be reduced by 50% in men who have one non-spousal partner, by 70% in men who have one spousal partner, by 80% in men who have two non-spousal partners, and by 90% in men who have one spousal partner as well as one non-spousal partner.

Women tend to engage in commercial sex work for short periods, mainly out of economic necessity, and the average duration of sex work in African countries is typically estimated to be between one and four years (Rees *et al*, 2000; Morison *et al*, 2001; Abdool Karim *et al*, 1995). It is therefore assumed that sex workers discontinue sex work at a constant rate of 0.5 per annum. Women are assumed to become sex workers at a rate sufficient to meet the male demand for commercial sex, with the relative rates of entry into sex work at different ages being determined in such a way that the age distribution of sex workers is consistent with that observed in a study of sex workers in Johannesburg (Rees *et al*, 2000). Studies suggest that South African sex workers usually have between 20 and 25 sex acts with clients per week (Ramjee *et al*, 1999; Abdool Karim *et al*, 1995; Rees *et al*, 2000; Varga 1997a), and on the

basis of this evidence it is assumed that sex workers have an average of 1 000 sex acts with clients per annum.

3.2.6 Preferences regarding partner age and sex activity class

The approach to modelling interactions between the high risk and low risk groups follows that described by Garnett and Anderson (1996). If ρ_{ij} is the desired proportion of new partners in group j , for an individual in group i , then this is calculated using the equation

$$\rho_{ij} = (1 - \varepsilon)\delta_{ij} + \varepsilon \left(\frac{N_j c_j}{\sum_u N_u c_u} \right), \quad (3.4)$$

where $\delta_{ij} = 1$ if $i = j$ and 0 otherwise, N_j is the number of potential partners in group j , and c_j is the rate at which individuals in group j wish to form partnerships (for the more formal model exposition, see Appendix A). The parameter ε is referred to as the ‘degree of assortative mixing’, and can take on any value between 0 and 1. When ε is 0, sexual mixing is said to be perfectly assortative, i.e. individuals only form relationships with partners in the same group. When ε is 1, sexual mixing is random, and individuals have no preferences regarding the sex activity class of their partner. Although it is difficult to estimate this parameter reliably, data from the U.S. (Garnett *et al*, 1996; Manhart *et al*, 2002) and Sweden (Granath *et al*, 1991) suggest that sexual mixing is only weakly assortative, with most estimates lying between 0.75 and 0.95, and one estimate at 0.65 (Laumann *et al*, 1994). However, data collected from Botswana suggest that ε may be as low as 0.53 (Carter *et al*, 2007). In addition, it has been demonstrated that empirical estimates of ε are likely to be significant overestimates, due to sampling biases (Ghani *et al*, 1998). There is thus substantial uncertainty regarding the true value of ε , and this parameter has therefore been assigned a beta prior with a mean of 0.6 and a standard deviation of 0.15.

Proportions of partners in each five-year age band are specified separately for males and females, for each five-year age band. In the case of females between the ages of

10 and 50 these proportions are estimated from women's reports of their husband's age in the 1998 Demographic and Health Survey (Department of Health 1999), and from gamma fits to age differences between men and women in non-spousal partnerships (a gamma distribution with mean 3 and variance 9 gives a good fit to non-spousal partner age differences in South African studies (Williams *et al*, 2000; Hallman 2004; Kelly 2000; Shisana *et al*, 2005)). The weights given to the spousal and non-spousal partner age distributions at each female age are determined by the relative numbers of married and sexually active unmarried women at the relevant age. In the case of women over the age of 50, there are no data on partner age differences, but it is assumed that the negative linear relationship between female age and husband's age difference observed in the 1998 DHS continues at older ages (see Figure 3.2.5), and the resulting age distribution for spousal partners is assumed to apply for all partners.



Figure 3.2.5: Observed and assumed mean age differences between married partners

Source: 1998 Demographic and Health Survey

In the case of males, the proportions of female partners in each age group are determined from the corresponding calculations for females, i.e. by tabulating the total numbers of partnerships between women of age x and men of age y at the start of the projection, it is possible to determine the proportion of female partners in each age group, for men of age y . Men who have sex with sex workers are assumed to have no preference regarding the age of the sex worker. Although this is probably not realistic, the simulated age distribution of the sex worker population has a low variance, and

hence any allowance for age preferences in the context of commercial sex would have little effect on the results of the model.

3.2.7 Frequency of sex

The method most commonly used to determine coital frequency in sexual behaviour surveys is to ask individuals about the number of times they have had sex in the last four weeks. Estimates of the daily probability of sex in married women, obtained using this method, typically lie between 0.098 and 0.240 in southern and eastern Africa (Brown 2000; Blanc and Rutenberg 1991). However, these reported frequencies are likely to over-estimate the true coital frequency among married individuals, as several studies have found that when coital frequency is recorded over shorter time intervals (over which there is likely to be less recall bias), reported coital frequency is lower (Hornsby and Wilcox 1989; Lagarde *et al*, 1995; Høgsborg and Aaby 1992). It has also been found that coital frequencies among married women reduce significantly as they age (Brewis and Meyer 2005). On the basis of these studies, it is assumed that the average marital coital frequency among married women aged 20 to 24 is five times per month, and that this frequency reduces exponentially with respect to age, halving with every 20-year increase in age. For each male age, the monthly number of sex acts between men and their wives are determined from the assumed age-specific frequencies for married women, based on the assumed distribution of female partner ages.

In contrast to married individuals, unmarried individuals and individuals with high rates of partner change tend to report numbers of sex acts in the last four weeks close to or less than those estimated over shorter time intervals (Leigh *et al*, 1998; Allen *et al*, 2007; McAuliffe *et al*, 2007). In a survey of South African youth, Kelly (2000) found that the average number of sex acts per four-week period was three among those who were sexually active and in non-cohabiting relationships. Although data from other African countries suggest lower coital frequencies experienced by unmarried individuals (Meekers and Van Rossem 2005), this estimate of three sex acts per month is used in the model for all non-spousal partnerships. In the absence of any data concerning the relationship between age and coital frequency in non-spousal partnerships, it is assumed that the same coital frequency applies at all ages (age is

assumed to affect the incidence of non-spousal partnerships rather than the frequency of sex within non-spousal relationships). The assumed frequencies of sex in spousal and non-spousal partnerships result in numbers of sex acts that are roughly consistent with the aggregate reported coital frequencies in the 15-24 and 25-49 age bands in the 2005 HSRC Household Survey (Shisana *et al*, 2005).

3.2.8 Condom usage

Rates of condom use are assumed to depend on the individual's age and sex and the nature of the relationship they are currently in. Rates of condom use are also assumed to increase over time, as there is strong evidence of trends towards greater condom use in South Africa, particularly among youth (Bradshaw *et al*, 2004b). The approach taken is to calculate $\gamma_{2,l}(x,t)$, the probability that a woman aged x uses a condom in a single act of sex with a partner of type l at time t , as a function of a 'baseline' rate of condom usage, $\gamma_{2,1}(15,13)$, which is the probability of condom use for a woman aged 15-19 in a short-term relationship in 1998 ($t = 13$)³. The following formula is used to calculate $\gamma_{2,l}(x,t)$:

$$\ln\left(\frac{\gamma_{2,l}(x,t)}{1-\gamma_{2,l}(x,t)}\right) = \ln\left(\frac{\gamma_{2,1}(15,13)}{1-\gamma_{2,1}(15,13)}\right) + \chi_l + \nu_l(x-15) + [\kappa_l^i + (\kappa_l^u - \kappa_l^i)(1 - 0.5^{(t/M_l)^{Q_l}})] \quad (3.5)$$

where

$\exp(\chi_l)$ = the odds of using a condom in relationship type l , relative to that in short-term relationships ($l = 1$), in 1998;

$\exp(\nu_l)$ = the factor by which the odds of condom use increases, per year of age;

$\exp(\kappa_l^i)$ = the initial odds of using a condom in relationship type l , before the onset of behaviour change, relative to the odds in 1998;

$\exp(\kappa_l^u)$ = the ultimate odds of using a condom in relationship type l , once behaviour change is at its maximum, relative to the odds in 1998;

³ 1998 ($t = 13$) has been chosen as the 'baseline' because 1998 is the year for which the most condom usage data are available, and because there is little reliable data on condom usage prior to 1998.

M_l = the median time to behaviour change in relationships of type l , i.e. the time at which the log odds of condom use is half-way between its initial and ultimate levels;
 Q_l = the Weibull shape parameter controlling the speed of behaviour change in relationships of type l .

The logistic transformation avoids rates of condom use greater than 100%, and facilitates a ‘logistic regression’ interpretation of the condom parameters. The probability of condom use in the baseline group, $\gamma_{2,1}(15,13)$, was initially set at 0.2 on the basis of the 1998 DHS (Department of Health 1999). The remaining parameters have been set on the basis of national survey data (Kaufman 1996; Department of Health 1999; Department of Health 2004b; Shisana *et al*, 2005) and data collected from sex workers (Jochelson *et al*, 1991; Williams *et al*, 2003; Rees *et al*, 2000; Peltzer *et al*, 2004), and are summarized in Table 3.2.2. The Weibull shape parameter, Q_l , is calculated as a function of κ_l^i , κ_l^u and M_l , by noting that when $t = 13$, the term in the square brackets of equation (3.5) must be equal to zero.

Table 3.2.2: Condom usage parameters

Parameter	Symbol	Short-term partnerships ($l = 1$)	Long-term partnerships ($l = 2$)	Sex worker-client sex ($l = 3$)
Effect of relationship type on odds of condom use at baseline	$\exp(\chi_l)$	1.00	0.46	6.00
Increase in log odds of condom use per year increase in age	ν_l	-0.025	-0.025	0
Ratio of initial odds of condom use to baseline odds (in 1998)	$\exp(\kappa_l^i)$	0.07	0.07	0.17
Ratio of ultimate odds of condom use to baseline odds (in 1998)	$\exp(\kappa_l^u)$	7.5	3.5	6.0
Median time to behaviour change (in years since 1985)	M_l	12.3	11.0	13.02
Speed of behaviour change	Q_l	3.50	2.97	5.22

Although the assumptions about the use of condoms in spousal and non-spousal relationships are based mostly on the proportion of individuals reporting use of

condoms at last intercourse, this could over-estimate the true proportion of sex acts in which condoms are used, if individuals with higher coital frequencies tend to use condoms less frequently (Pettifor *et al*, 2004a). A better measure of the proportion of sex acts in which condoms are used might be the proportion of individuals who used condoms if they had sex in the last day, since this is less likely to be affected by recall bias and more likely to reflect differences in coital frequencies between condom users and non-users. Meekers and Van Rossem (2005) compared this alternative measure with the more commonly used ‘condom at last sex’ measure, and found that the former measure usually gave lower proportions, the median ratio of the former proportion to the latter being 0.58. When fitting the model to HIV prevalence data, it was found that setting the baseline condom use at 0.20 (consistent with the ‘condom at last sex’ measure) yielded a much steeper decline in HIV prevalence among youth in recent years than has been observed, but setting the baseline condom use at 0.12 (consistent with the bias estimated by Meekers and Van Rossem) yielded a more plausible HIV prevalence trend in youth. The baseline condom use has therefore been set at 0.12.

Equation (3.5) specifies the probability of condom use among females only. To ensure that male and female assumptions are consistent, the probability that a male uses a condom in a short-term or long-term relationship is calculated as

$$\gamma_{1,l}(x,t) = \sum_y f_1(y|x)\gamma_{2,l}(y,t), \quad (3.6)$$

where $f_1(y|x)$ is the probability that the female partner is aged y , if the male is aged x . The rate of condom use among clients of sex workers is the same as that estimated for sex workers, with no age dependency.

3.2.9 The effect of HIV symptoms and treatment on sexual behaviour

Although there is much evidence to suggest that women generally have fewer sexual partners as they enter the later stages of HIV disease (Ross *et al*, 2004; Terceira *et al*, 2003; Hankins *et al*, 1998; Greenblatt *et al*, 1999), there is little data concerning the effect of HIV disease stage on the frequency of sex among individuals in sexual

relationships. The few studies that have been conducted suggest that coital frequency within partnerships is only slightly reduced as individuals experience more advanced disease (Ross *et al*, 2004; Terceira *et al*, 2003). Similarly, the initiation of highly active antiretroviral treatment (HAART) appears to be associated with increases in the proportion of individuals who report sexual activity, but not with changes in coital frequency among those who are sexually active (Bunnell *et al*, 2006; Moatti *et al*, 2003). It is therefore assumed that the rate at which individuals acquire new sexual partners reduces as they experience more severe symptoms, but the frequency of sex within partnerships is assumed to be unaffected by the HIV status or HIV disease stage of either partner. The factors by which the desired partner acquisition rates in uninfected individuals are multiplied, in order to obtain the rates in each HIV stage, are shown in Table 3.2.3. These have been set at the same level as the factors used to adjust coital frequencies in the corresponding HIV stages in the ASSA2003 model.

HIV disease stage is also assumed to affect the rate at which women become sex workers, and the rate at which women discontinue sex work. Although there is evidence to suggest that women are more likely to discontinue sex work in the more advanced HIV disease stages (McClelland *et al*, 2006), little is known about the effect of HIV symptoms on the rate of entry into sex work. The effects are therefore assumed to be the same as those on rates of partner acquisition. The assumed factors by which the HIV-negative rates of sex worker entry and exit are multiplied, in each HIV stage, are shown in Table 3.2.3.

Table 3.2.3: Multiplicative adjustments to sexual behaviour parameters, by HIV stage

Parameter	Primary HIV	Asymptomatic HIV	Pre-AIDS symptoms	AIDS symptoms	HAART
Partner acquisition rate	1.00	1.00	0.65	0.25	0.80
Entry into sex work	1.00	1.00	0.65	0.25	0.80
Exit from sex work	1.00	1.00	1.50	3.00	2.00

Evidence suggests that the frequency of condom use increases after individuals learn they are HIV-positive (Voluntary HIV-1 Counselling and Testing Efficacy Study Group 2000), and after starting HAART (Moatti *et al*, 2003; Bunnell *et al*, 2006; van

der Straten *et al*, 2000). However, in the interests of mathematical simplicity, no allowance is made in the model for changes in condom use over the course of HIV infection.

3.3 HIV/AIDS and STI assumptions

This section outlines the assumptions made about the biology of HIV and other STIs. Section 3.3.1 outlines the assumptions made about the course of infection, and section 3.3.2 describes the modelling of STI transmission and STI incidence. This is followed, in section 3.3.3, by a description of the assumed effect of HIV co-infection on the course of STIs. Finally, in section 3.3.4, assumptions about STI treatment in South Africa are explained. As in section 3.2, many of the parameters cannot be determined reliably based on the limited evidence available, and we therefore adopt a Bayesian approach to determine the likely parameter values. For those parameters that are considered most uncertain, prior distributions are chosen to represent *a priori* uncertainty regarding plausible parameter values. In most cases, beta and gamma priors are used, as these are natural distributions for parameters defined on the ranges $[0, 1]$ and $[0, \infty)$ respectively.

3.3.1 HIV/AIDS and STI natural history

This section describes the disease states used to represent the natural history of each STI, and the assumptions regarding the rates of transition between the various disease states. Multi-state model diagrams are presented for each STI, considered independently of other STIs and demographic processes. For ease of representation, subscripts and superscripts indicating sex, relationship status, risk group and STI are omitted from symbols introduced here, as are age and time arguments. Parameters determining the rate at which individuals seek treatment (ν), the effectiveness of treatment (ψ) and the rate at which individuals are cured of STIs through screening (η) are introduced in the multi-state diagrams, but their explanation is deferred until section 3.3.4. The parameter λ , representing the incidence of infection, is also introduced in the diagrams, but the method used to calculate it is deferred to section 3.3.2. A more formal mathematical description of the model is given in Appendix B.

3.3.1.1 Syphilis (*Treponema pallidum*)

Syphilis is traditionally characterized as starting with a painless genital ulcer (primary syphilis) and then progressing to rashes and lesions on other parts of the body (secondary syphilis), after which individuals enter a long asymptomatic phase. This asymptomatic phase may be followed several years later by severe damage to the cardiovascular system, central nervous system and other parts of the body (tertiary syphilis) in a minority of individuals. The model developed here follows this scheme, but does not allow for progression to tertiary syphilis, as the frequent use of antibiotics to treat other infections prevents the progression of most latent syphilis cases (Sparling 1990). Figure 3.3.1 summarizes the disease states modelled.

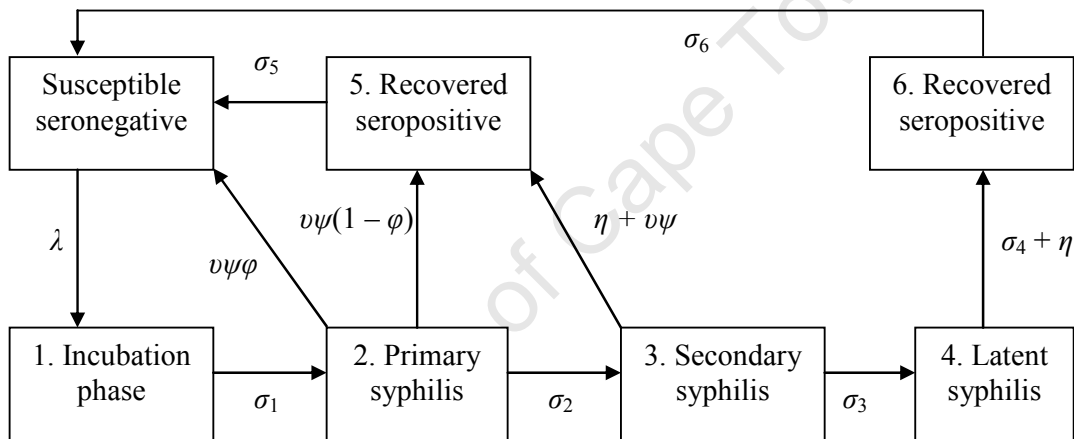


Figure 3.3.1: Multi-state model of the natural history of syphilis

Based on a re-analysis of data collected in France in the nineteenth century, Garnett *et al* (1997) estimate that the average duration of the incubation period is 31 days, and the average interval between the onset of primary and secondary symptoms is 46 days. These estimates are consistent with the ranges quoted in most other sources (Rowley and Berkley 1998; Goh 2005; Merck 1999). It is therefore assumed that the average duration of the incubation period ($1/\sigma_1$) is 31 days and the average duration of primary syphilis ($1/\sigma_2$) is 46 days, in the absence of treatment. Data regarding the duration of secondary syphilis are very scarce, with only one Norwegian study cited by Garnett *et al* (1997) suggesting that the average duration of secondary syphilis symptoms is 3.6 months. This estimate of 3.6 months has been used to set the

parameter $1/\sigma_3$. Following the approach of Korenromp *et al* (2000b), it is assumed that in the absence of screening, individuals remain in the latent phase for 10 years on average ($1/\sigma_4$) before experiencing either spontaneous resolution of syphilis or cure due to treatment of other infections.

Because the model is calibrated to seroprevalence data, it is necessary to make assumptions about the presence of syphilis antibodies in different stages of infection. In the incubation phase, all individuals are assumed to be seronegative, as it takes some time for syphilis antibodies to develop. In the primary stage, between 29% and 43% of patients experiencing genital ulcers due to syphilis are seronegative on non-treponemal tests (Orle *et al*, 1996; Morse *et al*, 1997). For the sake of simplicity, it is assumed that all individuals in the primary syphilis phase are seropositive, though there is implicit allowance for the limited sensitivity of the non-treponemal tests in primary syphilis in the diagnostic sensitivity assumptions (discussed in Appendix D). In all subsequent phases (stages 3 to 6 in Figure 3.3.1), individuals are assumed to be seropositive.

Individuals who are cured of syphilis usually remain seropositive for several months. The rate of seroreversion is more rapid in patients treated in earlier disease stages, and the model therefore has two ‘post-treatment’ states to represent individuals who are still seropositive after treatment in early syphilis and those who are still seropositive after recovery from latent syphilis. Data collected by Rolfs *et al* (1997) suggest that the mean time to seroreversion or a more than two-fold reduction in RPR titre is 0.81 years for patients treated in early latent syphilis, and 0.37 years in patients treated in primary or secondary syphilis. Similar data collected by Schroeter *et al* (1972) suggest that the average time to seroreversion is 0.70 years for patients treated in primary syphilis and 1.84 years for patients treated in secondary syphilis. In the model it is assumed that the average time to seroreversion after treatment of latent syphilis ($1/\sigma_6$) is one year and the average time to seroreversion after treatment of early syphilis ($1/\sigma_5$) is six months. It is also assumed that a proportion (ϕ) of individuals successfully treated in primary syphilis immediately return to the seronegative state; this proportion is set at 0.4, roughly in line with the proportion of individuals who are observed to be seronegative at the time they seek treatment. All individuals in the

‘recovered seropositive’ states (states 5 and 6) are assumed to be protected against syphilis reinfection, based on evidence suggesting that individuals previously infected with syphilis acquire a degree of immunity (Magnuson *et al*, 1956).

Table 3.3.1 summarizes the parameter values specified previously, and shows the prior distributions chosen for those parameters considered in the Bayesian analysis described in section 4.2.

Table 3.3.1: Syphilis parameters

Parameter	Symbol	Prior distribution		
		Type	Mean	Std dev.
Average time (in weeks) from				
Infection to primary	$1/\sigma_1$	-	4.4*	-
Primary to secondary	$1/\sigma_2$	Gamma	6.6	2.0
Secondary to latent	$1/\sigma_3$	Gamma	15.6	4.0
Latent to spontaneous resolution	$1/\sigma_4$	Gamma	520	150
Recovery in early disease to seronegative	$1/\sigma_5$	Gamma	26.0	8.0
Recovery in latent infection to seronegative	$1/\sigma_6$	Gamma	52.0	16.0
Proportion of primary cases seronegative immediately after successful treatment	φ	Beta	0.40	0.10

* Fixed parameter, not included in Bayesian analysis.

3.3.1.2 Genital herpes (herpes simplex virus type 2)

Genital herpes is a chronic condition caused by herpes simplex virus type 2 (HSV-2), and characterized by periodic recurrences of ulcers in the genital region, which become less frequent as the duration of infection increases. Although it is commonly assumed that all individuals who acquire HSV-2 experience ulcerative symptoms, the majority of HSV-2–seropositive individuals report never having experienced these symptoms, and would therefore never seek treatment for genital herpes. In order to assess the health-seeking behaviours associated with genital herpes realistically, the model therefore splits those acquiring HSV-2 into those who never experience symptoms and those who do experience symptoms, as shown in Figure 3.3.2. The

proportions of HSV-2–seropositive individuals who report having ever experienced herpes symptoms range from 9% in the USA (Fleming *et al*, 1997), to 27% in female university students in the US (Koutsky *et al*, 1990) and 30% among blood donors in London (Cowan *et al*, 1996). In a study of Zimbabwean men, it was found that in the year of HSV-2 seroconversion, when HSV-2 recurrences are believed to be most severe, only 15% of men reported experiencing herpes symptoms (McFarland *et al*, 1999). Since the latter study is most relevant to the African context, the assumption made in the model is that the proportion of individuals acquiring HSV-2 who experience symptoms (φ) is 15%.

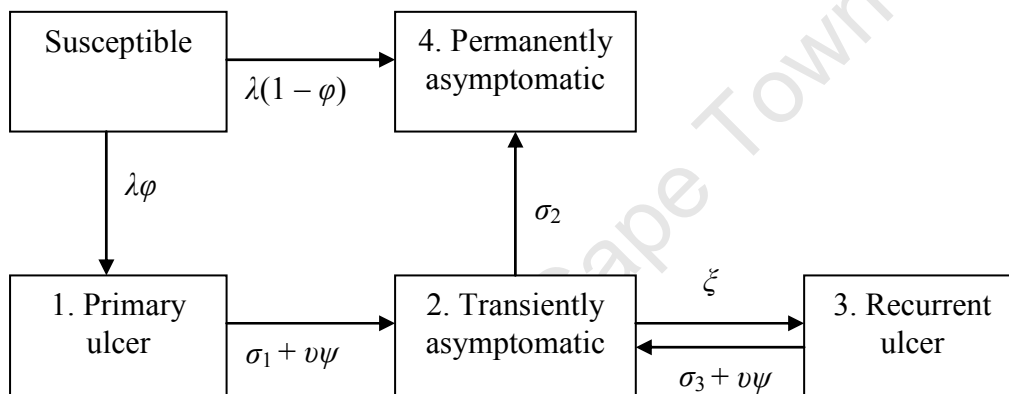


Figure 3.3.2: Multi-state model of the natural history of HSV-2

The ulcers that develop following initial infection with HSV-2 usually last two to three weeks. In individuals previously infected with HSV-1, first episodes of HSV-2 ulcers have been estimated to last for a median of 15 days by Koelle *et al* (1992) and for a mean of 16 days by Corey *et al* (1983). Subsequent ulcers are of shorter duration; estimates of the median ulcer duration lie between 3 and 6 days (Wald *et al*, 2000; Schacker *et al*, 1998b), while estimates of the mean duration lie between 6 and 11 days (Brown *et al*, 1985; Corey *et al*, 1983; Rattray *et al*, 1978). Assuming that ulcer durations are exponentially distributed (so that median durations tend to be shorter than mean durations), the mean durations of the primary and subsequent ulcers ($1/\sigma_1$ and $1/\sigma_3$ respectively) are set at 18 days and 8 days respectively.

Estimates of the annual number of recurrences occurring soon after infection range between 3.5 and 6.3 (Koelle *et al*, 1992; Corey *et al*, 1983; Benedetti *et al*, 1999), with recurrences tending to be more frequent in men than in women (Benedetti *et al*, 1994; Corey *et al*, 1983; Obasi *et al*, 1999). Consistent with the approach of Korenromp *et al* (2002b), it is assumed that the rate at which symptomatic recurrences occur, ζ , is twice as high in men as in women. This rate is set at 3 per annum in women and 6 per annum in men. To model the effect of recurrences becoming less frequent as the duration of infection increases, it is assumed that individuals progress from the ‘transiently asymptomatic’ state to the ‘permanently asymptomatic’ state at rate σ_2 . Benedetti *et al* (1999) have found that the average annual number of recurrences reduces by 13% and 8% per annum in primary and recurrent herpes cases respectively, and it is therefore assumed that individuals who are initially symptomatic enter the permanently asymptomatic state at a rate σ_2 of 0.1 per annum.

Table 3.3.2 summarizes the parameter values specified previously, and shows the prior distributions chosen for those parameters considered in the Bayesian analysis.

Table 3.3.2: Genital herpes parameters

Parameter	Symbol	Prior distribution		
		Type	Mean	Std dev.
Proportion of cases becoming symptomatic	φ	Beta	0.15	0.05
Annual incidence of symptomatic recurrences in the transiently asymptomatic state				
Males	ζ	Gamma	6.0	1.0
Females		Gamma	3.0	0.5
Average duration of primary ulcer (weeks)	$1/\sigma_1$	-	2.6*	-
Average duration of recurrent ulcer (weeks)	$1/\sigma_3$	-	1.1*	-
Annual rate of transition from transiently asymptomatic to permanently asymptomatic	σ_2	Gamma	0.1	0.02

* Fixed parameter, not included in Bayesian analysis.

3.3.1.3 Gonorrhoea (*Neisseria gonorrhoeae*)

Gonorrhoea is an acute bacterial STI causing urethral discharge and dysuria in men and cervical discharge and dysuria in women. The modelled progression of infection is shown in Figure 3.3.3.

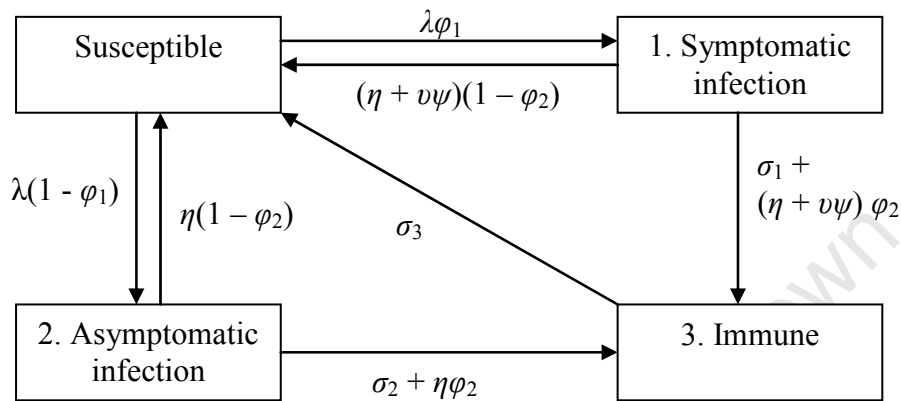


Figure 3.3.3: Multi-state model of the natural history of gonorrhoea

A high proportion of men become symptomatic after acquiring gonorrhoea. In studies of men followed after known exposure to gonorrhoea, symptoms developed in 57 of 58 infected men observed by Harrison *et al* (1979), and in all 11 infected men observed by Schmidt *et al* (2001). Studies of men attending STI clinics also suggest high upper bounds on symptomatic proportions, with between 83% and 98% of men with gonorrhoea reporting symptoms (Buimer *et al*, 1996; Price *et al*, 2004; Joyner *et al*, 2000; Hobbs *et al*, 1999). Data on gonorrhoea in women are less clear; Platt *et al* (1983) found that 10 out of 19 women infected with gonorrhoea by their male partners had ‘normal’ gynaecological examinations, while Korenromp *et al* (2002d) estimated that fewer than 40% of women acquiring gonorrhoea developed symptoms. The assumption made here is that the proportion of newly infected individuals who develop symptoms (ϕ_1) is 40% in women and 90% in men.

Very few studies have been conducted to determine the rate at which gonococcal infections resolve. In a review by Korenromp *et al* (2002d), only two such studies were identified, both being studies of symptomatically infected individuals. On the

basis of the one study conducted in men, the average duration of untreated infection was estimated to be 16.9 weeks, while on the basis of the other study in women, the average duration of untreated infection was estimated to be 15.3 weeks. Another study, conducted in 28 men who were asymptotically infected with gonorrhoea, reported the proportion of men whose infections resolved spontaneously after variable follow-up times (Handsfield *et al*, 1974). Using the same method as that used by Korenromp *et al*, the average duration of untreated infection in this study is estimated to be 12.2 weeks. Although the model allows for differences in rates of spontaneous resolution between asymptomatic and symptomatic gonorrhoea cases, and between men and women, the same assumed average duration of infection (15 weeks if left untreated) is assumed in all cases, in the absence of strong evidence to suggest that such differences exist.

There is some evidence to suggest that individuals who have been infected with gonorrhoea may develop a degree of immunity. In a study of Kenyan sex workers, Plummer *et al* (1989) found that women infected with a particular strain were significantly less likely to be reinfected with the same strain, and that the incidence of gonorrhoea infection decreased as the duration of sex work increased. Moodley *et al* (2002) found that women reinfected with gonorrhoea shortly after successful treatment were in almost all cases infected with a different strain from that initially acquired, which also suggests that there may be strain-specific immunity. However, Schmidt *et al* (2001) found that men who had been experimentally inoculated and treated for gonorrhoea two weeks previously were as likely to acquire gonorrhoea upon subsequent challenge as men who had not been previously inoculated, which suggests that any immunity that exists after successful treatment is likely to be relatively weak. In the baseline scenario, it is assumed that none of the individuals successfully treated for gonorrhoea are immune after recovery ($\phi_2 = 0$), but those who experience spontaneous resolution are resistant to reinfection for a short time ($1/\sigma_3 = 1$ year). The effect of alternative assumptions about immune protection is explored in section 4.3.

Table 3.3.3 summarizes the parameter values specified previously, and shows the prior distributions chosen for those parameters considered in the Bayesian analysis.

Table 3.3.3: Gonorrhoea parameters

Parameter	Symbol	Prior distribution		
		Type	Mean	Std dev
Proportion of cases becoming symptomatic				
Male	ϕ_1	Beta	0.90	0.05
Female		Beta	0.40	0.15
Average duration of untreated infection (weeks)				
Male	$1/\sigma_1^*$	Gamma	15.0	5.0
Female		Gamma	15.0	5.0
Average duration of immunity (weeks)	$1/\sigma_3$	Gamma	52.0	26.0
Proportion immune after successful treatment	ϕ_2	-	0.0 [†]	-

* Same parameter is used for symptomatic duration ($1/\sigma_1$) and asymptomatic duration ($1/\sigma_2$). † Fixed parameter, not included in Bayesian analysis.

3.3.1.4 Chlamydial infection (*Chlamydia trachomatis*)

Like gonorrhoea, chlamydial infection is a bacterial infection that causes urethritis in men and cervicitis in women. Chlamydial infection differs from gonorrhoea in that it is asymptomatic in a high proportion of cases. Studies of men with chlamydial infection attending STI clinics have found that approximately 50% report symptoms (Joyner *et al*, 2000; Krieger *et al*, 1993a; Buimer *et al*, 1996), and in a study of female STI clinic attenders with chlamydial infection, only 35% reported symptoms (Buimer *et al*, 1996). These proportions are likely to represent upper bounds on the proportions of infections that become symptomatic, as asymptotically infected individuals are less likely to attend STI clinics than symptomatic individuals. In an analysis of Ugandan data, Korenromp *et al* (2002d) estimated that the proportion of chlamydial infections that become symptomatic is less than 35% in men and less than 25% in females, with best estimates being only 11% and 6% in males and females respectively.

The multi-state model used to model the natural history of chlamydial infection is identical in structure to that used to model gonorrhoea (Figure 3.3.3). The proportion

of new infections that become symptomatic (ρ_1) is assumed to be 30% in males and 15% in females, on the basis of the above evidence.

A significant number of studies have measured rates at which untreated chlamydial infection resolves, and these are reviewed by Korenromp *et al* (2002d) and Golden *et al* (2000). In seven studies of men with symptomatic chlamydial infection, the average mean duration of infection estimated by Korenromp *et al* is 113 days, in the absence of treatment. Similar rates of spontaneous resolution were observed in a large study of female chlamydial cases; 51 out of 69 women (mostly symptomatic) were found to still be culture-positive for chlamydia between 4 and 45 days after initial diagnosis (Parks *et al*, 1997). Korenromp *et al* estimate from these data that the implied average duration of chlamydial infection in the absence of treatment is 128 days. However, another large study of untreated chlamydial infection found significantly lower rates of spontaneous resolution; in this study, 68 out of 85 initially asymptomatic teenage girls were found to still be culture-positive for chlamydia 90 days after initial diagnosis (Rahm *et al*, 1988). Using the method of Korenromp *et al*, this implies an average duration of untreated infection equal to 764 days. Recent studies that use more sensitive diagnostic techniques estimate the proportion of asymptomatically infected women who experience spontaneous resolution within one year to be 54% (Molano *et al*, 2005) and 45% (Morré *et al*, 2002), suggesting average durations of 470 days and 616 days respectively. It therefore appears that symptomatic infections tend to resolve more rapidly than asymptomatic infections, in the absence of treatment. It is thus assumed that the average duration of chlamydial infection is 16 weeks in symptomatic cases and 90 weeks in asymptomatic cases.

There is substantial evidence of partial immunity to reinfection after resolution of chlamydial infection, though much of the evidence is from animal experiments (Su *et al*, 1999; Johansson and Lycke 2001; Golden *et al*, 2000). Brunham *et al* (1996) suggest that an accumulation of immunity to different chlamydial strains would result in overall immunity over time, and support this with evidence from Kenyan sex workers, who were found to be less susceptible to chlamydial infection the greater the duration of sex work. Cellular immune responses to *Chlamydia trachomatis* have been found to be significantly associated with older age (Arno *et al*, 1994), and antibodies to *Chlamydia trachomatis* have been found to be more prevalent in groups

of STI patients with a low prevalence of chlamydial infection than in groups with a high prevalence of chlamydial infection, which suggests that past chlamydial infection may partially protect against reinfection (Schachter *et al*, 1983). However, immunity appears to wane over time; Katz *et al* (1987) observed that men and women who had been treated for chlamydial infection within the last six months were significantly less likely to experience chlamydial infection than those who had been treated more than six months previously. Immunity may also be weaker when treatment is initiated early in infection; in a study of mice, for example, Su *et al* (1999) observed that the earlier chlamydial treatment was initiated, the weaker the immune response was, and the more susceptible the mice were to chlamydial reinfection. In the baseline scenario, it is assumed that all individuals who experience spontaneous resolution are temporarily immune, but only half of successfully treated individuals are immune. The average duration of immunity is assumed to be ten years. Alternative models of immunity are considered in section 4.3.

Table 3.3.4 summarizes the parameter values specified previously, and shows the prior distributions chosen for those parameters considered in the Bayesian analysis.

Table 3.3.4: Parameters for chlamydial infection

Parameter	Symbol	Prior distribution		
		Type	Mean	Std dev.
Proportion of cases becoming symptomatic				
Male	φ_1	Beta	0.30	0.15
Female		Beta	0.15	0.08
Average duration of untreated infection				
Symptomatic (weeks)	$1/\sigma_1$	Gamma	16.0	5.0
Asymptomatic (weeks)	$1/\sigma_2$	Gamma	90.0	15.0
Average duration of immunity (weeks)	$1/\sigma_3$	Gamma	520	200
Proportion immune after successful treatment	φ_2	Uniform	0.50	0.29

3.3.1.5 Chancroid (*Haemophilus ducreyi*)

Chancroid is a bacterial STI that causes genital ulcers. Although little is known about its natural history, the model structure is assumed to be the same as that used for gonorrhoea (Figure 3.3.3).

Evidence suggests that a high proportion of chancroid infections in women are symptomatic. Plummer *et al* (1983) detected ulcers in 10 out of 13 Kenyan women who had been infected with chancroid by their partners, and in 5 out of 10 Kenyan sex workers who were infected with chancroid. In another study of sex workers in the Gambia, ulcers were found upon examination in 8 out of 12 women with chancroid (Hawkes *et al*, 1995). It is assumed that the proportion of female chancroid cases that become symptomatic (ϕ_1) is 70%. In the absence of any data for males, the corresponding proportion for male chancroid cases is set at 90%, since STIs tend to be more symptomatic in men than in women.

Data on the rate at which chancroid resolves in the absence of treatment are scarce, though Ronald and Plummer (1985) state that symptoms usually resolve within one to three months of infection. It is therefore assumed that the average duration of symptomatic infection ($1/\sigma_1$) is two months, and in the absence of data on the rate at which asymptomatic infections resolve, the same assumption is made for the average duration of asymptomatic chancroid ($1/\sigma_2$). Infection with chancroid is generally not believed to confer protection against reinfection (Lewis 2000), as individuals who are successfully treated do not appear to be protected when subsequently challenged under experimental conditions (Al-Tawfiq *et al*, 1999; Spinola *et al*, 1994). However, it is possible that individuals who experience spontaneous resolution may be partially protected against reinfection. It is therefore assumed that there is no immunity following successful treatment of chancroid (i.e. $\phi_2 = 0$), but individuals who experience spontaneous resolution are assumed to be immune to reinfection for one year on average.

No Bayesian analysis is conducted in the case of chancroid, due to the lack of reliable prevalence data (see section 4.2). There are thus no prior distributions specified to represent uncertainty regarding the chancroid parameters.

3.3.1.6 Trichomoniasis (*Trichomonas vaginalis*)

Trichomoniasis is a protozoan infection that causes urethral discharges and prostatitis in men, and vaginal discharges in women. The model used to represent the natural history of this infection is the same as that used to represent the natural history of gonorrhoea and chlamydial infection (see Figure 3.3.3).

There appears to be significant heterogeneity in the rates at which trichomoniasis resolves. Studies of symptomatic males suggest symptomatic infection may resolve after an average of 10 to 20 days (Price *et al*, 2003; Weston and Nicol 1963), while other studies suggest that men may be asymptomatically infected with trichomoniasis for an average of 50 days (Krieger *et al*, 1993b) or an average of more than 140 days (Watson-Jones *et al*, 2000). The largest study of the natural history of asymptomatic trichomoniasis in untreated women suggests an average duration of two years or more (Klebanoff *et al*, 2001), but some experts have argued that the average duration of untreated infection in females is likely to be considerably longer (as much as 15 years), on the basis of the monotonically increasing prevalence of trichomoniasis with respect to age in some populations (Ipsen and Feigl 1970; Bowden and Garnett 2000). In the model it is assumed that the average duration of untreated asymptomatic infection is 20 weeks in males and 150 weeks in females. The average duration of untreated symptomatic infection is assumed to be 2 weeks in males and 15 weeks in females (although there is no evidence to support the latter assumption, it seems likely that if symptomatic infections in men resolve more swiftly than asymptomatic infections, the same would be true for women).

There is much uncertainty regarding the proportion of trichomoniasis infections that become symptomatic. Studies of STI clinic attenders have reported symptomatic proportions of between 42% and 73% in males (Price *et al*, 2004; Krieger *et al*, 1993a; Joyner *et al*, 2000; Hobbs *et al*, 1999) and 42% in females (Wølner-Hanssen *et al*, 1989). A large household survey conducted in Tanzania found that 45% of men

with trichomoniasis reported symptoms, as compared with 23% of men with no trichomoniasis (Watson-Jones *et al*, 2000). However, in a large survey of Kenyan women attending antenatal clinics (Thomas *et al*, 1996), it was found that the proportion of trichomoniasis-infected women who reported symptoms (33%) was similar to that in uninfected women (26%). The evidence therefore suggests that the infection is more frequently symptomatic in males than in females. It is assumed in the baseline scenario that trichomoniasis infections become symptomatic in 40% of males and 30% of females.

There is little evidence to suggest that infection with trichomoniasis confers protective immunity (Petrin *et al*, 1998). Studies of women treated for trichomoniasis have often noted rapid reinfection after cure (Lyng and Christensen 1981; Ackers 1990), which suggests that there is little immunity after treatment. However, Abrahams *et al* (1996) found that it was possible to induce a strong protective immune response in untreated mice. Ackers (1990) suggests that immunity to trichomoniasis could be acquired gradually, which might explain the absence of strong immune responses after treatment in the early stages of trichomoniasis infection. It is therefore assumed that individuals who are successfully treated for trichomoniasis are not immune after recovery, but that individuals who experience spontaneous resolution are immune for an average of one year following resolution. Alternative models of immunity to trichomoniasis are considered in section 4.3.

Table 3.3.5 summarizes the parameter values specified previously, and shows the prior distributions chosen for those parameters considered in the Bayesian analysis.

Table 3.3.5: Trichomoniasis parameters

Parameter	Symbol	Prior distribution		
		Type	Mean	Std dev.
Proportion of cases becoming symptomatic				
Male	φ_1	Beta	0.40	0.10
Female		Beta	0.30	0.10
Average duration of untreated infection				
Symptomatic males (weeks)	$1/\sigma_1$	Gamma	2.0	0.7
Symptomatic females (weeks)		Gamma	20.0	7.0
Asymptomatic males (weeks)	$1/\sigma_2$	Gamma	15.0	5.0
Asymptomatic females (weeks)		Gamma	150	50.0
Average duration of immunity (weeks)	$1/\sigma_3$	Gamma	52.0	26.0
Proportion immune after successful treatment	φ_2	-	0.0*	-

* Fixed parameter, not included in Bayesian analysis.

3.3.1.7 Bacterial vaginosis

Bacterial vaginosis is a condition that occurs frequently in women, sometimes producing symptoms of vaginitis, but more often asymptomatic. Unlike the other diseases considered here, there is no single organism that can be isolated as the cause of the disease. The disease is defined in terms of the *relative* abnormality of the vaginal flora, not in terms of any absolute marker. Nugent *et al* (1991) have proposed a ten-point scoring method for grading the extent of this abnormality, and have proposed that a score of 7 or higher be considered defining of ‘bacterial vaginosis’, while a score of 3 or less should be considered ‘normal’ and a score of 4 to 6 should be considered ‘intermediate’. The model developed here follows this three-stage approach to categorizing women on the basis of their vaginal flora patterns. Suppose that women’s progression through the three different disease states can be represented by a Markov chain, with p_{ij} representing the transition probability from state i to state j in a one-week period (states 1, 2 and 3 represent normal, intermediate and bacterial vaginosis states respectively). These transition probabilities can be estimated from various studies of bacterial vaginosis.

The largest of these studies that uses Nugent's scoring method is that of Hillier *et al* (1992b). In this study, vaginal flora were assessed in pregnant women at 23 to 26 weeks gestation, and then again at 31 to 36 weeks gestation (no woman received antibiotic treatment between baseline and follow-up). Table 3.3.6 shows the numbers of women in each of the three groups at follow-up according to the vaginal flora pattern at baseline, and the maximum likelihood estimates of the p_{ij} values estimated from these data. (For the purpose of calculating the likelihood, it is assumed that follow-up occurred 9 weeks after baseline, and that the number of women in each of the three groups at 9 weeks is multinomially distributed.) The p_{13} value has been constrained to zero in order to simplify the modelling of bacterial vaginosis incidence later. The results suggest that the average duration of untreated bacterial vaginosis ($-1/\ln(p_{33})$) is 17 weeks, while the average length of time that a woman remains in the 'normal' state ($-1/\ln(p_{11})$) is 33 weeks. The stationary probabilities for the normal, intermediate and bacterial vaginosis states are 0.49, 0.19 and 0.32 respectively.

Table 3.3.6: Numbers of women according to vaginal flora patterns at baseline and follow-up, and corresponding estimates of weekly transition probabilities

Vaginal flora pattern at baseline	Number at follow-up			Weekly transition probability		
	Normal	Inter-mediate	BV	Normal	Inter-mediate	BV
Normal	404	61	37	0.970	0.030	0
Intermediate	36	45	38	0.063	0.843	0.094
BV	17	27	97	0.008	0.050	0.943

The model developed here extends the basic three-stage model by allowing for a distinction between symptomatic and asymptomatic bacterial vaginosis. The possible movements between the various states are represented in Figure 3.3.4. The continuous weekly rates of transition between these states in the absence of treatment, σ_{ij} , have been estimated from the p_{ij} values in the previous table, with $\sigma_{12} = 0.030$, $\sigma_{21} = 0.069$, $\sigma_{31} = \sigma_{41} = 0.008$, and $\sigma_{32} = \sigma_{42} = 0.051$. It is thus assumed that symptomatic and asymptomatic infections resolve spontaneously at the same rate. Although there is some evidence to suggest that symptomatic bacterial vaginosis may

become asymptomatic (Dhar *et al*, 1994), it is assumed in the baseline scenario that there are no movements between the symptomatic and asymptomatic bacterial vaginosis states, and σ_{34} has therefore been set to zero.

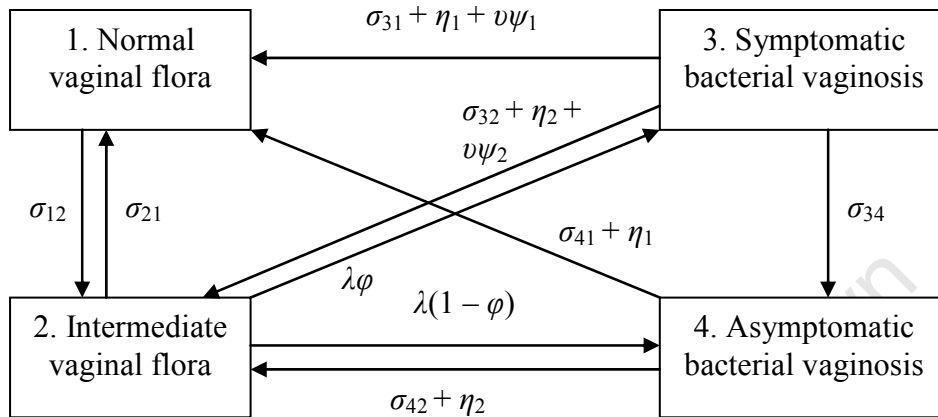


Figure 3.3.4: Multi-state model of the natural history of bacterial vaginosis

The proportion of incident cases that become symptomatic, ϕ , is difficult to estimate. Eschenbach *et al* (1988) found that among 311 women attending STI clinics with bacterial vaginosis (diagnosed using a method similar to Nugent's scoring method), 50% reported symptoms of increased discharge, and this suggests an upper bound on ϕ . However, in a smaller sample of 29 family planning clinic attenders with bacterial vaginosis (diagnosed using Nugent's method), Wilkinson *et al* (1997) found that the proportion reporting symptoms (41%) was no different from that in women who did not have bacterial vaginosis (39%). This suggests that the proportion of women who develop symptoms could be very low, and the proportion ϕ is therefore set at 25%.

Table 3.3.7 summarizes the parameter values specified previously, and shows the prior distributions chosen for those parameters considered in the Bayesian analysis.

Table 3.3.7: Bacterial vaginosis parameters

Parameter	Symbol	Prior distribution		
		Type	Mean	Std dev.
Proportion of cases becoming symptomatic	φ_1	Beta	0.25	0.10
Weekly rates of transition				
Bacterial vaginosis to normal flora	σ_{31}, σ_{41}	Gamma	0.008	0.003
Bacterial vaginosis to intermediate flora	σ_{32}, σ_{42}	Gamma	0.051	0.015
Normal flora to intermediate flora	σ_{12}	Gamma	0.030	0.010
Intermediate flora to normal flora	σ_{21}	Gamma	0.069	0.020
Intermediate flora to bacterial vaginosis*	λ	Gamma	0.100	0.030

* See explanation in section 3.3.2.2.

3.3.1.8 Vulvovaginal candidiasis

Vulvovaginal candidiasis is a common disease in women, most often associated with symptoms of itching and vaginal discharge. It is caused by various *Candida* species (also known as yeasts), most common among them being *Candida albicans*. These *Candida* species can inhabit the vaginal mucosa either as commensals (not causing symptoms) or as pathogens (Calderone and Fonzi 2001), but it is not clear why some yeast colonies become pathogenic, while others remain in a commensal state for long periods. To reflect the dual nature of the infection, the model developed here divides women infected with *Candida* into ‘asymptomatic candidiasis’ and ‘symptomatic candidiasis’ states (Figure 3.3.5).

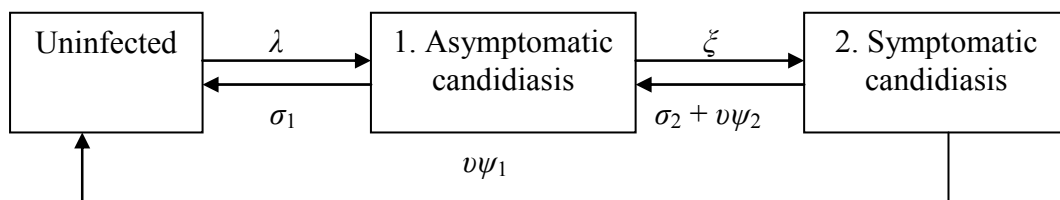


Figure 3.3.5: Multi-state model of the natural history of vulvovaginal candidiasis

The incidence of yeast infection (parameter λ) varies between settings, but is consistently high. Barbone *et al* (1990) measured a yeast incidence of 77.1 per 100 person years (PY) in women recruited from STI clinics in the US, and Ohmit *et al* (2003) found the incidence of yeast infection in HIV-negative US women to be 35.1 per 100 PY. The incidence of yeast infection in women recruited from health facilities in Durban and Hlabisa (South Africa) has been estimated at 37.7 and 54.3 per 100 PY respectively (Dladla-Qwabe *et al*, 2005). In another African study, conducted among sex workers in Kenya, the incidence of yeast infection was 55.6 per 100 PY (McClelland *et al*, 2005). These estimates are probably under-estimates of the true incidence of yeast infection, as (a) low follow-up frequencies (e.g. semi-annually in the case of Ohmit *et al* and quarterly in the case of Dladla-Qwabe *et al*) may be expected to lead to under-estimation of incidence, and (b) the microscopy and culture methods used in these studies have limited sensitivity. It is therefore assumed that the incidence of yeast infection is 0.8 per annum.

Studies suggest that symptomatic candidiasis infections resolve more rapidly, in the absence of treatment, than asymptomatic infections (del Palacio *et al*, 2000; Ohmit *et al*, 2003). Some yeast colonies may persist for long periods of time, even after appropriate treatment, with colonies being too small to be detected by culture methods. It has been suggested that this may account for the frequent 'relapse' of symptoms after treatment in women with recurrent vulvovaginal candidiasis (Sobel *et al*, 2004; Sobel 1993; El-Din *et al*, 2001). The approach taken to modelling vulvovaginal candidiasis is therefore to model 'asymptomatic candidiasis' as an intermediate state between 'uninfected' and 'symptomatic candidiasis'. It is thus assumed that women who are symptomatic would still be asymptotically colonized with *Candida* after spontaneous resolution of symptoms. The rate at which symptoms resolve (σ_2) is estimated to be 4.3 per annum, based on the study of Brown *et al* (1986), which found that 25 out of 70 women ceased to experience vulvovaginal candidiasis symptoms over a one-month period. The rate at which asymptomatic infection resolves (σ_1) is more difficult to estimate, as it is very dependent on the sensitivity of the culture methods used, especially at short follow-up durations. In a study with six-monthly follow-up, Ohmit *et al* (2003) estimated the rate to be 1.15 per

annum. Parameter σ_1 is set at 2 per annum, in order to make allowance for the under-estimation associated with the low frequency of follow-up in this study.

The incidence of symptomatic vulvovaginal candidiasis appears to be lower than the incidence of yeast infection. Ohmit *et al* (2003) measured an incidence in HIV-negative women of 3.7 per 100 PY, though again, this is probably an under-estimate due to the low frequency of follow-up. Fennema *et al* (1995) measured an incidence of symptomatic candidiasis of 10.7 per 100 PY in a cohort of HIV-negative sex workers, based on STI clinic attendances (this too may be an under-estimate, as not all women experiencing candidiasis symptoms would have sought treatment). Self-reported cumulative incidence rates, over a one-year period, have been estimated at between 29% and 39% (Fleming *et al*, 2006; Foxman *et al*, 2000), but these self-reports are generally not regarded as reliable, and are likely to over-estimate the true incidence of symptomatic infection if women often experience vulvovaginal symptoms due to other conditions. It is assumed that the incidence of symptomatic candidiasis is 0.15 per annum, which is equivalent to setting the ζ parameter to 0.53 per annum. (This equivalence follows by noting that in the steady-state equilibrium, ignoring treatment, the incidence of symptomatic infection in all asymptomatic women, λ^* , is $\lambda\zeta/(\lambda + \sigma_1)$. The assumed values of λ and σ_1 , 0.8 and 2 respectively, were substituted into this equation in order to solve for ζ .)

Table 3.3.8 summarizes the parameter values specified previously, and shows the prior distributions chosen for those parameters considered in the Bayesian analysis.

Table 3.3.8: Vulvovaginal candidiasis parameters

Parameter	Symbol	Prior distribution		
		Type	Mean	Std dev.
Average duration of symptoms (weeks)	$1/\sigma_2$	Gamma	12.0	3.0
Average time to clearance of asymptomatic infection (weeks)	$1/\sigma_1$	Gamma	26.0	6.0
Annual incidence of yeast infection	λ	Gamma	0.80	0.20
Annual incidence of symptoms (in all asymptomatic women) [†]	λ^*	Gamma	0.15	0.05

[†] This parameter is used to determine the parameter ζ , using the equation $\zeta = \lambda^* \times (\lambda + \sigma_1)/\lambda$.

3.3.1.9 HIV/AIDS

The model developed here follows the approach to staging HIV/AIDS progression recommended by the Centre for Disease Control (CDC) and World Health Organization (WHO). Individuals with HIV are categorized as being either asymptomatic (equivalent to WHO clinical stages I and II, or CDC stage A), experiencing pre-AIDS symptoms (WHO clinical stage III, roughly equivalent to CDC stage B) or having progressed to AIDS (WHO clinical stage IV or CDC stage C). In addition, individuals who are infected are assumed to remain in an ‘acute infection’ phase for the first few months after acquiring HIV, during which time they are highly infectious. A proportion of individuals are assumed to initiate highly active antiretroviral treatment (HAART) at the time that they progress to AIDS. This pattern of disease progression is presented in Figure 3.3.6.

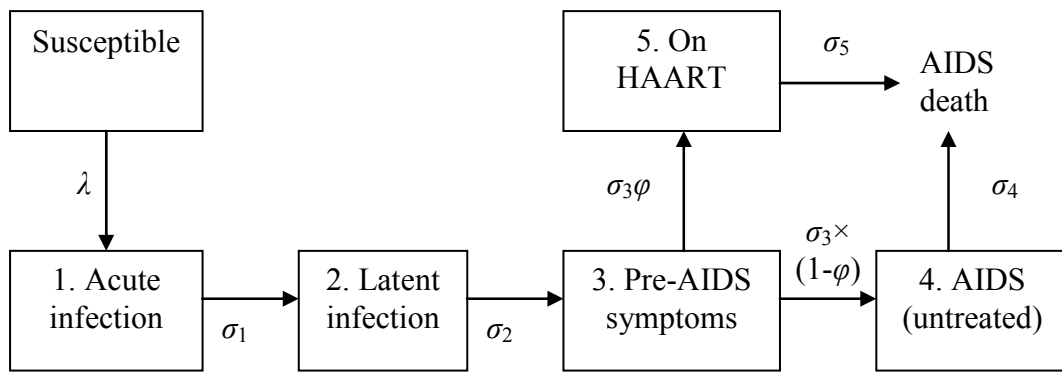


Figure 3.3.6: Multi-state model of the natural history of HIV

Models of HIV/AIDS in Africa have usually assumed average HIV survival times of less than 10 years in the absence of treatment (Robinson *et al*, 1997; Bracher *et al*, 2004; Korenromp *et al*, 2002c). However, HIV survival times in South Africa appear to be longer (Glynn *et al*, 2005), and in a recent analysis of HIV prevalence and vital registration data in South Africa it was estimated that the mean HIV survival time, for an untreated individual infected at age 29, was 11.5 years (Johnson *et al*, 2007). This value of 11.5 years is used as the assumed mean survival time, in the absence of treatment. In the interests of simplicity, no allowance is made for age variation in HIV survival rates, although there is evidence to suggest that older individuals have shorter survival times than individuals infected at young ages (Collaborative Group on AIDS Incubation and HIV Survival 2000).

The length of time spent in each stage of HIV disease is highly variable. In fitting simple Markov models to data from studies that have estimated rates of transition between clinical stages in the pre-HAART era, it has been estimated that on average 47% of HIV survival time is spent in WHO stages 1 and 2, 36% of survival time is spent in WHO stage 3, and the remaining 17% of time is spent in WHO stage 4 (Johnson and Dorrington 2006). The assumptions made here are therefore that the mean length of time spent in the AIDS phase ($1/\sigma_4$) is $0.17 \times 11.5 = 1.96$ years, and the mean length of time spent in the pre-AIDS phase ($1/\sigma_3$) is $0.36 \times 11.5 = 4.14$ years. The period of high infectiousness following acquisition of HIV appears to correspond to the first three months of infection (Wawer *et al*, 2005; Lavreys *et al*,

2006), and the mean duration of the acute infection phase ($1/\sigma_1$) is therefore set at 3 months. The remainder of the HIV survival time, in the absence of antiretroviral treatment, is spent in the asymptomatic phase (mean duration of 5.16 years).

To model the effect of HAART, it is assumed that a proportion of individuals progressing to AIDS, ϕ , start treatment. This parameter varies over time, and the values in each year are set to be the same as the corresponding rates of HAART rollout in the ASSA2003 AIDS and Demographic model (Actuarial Society of South Africa 2005). The rates of rollout in the ASSA2003 model have been set to produce results consistent with reported numbers on HAART in the South African private and public health sectors up to 2005, and thereafter rollout rates increase to 50% of all individuals progressing to AIDS by mid-2008, remaining constant at this level in subsequent years. In reality, not all individuals starting HAART would do so at the time that they experience their first AIDS-defining illness, and most treatment guidelines recommend earlier initiation of antiretroviral treatment (World Health Organization 2004). However, this timing assumption is made in order to ensure consistency with the ASSA2003 modelling of treatment initiation.

HAART has been shown to reduce the mortality rate by 78% in a US study (Palella *et al*, 1998), and by 90% in a South African study (Badri *et al*, 2004). It is assumed that the AIDS mortality rate is reduced by 85% after starting HAART, so that the continuous mortality rate after starting HAART (σ_5) is $\sigma_4(1 - 0.85) = 0.077$ per annum. This is higher than the rates of mortality of 0.01 to 0.03 per annum typically measured after the first six months on HAART (Nachega *et al*, 2006; Lohse *et al*, 2007; ART-LINC Collaboration and ART-CC groups 2006), but lower than the rate of around 0.1 per annum typically experienced in the first six months on HAART (ART-LINC Collaboration and ART-CC groups 2006). Estimates from these studies may be biased towards understatement of mortality, due to the high rates of loss to follow-up often experienced (Rosen *et al*, 2007), and it is therefore appropriate that the assumed AIDS mortality rate on HAART should be higher than that usually measured after the first six months on HAART. Discontinuation of antiretroviral treatment is not modelled explicitly.

3.3.2 HIV/AIDS and STI transmission

This section describes and motivates the various assumptions made about STI incidence. In general, a constant probability of transmission per act of sex is assumed for each STI, and this probability is then multiplied by various adjustment factors to represent the effects of age, disease stage, condom use, risk group and partnership type. A more detailed mathematical explanation of the method used to model STI transmission is given in Appendix B. In the case of bacterial vaginosis and vulvovaginal candidiasis, which are generally not considered to be sexually transmissible, a constant incidence rate is assumed.

3.3.2.1 Probability of STI transmission per act of sex

Table 3.3.9 summarizes the assumptions made about the STI transmission probabilities per act of sex. As these transmission probabilities are extremely difficult to determine with any degree of certainty, these parameters are included in the Bayesian analysis in chapter 4. Beta priors have been specified for all the transmission probabilities, and the table shows the means and standard deviations of these beta priors. These prior distributions have been set with reference to both empirical evidence (discussed below) and parameter values that have been found to yield plausible results in other modelling studies (Orroth *et al*, 2007; Bracher *et al*, 2003; Korenromp *et al*, 2000b; Korenromp *et al*, 2002b; Ghani and Aral 2005; White *et al*, 2004; Williams *et al*, 2006b).

In the case of the non-viral STIs, empirical estimates of transmission probabilities tend to lie at the upper end of the distributions specified in Table 3.3.9. (Empirical estimates of transmission probabilities per sex act have been derived in the case of gonorrhoea (Hooper *et al*, 1978; Holmes *et al*, 1970; Platt *et al*, 1983), chlamydial infection (Lin *et al*, 1998), syphilis (Schroeter *et al*, 1971) and chancroid (Plummer *et al*, 1983).) The prior distributions have been set in this way because the empirical estimates are all derived from contact tracing studies and studies of male exposure to sex workers, which are likely to over-estimate transmission probabilities. Contact tracing studies are likely to over-estimate transmission probabilities because the index partner is not necessarily the source of infection (Garnett and Bowden 2000), and

studies of male exposure to sex workers are likely to over-estimate transmission probabilities because men tend to under-report the extent of their contact with sex workers (Des Jarlais *et al*, 1999; Lau *et al*, 2003). Mathematical models tend to assume lower transmission probabilities than those estimated empirically in order to obtain plausible STI prevalence estimates.

Table 3.3.9: Prior distributions on the probability of STI transmission per act of sex

STI	Male-to-female		Female-to-male	
	Mean	Std dev.	Mean	Std dev.
Gonorrhoea	0.40	0.10	0.20	0.05
Chlamydial infection	0.16	0.10	0.12	0.06
Syphilis	0.18	0.05	0.15	0.05
Chancroid	0.20 ^a	-	0.20 ^a	-
Trichomoniasis	0.15	0.08	0.04	0.02
HSV-2 (asymptomatic)				
CSW-client relationships	0.002	0.0005	- ^b	-
Short-term relationships	0.0075	0.0010	0.0025	0.0005
Long-term relationships	0.0009	0.00015	0.00015	0.00003
HIV (ignoring STI cofactors)				
CSW-client relationships	0.003 ^a	-	0.030 ^a	-
Short-term relationships	0.012	0.005	0.010	0.003
Long-term relationships	0.002	0.00075	0.002	0.00075

CSW = commercial sex worker.

^a Fixed parameter, not included in Bayesian analysis. ^b Female-to-male transmission probability is assumed to be the same in short-term and CSW-client relationships.

In the case of the viral STIs, HIV and HSV-2, there is strong evidence to suggest that the probability of transmission per sex act reduces as the cumulative number of sex acts with the infected partner increases (Downs and De Vincenzi 1996; Saracco *et al*, 1993; Padian *et al*, 1990; Wald *et al*, 2001; Corey *et al*, 2004). This phenomenon may be explained by heterogeneity between individuals, both in terms of susceptibility and infectiousness, i.e. partnerships in which transmission does not occur after a large number of exposures are likely to be partnerships in which the transmission risk per act of sex is relatively low. Alternatively, it may be due to the development of a

protective immune response. Studies in sex workers have demonstrated that some women develop HIV-specific T-cell responses that appear to protect against HIV infection (Rowland-Jones *et al*, 1998), and HSV-specific T-cell responses have also been identified in HSV-negative women (Posavad *et al*, 2003). Because of this heterogeneity in transmission probabilities, transmission probabilities are assumed to differ according to the relationship type.

Estimates of HIV and HSV-2 transmission probabilities per act of sex are usually calculated from the cumulative risk of infection over some period, since both infections are incurable. Supposing that the risk of transmission per act of sex is β , the probability of condom use per act of sex is γ , the average number of sex acts over the period of interest is n , and the STI prevalence among partners is θ , the cumulative probability of STI transmission over the period can be crudely estimated as

$$1 - (1 - \theta\beta(1 - \gamma))^n. \quad (3.7)$$

The probability of transmission per act of sex, β , can thus be estimated from the cumulative probability of transmission, if information on sexual behaviour and STI prevalence among partners is available. Estimates of HIV and HSV-2 transmission probabilities per act of sex in short-term relationships, calculated using this formula, are shown in Table 3.3.10. The client-to-sex worker HIV transmission probability is assumed to be 0.003, on the basis of the estimates of Ramjee *et al* (2005) and Hayes *et al* (1995b), while the male-to-female transmission probability in short-term relationships is assumed to be higher, at 0.012, based on two South African studies that have estimated the probability of HIV transmission per partnership in young women (Auvert *et al*, 2001a; Pettifor *et al*, 2007); the lower assumed susceptibility in sex workers can be justified on the basis of possible resistance to HIV in highly exposed individuals. The sex worker-to-client probability of HIV transmission is set at 0.03 per act of sex, on the basis of a study of military recruits in Thailand, for whom contact with sex workers was the main HIV risk factor (Mastro *et al*, 1994); higher transmission probabilities have been estimated among male contacts of sex workers in Kenya (Cameron *et al*, 1989). Estimates of the female-to-male HIV transmission probability in non-commercial short-term relationships appear to be

around 0.01 per act of sex (Baeten *et al*, 2005; Auvert *et al*, 2005), and the prior mean for this parameter has therefore been set at 0.01. The prior distributions on the HSV-2 transmission probabilities in Table 3.3.9 are lower than the corresponding empirical estimates in Table 3.3.10, as the former relate only to asymptomatic infection, and the substantial increase in transmission probability in the symptomatic phases of infection renders the overall probability of transmission more consistent with the empirical estimates.

Table 3.3.10: Estimates of HIV and HSV-2 transmission probabilities per act of sex, in short-term partnerships

Parameter	Population	Reference	STI	Cum. % infected	θ	n	γ	β
Client-to-sex worker transmission	South Africa	Ramjee <i>et al</i> (2005)	HIV	14.7%	0.25 ^a	1212 ^c	0.89 ^c	0.0047
			HSV-2	35%	0.56 ^b	1212	0.89	0.0021
	Kenya	Hayes <i>et al</i> (1995b)	HIV	55%	0.11	?	0.25	0.0032 ^e
Non-spousal male-to-female transmission	South Africa	Pettifor <i>et al</i> (2007)	HIV	74% ^f	1.00	82	-	0.016
		Auvert <i>et al</i> (2001a)	HIV	49% ^f	1.00	82	-	0.008
Non-spousal female-to-male transmission	South Africa	Auvert <i>et al</i> (2005)	HIV	2.1%	0.25 ^a	8	-	0.0106
Short-term transmission ^g	USA	Wald <i>et al</i> (2006)	HSV-2	50%	1.00	40	-	0.017

^a Arbitrarily chosen. ^b Based on Ramjee and Gouws (2002). ^c Based on Ramjee *et al* (1999). ^d Based on HSV-2 prevalence in mineworkers (Ndhlovu *et al*, 2005). ^e Excluding sex workers experiencing genital ulcers. ^f Probability of transmission per partnership with an HIV-positive individual. ^g Relates to both males and females combined.

Probabilities of HIV and HSV-2 transmission per sex act in spousal partnerships are estimated from studies of serodiscordant couples, most of whom are in long-term partnerships. In a Ugandan study of couples who were either married or in stable consensual unions, the estimated probability of HIV transmission per act of sex was 0.0009 in those partnerships in which the initially infected partner was male and

0.0013 in those partnerships in which the initially infected partner was female (Gray *et al*, 2001). More substantial gender differences have been observed in the case of HSV-2. In HSV-2-serodiscordant couples in the U.S., the estimated male-to-female transmission probability per sex act was estimated to be 0.00089, and the corresponding estimate for female-to-male transmission was 0.00015 (Wald *et al*, 2001). These estimates have been used to set the prior distribution on transmission in spousal relationships in Table 3.3.9.

The HSV-2 transmission probabilities shown in Table 3.3.9 relate only to asymptotically infected individuals. The odds of detectable HSV-2 shedding in symptomatic infection is typically 10 to 20 times that in asymptomatic HSV-2 infection (Straus *et al*, 1989; Harger *et al*, 1989; Wald *et al*, 2000; Wald *et al*, 1995). The multiple by which HSV-2 infectiousness is increased in the presence of HSV-2 symptoms is therefore assigned a gamma prior with a mean of 15 and a standard deviation of 5.

The HIV transmission probabilities in Table 3.3.9 are the average transmission probabilities that apply over the course of HIV infection. HIV infectiousness in the acute infection stage is assumed to be ten times that in the asymptomatic stage (Wawer *et al*, 2005), and the transmission probabilities in the pre-AIDS and AIDS stages are assumed to be 2.5 times and 5 times those in the asymptomatic phase, respectively. The pre-AIDS and AIDS parameters are based on observed changes in blood plasma viral load over the course of HIV infection (Hubert *et al*, 2000; Lyles *et al*, 2000; Kassa *et al*, 1999; Wawer *et al*, 2005); it is assumed that the HIV transmission probability is increased by a factor of 2.5 for each log increase in viral load (Quinn *et al*, 2000; Fideli *et al*, 2001). The HIV transmission probabilities in each stage are set in such a way that when weighted by the average length of time spent in each stage of disease, the average transmission probability corresponds to that specified in Table 3.3.9. HAART is initiated only in the late stages of disease and is associated with an almost 3-log reduction in viral load (Frater *et al*, 2002; Laurent *et al*, 2002). It is therefore assumed that individuals receiving HAART are only half as infectious as individuals in the untreated asymptomatic phase of HIV infection. In the baseline scenario, probabilities of HIV transmission are assumed not to be

affected by the presence of other STIs; the potential effects of other STIs on HIV transmission probabilities are explored in chapter 5.

Apart from HIV and HSV-2, syphilis is the only other STI for which transmission probabilities are assumed to vary according to disease stage. The syphilis transmission probabilities shown in Table 3.3.9 apply only in the primary and secondary syphilis phases, after which individuals are assumed not to be infectious (Garnett *et al*, 1997). Although it is likely that other STIs are more transmissible when symptomatic than when asymptomatic, per act of sex, Garnett and Bowden (2000) argue that symptomatic individuals are also more likely to avoid sexual contact, and that it is therefore unclear whether symptomatically infected individuals are more likely to transmit infection than asymptomatically infected individuals. In the absence of reliable evidence regarding the infectiousness of other STIs, it is therefore assumed that asymptomatic individuals are as likely to transmit infection as symptomatic individuals (i.e. it is assumed that transmission probabilities are the same in symptomatic and asymptomatic infection and that coital frequencies are unaltered by symptoms of genital ulcers or discharges).

In the case of bacterial STIs, it is assumed that there is no risk of transmission between individuals in mutually monogamous long-term relationships (i.e. marital or cohabiting relationships in which neither partner has any propensity for concurrent relationships). The rationale for this assumption is that if one partner is infected with an STI, they would have acquired it before entry into the current partnership. Since long-term relationships are assumed to start as short-term relationships, and since there is a high cumulative risk of the bacterial STI being transmitted up to the point at which the short-term relationship becomes long-term, it seems reasonable to assume that any transmission that occurs after the relationship has become long-term would be negligible.

In the case of HIV and chlamydial infection, the model also allows for increased susceptibility to infection in women at young ages, which is due to the high prevalence of cervical ectopy in young women and possibly also immunological factors. Women in the 10 to 19 and 20 to 24 age groups are assumed to be 2.5 times and 1.5 times as susceptible to chlamydial infection as women aged 25 and older,

respectively, per act of sex with a chlamydia-infected partner (Buvé *et al*, 2001b; Quinn *et al*, 1996; Arno *et al*, 1994). The same multiples are assumed in the case of HIV, based on the rates of transmission observed in studies of serodiscordant couples (Carpenter *et al*, 1999).

3.3.2.2 Non-sexual incidence of infection

Although the organisms associated with bacterial vaginosis and vulvovaginal candidiasis appear to be sexually transmissible, bacterial vaginosis and candidiasis are generally not regarded as being STIs and are defined as conditions that affect only women. The approach adopted here is therefore to model these infections in women by assuming a constant weekly incidence that is independent of coital frequency.

In the case of bacterial vaginosis, the beta prior distribution on the weekly incidence rate λ (among women who are currently in the 'abnormal vaginal flora' state) is assigned a mean of 0.1 and a standard deviation of 0.03, consistent with the findings of Hillier *et al* (1992b) (see Table 3.3.6). As there is substantial evidence to suggest that women who report multiple partners experience bacterial vaginosis more frequently than women who are monogamous (Smart *et al*, 2004; Ness *et al*, 2006; Yen *et al*, 2003; Bradshaw *et al*, 2005; Shoubnikova *et al*, 1997), it is assumed that this incidence rate is doubled in sex workers and women who have more than one current partner. There is also evidence to suggest that virgins are significantly less susceptible to bacterial vaginosis than sexually experienced women (Yen *et al*, 2003; Amsel *et al*, 1983), and on the basis of this it is assumed that the above incidence rate is halved in women who currently have no sexual partner.

Vulvovaginal candidiasis is rare in women pre-menarche and post-menopause (Geiger *et al*, 1995; Ferrer 2000; Sobel 1993), probably because of the dependence of candidiasis on the production of oestrogen, which is limited to the reproductive years. Studies also show that the prevalence of candidiasis is particularly high at young ages (Greenblatt *et al*, 1999; Ohmit *et al*, 2003; Bradshaw *et al*, 2005; Eckert *et al*, 1998) and in pregnancy (Ohmit *et al*, 2003; Daus and Hafez 1975). It is therefore reasonable to assume that the incidence of yeast infection is proportional to the age-specific fertility rate. The gamma prior on the annual incidence of yeast infection in women

aged 15-19 is assigned a mean of 0.8 and a standard deviation of 0.2, based on the evidence reviewed in section 3.3.1.8. The annual incidence in other age groups is estimated by multiplying the 15-19 incidence by the ratio of the average fertility rate in the age group to the average fertility rate in the 15-19 age group.

3.3.2.3 Condom efficacy

In a meta-analytic review, Weller and Davis (2004) estimate that the average rate of HIV transmission in serodiscordant couples always using condoms is 1.14 per 100 PY, which compares with 5.75 per 100 PY in serodiscordant couples never using condoms. This suggests condoms are about 80% effective in preventing HIV transmission. However, this is probably an under-estimate, since it is likely that some individuals who report 'always' using condoms in fact do not use them as consistently as they claim (Holmes *et al*, 2004; Meekers and Van Rossem 2005). Condoms have been shown to be less effective in preventing the transmission of HSV-2 (Wald *et al*, 2001), and it is believed that this is because the shedding of HSV-2 through the skin is not limited to the parts of the genitals covered by the condom. Although numerous studies have been conducted to determine whether condoms are effective in preventing the transmission of other STIs (Holmes *et al*, 2004; National Institute of Allergy and Infectious Diseases 2000), the other STIs considered here are acute, curable infections, and this makes it almost impossible to estimate rates of condom effectiveness per sex act.

In the model it is assumed that condoms are 90% effective in preventing HIV transmission and 75% effective in preventing HSV-2 transmission, per sex act. In the absence of good data on condom efficacy in preventing other STIs, it is assumed that condoms are as effective in preventing other STIs as they are in preventing HIV (i.e. 90% efficacy is assumed). Condom use is assumed to have no effect on the incidence of bacterial vaginosis or yeast infection.

3.3.3 The effect of HIV on the natural history and transmission of other STIs

A large number of studies have investigated the effect of HIV on the incidence and natural history of various STIs, but only HSV-2 and vulvovaginal candidiasis have

consistently been shown to be affected by HIV. There is weak evidence to suggest that the course of primary and secondary syphilis is altered in the presence of HIV (Hutchinson *et al*, 1994; Rompalo *et al*, 2001), and that neurosyphilis may be more common in HIV-infected individuals (Musher *et al*, 1990), but these associations are not considered in the model developed here.

In the case of HSV-2, there is strong evidence to suggest that HIV increases infectiousness by promoting the shedding of HSV-2 in the genital tract. For example, LeGoff *et al* (2007) found that HIV doubled the odds of HSV-2 shedding, and Augenbraun *et al* (1995) detected HSV-2 shedding in 3.6% of HIV-negative, HSV-2-positive women, compared with 12.5%, 8.5% and 22.2% of HIV-HSV-2-coinfected women with CD4+ counts of ≥ 500 , 200-499 and < 200 cell/mm³ respectively. The rate at which HSV-2 ulcers recur is also increased in HIV-positive individuals, particularly in the late stages of HIV infection (Greenblatt *et al*, 1999; Ghys *et al*, 1995). In the model it is assumed that there is a doubling of the frequency of HSV-2 shedding and HSV-2 infectiousness in all HSV-2 disease states if the individual is coinfected with HIV. It is also assumed that the rate at which genital ulcers recur, ζ , is increased by a multiple of 2 in individuals in the acute HIV infection and asymptomatic HIV infection stages, by a multiple of 3 in the pre-AIDS symptomatic phase, and by a multiple of 4 in the AIDS phase. HAART appears to have little effect on the frequency of HSV-2 shedding, but does appear to reduce the frequency of genital ulcers in HIV-infected patients (Posavad *et al*, 2004). It is therefore assumed that ζ is increased by a multiple of 2 in individuals on HAART (the same frequency as in the asymptomatic HIV stage). In addition, it is assumed that individuals co-infected with HIV do not progress from the transiently asymptomatic state to the permanently asymptomatic state (this ensures that individuals do not experience reductions in HSV-2 recurrences as their HIV infection progresses, unless they start HAART).

In the case of candidiasis, there is strong evidence to suggest that immune suppression is associated with both increased yeast colonization and increased experience of symptomatic vulvovaginal candidiasis. Relevant studies are summarized in Table 3.3.11. On the basis of these studies, it is assumed that the incidence of yeast infection is the same in asymptomatic HIV infection as in HIV-negative women, but that the incidence increases by a factor of 1.5 in women after entry in the symptomatic pre-

AIDS stage, and is double that in asymptomatic infection after entry into the AIDS stage (these assumptions imply similar increases in the incidence of symptomatic infection). As HAART appears to have little effect on the incidence of candidiasis after controlling for CD4 count (van Benthem *et al*, 2000; Ohmit *et al*, 2003) and is associated with significant restoration of CD4 levels, it is assumed that the incidence of yeast infection in women on HAART is the same as that in HIV-negative women.

Table 3.3.11: Effects of HIV on the incidence and prevalence of vulvovaginal candidiasis (VVC)

Study	Outcome	HIV-	HIV-positive with CD4		
			> 500	200-500	< 200
Duerr <i>et al</i> (1997)	Prevalence of VVC	18%	19%	25%	41%
Clark <i>et al</i> (1993)	Prevalence of VVC		30.9%	31.8%	60%
Greenblatt <i>et al</i> (1999)	OR for VVC	1.00	1.37	1.55	1.52
Ohmit <i>et al</i> (2003)	OR for VVC	1.00	1.01	1.16	1.30
McClelland <i>et al</i> (2005)	RR for VVC	1.0	0.9	1.6	2.5
Rugpao <i>et al</i> (1998)	Prevalence of symptomatic VVC	5.9%	5.6%	7.5%	16.0%
Minkoff <i>et al</i> (1999)	Prevalence of symptomatic VVC	6.6%	11.1%	7.5%	19.4%
Farizo <i>et al</i> (1992)	Cumulative 12-month incidence of symptomatic VVC		9.6%	11.6%	16.8%
van Benthem <i>et al</i> (2000)	RR for VVC or self-reported VVC		1.00	1.16	1.17

3.3.4 STI health-seeking behaviour and treatment

The sections that follow describe the assumptions used to model the effects of STI treatment in South Africa and the sources on which these assumptions are based. In Appendix B, a more formal mathematical explanation is given of how these assumptions are used to determine the rates at which individuals are cured of STIs.

3.3.4.1 Health-seeking behaviour

To estimate the weekly rate at which individuals experiencing STI symptoms seek treatment, ν , suppose that symptoms resolve spontaneously at rate σ per week. Further suppose that of individuals reporting experience of STI symptoms over some past period, the proportion who report having sought treatment is R . Assuming that symptoms have resolved spontaneously in those who did not seek treatment, and assuming that both ν and σ are constant with respect to the duration of infection, $R = \nu/(\nu + \sigma)$. This equation can be re-expressed as $\nu = R\sigma/(1 - R)$, and it can also be shown that the mean time to seeking treatment is $(1 - R)/\sigma$. It is therefore possible to determine the rate at which individuals seek treatment if the rate of spontaneous resolution and the proportion of individuals seeking treatment are both known. Since the latter parameter is difficult to determine for each STI separately, we attempt to determine ‘average’ parameters for a generic STI, rather than separate parameters for each STI.

African studies consistently show that men are more likely to report seeking treatment for STI symptoms than women, with proportions usually being around 80% in men and around 65% in women (Voeten *et al*, 2004; Lewis *et al*, 2005; Paxton *et al*, 1998; Williams *et al*, 2000; Reddy *et al*, 2003). In a study conducted in Carletonville (South Africa), the proportions of men and women who reported seeking treatment for STI symptoms (of those who reported experience of symptoms) were 83% and 77% respectively, and a higher proportion (86%) was recorded among sex workers (Williams *et al*, 2000). However, in a study of South African learners, it was found that the proportions who reported seeking treatment were relatively low: 67% in male learners and 59% in female learners (Reddy *et al*, 2003). These results are consistent with a Zimbabwean study, which found that youth sought treatment for STIs at a lower rate than older adults, and that sex workers sought treatment very promptly (Lewis *et al*, 2005). The proportions of individuals who seek treatment, assumed on the basis of these studies, are shown in Table 3.3.12. As the assumed average duration of most STI symptoms, in the absence of treatment, is around 10 weeks, σ is set at 0.1 per week for the purpose of calculating the implied rate at which treatment is sought (also shown in Table 3.3.12). The corresponding mean times to seeking treatment are

roughly consistent with various African studies, which have generally estimated the mean time to seeking treatment to be around 14 days in men and around 30 days in women (Wilkinson *et al*, 1998; Voeten *et al*, 2004; O'Farrell *et al*, 1991a; O'Farrell *et al*, 1991b).

Table 3.3.12: Assumed rates of health seeking for STI treatment

Group	Assumed % who seek treatment (<i>R</i>)	Implied rate at which treatment is sought, per week (<i>v</i>)	Implied average time to seeking treatment (days)
Males			
Aged <20	70%	0.23	21
Aged 20+	85%	0.57	11
Females (not sex workers)			
Aged <20	55%	0.12	32
Aged 20+	70%	0.23	21
Sex workers	90%	0.90	7

Studies also suggest that men and women differ in terms of the sources from which they seek treatment. Women are more likely than men to seek treatment from public health facilities, while men are more likely than women to seek treatment from private practitioners, traditional healers and the 'informal' health sector (Voeten *et al*, 2004; Moses *et al*, 1994; Ndhlovu *et al*, 2005). South African studies suggest that just over half of STI cases are treated in the public health sector, between 5% and 20% are treated by traditional healers, and the balance of about a third are treated in the formal private health sector (Wilkinson *et al*, 1998; Wilkinson and Wilkinson 1998; Wilson *et al*, 2000; Ndhlovu *et al*, 2005). Antibiotic access is tightly controlled in South Africa (Hudson 1999), and it is therefore unlikely that other 'informal' providers of STI treatment would treat significant numbers of STI patients. It is assumed that the public health sector treats 45% of male STI cases and 60% of female STI cases, and that the private health sector treats 40% and 30% of male and female STI cases respectively. The remainder of STI cases (15% in men and 10% in women) are assumed to be treated by traditional healers.

3.3.4.2 Use of syndromic management protocols

Prior to 1994, syndromic management protocols were not used in the treatment of STIs in South Africa. Syndromic management protocols were introduced rapidly in public health facilities after 1994, and by 1999 almost all public STI clinics were following these protocols (D. Coetzee, personal communication). However, drug shortages and heavy patient loads at some public STI clinics have limited capacity to implement syndromic management protocols (Sonko *et al*, 2003), and surveys suggest that even when syndromic management protocols are in use, nurses do not necessarily prescribe the correct number of effective drugs at the correct dosage. Recent surveys suggest, for example, that only about 70% of nurses know the correct syndromic treatment for genital ulcer disease and roughly 85% know the correct treatment for male urethral discharge and vaginal discharge (Ramkissoon *et al*, 2004; Reagon *et al*, 2004). Proportions of public clinics reporting shortages of STI drugs have declined from around 10% in 1998 (Pick *et al*, 1998) to less than 5% since 2002 (Ramkissoon *et al*, 2004; Reagon *et al*, 2004), and greater reductions in drug shortages probably occurred prior to 1998. The proportions of clinics using syndromic management protocols correctly, assumed on the basis of these studies, are shown in Table 3.3.13.

The private health sector has been relatively slow to introduce syndromic management protocols in STI treatment, partly due to the high costs of treating STI patients with multiple drugs, and partly due to the lack of training provided to private practitioners regarding syndromic management. A national survey of private practitioners, conducted in 1997, found that the number of practitioners who prescribed the correct number of effective drugs for a particular syndrome varied between 4% and 29% (Dartnall *et al*, 1997). More recent studies in Gauteng suggest that there have been slight improvements in the use of syndromic management protocols (Chabikuli *et al*, 2002; Schneider *et al*, 2005b), and Schneider *et al* (2005b) found that private practitioners who had qualified since the development of syndromic management protocols in 1993 provided significantly more effective treatment than those who had qualified previously. This suggests that the proportion of private practitioners treating STIs according to syndromic protocols will continue to increase gradually in future, as the proportion of practitioners who have received education in syndromic management increases. The assumed proportions are shown in Table

3.3.13; these proportions are assumed to increase by 2% (absolute) per annum after 2003.

Table 3.3.13: Assumed use of syndromic management protocols

Year	% of providers correctly using syndromic management protocols		% of public clinics with STI drug shortages	Source
	Private	Public		
	1993	0%	0%	
1994	3%	10%	20%	
1995	7%	30%	18%	
1996	11%	50%	16%	Harrison <i>et al</i> (1998)*
1997	15%	65%	13%	Dartnall <i>et al</i> (1997)†
1998	18%	75%	10%	Pick <i>et al</i> (1998)*
1999	21%	78%	8%	Chabikuli <i>et al</i> (2002)†
2000	23%	80%	6%	
2001	25%	80%	5%	Schneider <i>et al</i> (2005b)†
2002	27%	80%	4%	Ramkissoo <i>et al</i> (2004)*
2003	29%	80%	4%	Reagon <i>et al</i> (2004)*

* Public health sector. † Private health sector.

3.3.4.3 Effectiveness of treatment

Prior to the introduction of syndromic management protocols, STI treatment in Africa was based mainly on clinical diagnosis, which was often inaccurate. Surveys of health workers' prescriptions for common STI syndromes prior to the introduction of syndromic management suggest that more than half of syphilis, gonorrhoea and chlamydial cases were appropriately treated (Somsé *et al*, 2000; Buvé *et al*, 2001a; Chilongozi *et al*, 1996; Mathews *et al*, 1998; Chabikuli *et al*, 2002). Treatment of other causes of vaginal discharge (bacterial vaginosis, trichomoniasis and candidiasis) was found to be appropriate in roughly half of cases in a Central African Republic study (Somsé *et al*, 2000), higher than in a South African study (Mathews *et al*, 1998). In another South African study, treatment of male urethral discharge was found to be appropriate in treating trichomoniasis in a third of cases (Chabikuli *et al*, 2002).

Although there are no South African estimates of appropriateness of treatment for chancroid prior to syndromic management, it appears that early treatment protocols were effective in many chancroid cases (Department of National Health and Population Development 1991; Ye *et al*, 2007). These studies provide some clues regarding the appropriateness of treatment prior to the adoption of syndromic management protocols in South Africa, but there remains much uncertainty, and the model parameters determining the appropriateness of treatment have therefore been included in the Bayesian uncertainty analysis. For each STI, a beta prior distribution was specified for the proportion treated appropriately, with means and standard deviations shown in Table 3.3.14.

It is assumed that health workers following syndromic management guidelines would treat appropriately all STIs, with three exceptions. Firstly, South African syndromic management guidelines do not include treatment of genital herpes in the management of genital ulcer disease (Department of Health 2003), although recent WHO protocols recommend the inclusion of antiviral treatment in the management of genital ulcer disease in countries with a high HSV-2 prevalence (World Health Organization 2003). It is therefore assumed that genital herpes is not treated at all under syndromic management guidelines. Secondly, most protocols recommend that treatment for male urethral discharge include drugs effective against trichomoniasis only as a second-line, i.e. only if treatment against gonorrhoea and chlamydial infection proves ineffective (World Health Organization 2003). It is therefore assumed that only half of symptomatic male trichomoniasis cases are correctly treated under syndromic management (on the optimistic assumption that all men would return to the same provider to be retreated if their symptoms did not resolve). Lastly, syndromic management guidelines generally recommend that antifungal treatment against vulvovaginal candidiasis only be provided if the disease is clinically suspected (i.e. if there is vulval oedema, erythema and/or a curd-like discharge). This is effectively no different from standard treatment practices prior to the introduction of syndromic management, and the assumed proportion of cases that are appropriately treated is therefore the same as that prior to syndromic management.

If appropriate antibiotic treatment is prescribed, it is assumed that the probability of cure is 0.9 in the case of syphilis (Schroeter *et al*, 1972; Rolfs *et al*, 1997), chancroid

(Ballard *et al*, 1990), gonorrhoea (Moodley *et al*, 2003b; Rustomjee *et al*, 2002), chlamydial infection (Moodley *et al*, 2003b; Rustomjee *et al*, 2002) and trichomoniasis (Moodley *et al*, 2003b). In the cases of bacterial vaginosis and vulvovaginal candidiasis, separate parameters determine the probability of ‘complete cure’ and ‘partial cure’. For bacterial vaginosis, ‘complete cure’ is defined as having normal vaginal flora after treatment and ‘partial cure’ is defined as having intermediate vaginal flora. The rates of cure are set on the basis of a study of pregnant women with bacterial vaginosis, of whom 22% still had bacterial vaginosis and 60% had normal vaginal flora two to four weeks after receiving metronidazole treatment (Klebanoff *et al*, 2004). In the case of vulvovaginal candidiasis, ‘complete cure’ is defined as resolution of both symptoms and yeast infection after treatment, and ‘partial cure’ is defined as resolution of symptoms without clearance of yeast infection. The effectiveness parameters are based on a number of studies of the effectiveness of antifungal treatment (del Palacio *et al*, 2000; Brown *et al*, 1986; El-Din *et al*, 2001). Treatment provided by traditional healers is assumed not to be effective for any of the STIs.

Table 3.3.14: Assumed effectiveness of treatment

Parameter	HSV-2	TP	HD	NG	CT	TV	BV	VC
% cases correctly treated before SM (std dev.)	0%	70% (10%)	50%	70% (10%)	70% (10%)	40% (15%)	40% (15%)	50% (20%)
% cases treated under SM								
Male	0%	100%	100%	100%	100%	50%	-	-
Female	0%	100%	100%	100%	100%	100%	100%	50% ^a
Probability of cure if effective drugs prescribed	0.90	0.90	0.90	0.90	0.90	0.90	0.60 ^b 0.20 ^c	0.55 ^b 0.30 ^c
Probability of cure if treated by traditional healer	0	0	0	0	0	0	0	0

BV = bacterial vaginosis. CT = *Chlamydia trachomatis* (chlamydial infection). HD = *Haemophilus ducreyi* (chancroid). NG = *Neisseria gonorrhoeae* (gonorrhoea). SM = syndromic management. TP = *Treponema pallidum* (syphilis). TV = *Trichomonas vaginalis* (trichomoniasis). VC = vaginal candidiasis

^a The value is the same as that simulated to represent practice pre-SM. ^b Complete cure. ^c Partial cure.

Symptoms that occur during secondary syphilis are extremely variable, and do not correspond to any particular syndromic management protocol. It is therefore assumed

that the individuals who seek treatment for secondary syphilis are only half as likely to be cured as the individuals who seek treatment for primary syphilis.

3.3.4.4 Treatment of asymptomatic infection

The model does not allow for treatment of asymptomatic STIs, except in two special cases: antenatal screening for syphilis and treatment of STIs in sex workers.

The rates at which women are screened for syphilis are determined by their fertility rates, i.e. the rates at which women are screened for syphilis are assumed to be proportional to their age-specific fertility rates. South African studies suggest that on average around 75% of pregnant women receive screening for syphilis, though rates are extremely variable (Jackson *et al*, 2007; Dawadi *et al*, 2001; Searle *et al*, 2003). Of those women who are screened for syphilis and test positive, the proportion who receive treatment varies between 57% and 96% (Bam *et al*, 1994; Swingler and van Coeverden de Groot 1993; Wilkinson and Sach 1998; Myer *et al*, 2003; Dawadi *et al*, 2001). It is assumed that the proportion of pregnant women who are screened is 75% and the proportion of those testing positive who receive treatment is 80%. As is the case for treated symptomatic syphilis, treatment is assumed to be effective in 90% of cases. The rate at which women are cured of syphilis through antenatal screening is therefore 54% ($75\% \times 80\% \times 90\%$) of their age-specific fertility rate.

Because sex workers are highly exposed to STIs, they are likely to seek treatment for STIs at a much higher frequency than the rest of the population. It is therefore realistic to assume that asymptomatic STIs in sex workers would resolve more rapidly than asymptomatic STIs in other women, due to frequent receipt of treatment for other symptomatic STIs, which will in some cases be effective against the asymptomatic STI. Studies of sex workers in other African countries suggest that between 5% and 17% of sex workers seek STI treatment every month (Morison *et al*, 2001). On the basis of this evidence, it is assumed that asymptomatic STIs in sex workers are treated at a rate of 0.025 per week. Since this treatment is not directed specifically at the asymptomatic STI, the probability of cure is assumed to be only half of that for symptomatic STIs.

3.4 Programming

The model was initially programmed in Excel/VBA. As this model was too slow for the purpose of the Bayesian uncertainty analysis, it was reprogrammed in Visual C++ .NET. A reconciliation of the C++ and Excel models was performed, by projecting both models for 40 years and comparing 27 arbitrarily chosen model outputs at the end of this projection period. The largest difference in outputs was 0.012%, which is likely to be due to rounding differences between Excel and C++.

For the purpose of the uncertainty analysis, two libraries of C++ functions were copied into the C++ code. The DCDFLIB library (downloaded on 4 March 2005 from http://www.csit.fsu.edu/~burkardt/cpp_src/dcdflib/dcdflib.html) is used for its statistical functions, notably the cumulative beta and gamma distributions. The 'randomc' library (downloaded from <http://www.agner.org/random/randomc.htm> on 3 May 2005) is used to generate random numbers from the uniform (0,1) distribution. The 'Mersenne Twister' random number generator is used for this purpose.

3.5 Strengths and limitations

The model presented here follows a deterministic frequency-dependent approach to sexual behaviour and STI transmission. Although the pair-formation approach might be more realistic (Eames and Keeling 2002; Lloyd-Smith *et al*, 2004), a pair-formation approach would probably not be computationally feasible when attempting to model interactions between HIV and other STIs. For example, if one were to model gonorrhoea using a four-state process and HIV using a six-state process in a very simple two-sex model, the total number of cohorts one would need to define in a frequency-dependent model would be $4 \times 6 = 24$ for each sex, i.e. 48 in total. Using a pair-formation approach, however, one would need to define couple cohorts for all possible permutations of HIV and gonorrhoea infections states in both partners, i.e. 24×24 couple cohorts, plus 24 cohorts for single individuals of both sexes – a total of 624 cohorts. Extending the standard pair-formation model to allow for concurrency

would require an even greater number of cohorts (Ferguson and Garnett 2000; Bauch and Rand 2000; Eames and Keeling 2004), which would clearly not be feasible.

The model presented here avoids the serial monogamy assumption implicit in most frequency-dependent models. In addition to stratifying the population on the basis of rates of partnership formation (the conventional approach in frequency-dependent models), the model stratifies the population on the basis of the actual number of current partners, the risk groups of partners and the nature of partnerships (spousal/non-spousal), allowing individuals to move between these strata as they form new partnerships, marry and separate. This more realistic approach has several advantages over the approach conventionally adopted in deterministic models. Firstly, it allows a more detailed assessment of which sexual behaviours are contributing most to the spread of HIV and other STIs, and which forms of behaviour change would have the greatest impact. Secondly, sexual behaviour data can be used to determine model parameters more reliably. STI models have typically been calibrated to retrospective data on numbers of partners over some past period (Merli *et al*, 2006; Korenromp *et al*, 2000b; Garnett *et al*, 1999), whereas our model is calibrated to data on current numbers of partners. These data are arguably more important than retrospective data because they provide information on the extent of concurrent partnerships, which are considered to be particularly important drivers of HIV transmission (Halperin and Epstein 2004). Retrospective data are affected by recall bias, and since most surveys ask respondents about the number of partners they have had in the last year, rather than the number of *new* partners in the last year, they provide little information on the rate at which new partnerships are formed.

Relatively few previously developed deterministic models allow for the distinction between spousal and non-spousal relationships. Sexual behaviour data such as coital frequency and condom usage are often reported separately for married and unmarried individuals (Kelly 2000; Department of Health 1999; Meekers and Van Rossem 2005), and a model that distinguishes between spousal and non-spousal relationships is capable of incorporating such data more accurately. Our model also assumes that spousal and non-spousal relationships differ significantly in their rate of formation, their duration and in the rate at which additional partners are acquired.

Although the model of sexual behaviour is relatively detailed, a number of important simplifications have been necessary in the interests of computational speed. It is assumed that no individual ever has more than two current sexual partners. Although qualitative studies suggest that it is not uncommon for individuals to have more than two current partners (Parker *et al*, 2007; Varga 1997b; Twa-Twa *et al*, 1997), a recent survey in Botswana suggests that the proportion of individuals with more than two current partners is only about 1% (Carter *et al*, 2007). This suggests that extending the model to allow for more than two current partners would not change the results substantially. Another simplification is the broad division of the population into two risk groups: those with a propensity for concurrent partnerships and those who never engage in concurrent partnerships. In reality there is likely to be much greater heterogeneity; some 'high risk' individuals may be involved in multiple partnerships for short periods of time on an irregular basis, while others may be inclined towards longer-term concurrency. Similarly, some 'low risk' individuals may be inclined towards long periods of sexual abstinence, while others may be sexually active almost all the time, with relatively short gaps between partnerships. Another limitation of our model is that it does not allow for 'casual sex'; although the model allows for non-spousal relationships and sex between commercial sex workers and clients, once-off sexual encounters that do not involve exchange of money are arguably a different type of sexual activity. Qualitative studies suggest that casual sex is common in South Africa (Parker *et al*, 2007; Harrison *et al*, 1997), but there is a lack of quantitative data to support this. It may be possible to extend the model to allow for casual sex if better data become available in future.

There is also substantial uncertainty regarding several of the sexual behaviour parameters. For example, there is little information on sexual behaviour at older ages, as most studies report on sexual activity in the 15 to 49 age range. Another set of parameters about which there is substantial uncertainty is the commercial sex assumptions. Most of the studies on which the sex worker activity assumptions are based have been conducted in urban areas or on highways, and the assumed frequency of client contact would probably not be appropriate for women who exchange sex for money in more remote rural areas or women who engage in transactional sex on an infrequent basis (Peltzer *et al*, 2004). The model parameterization is therefore based on a fairly narrow definition of commercial sex workers, i.e. women who earn all or

most of their income by having sex in exchange for money. Alternative definitions of commercial sex could yield very different estimates of the prevalence of commercial sex activity and the behaviour of commercial sex workers (Morison *et al*, 2001).

A further limitation of our sexual behaviour model is that age of partner preferences are assumed to be independent of risk group preferences, and in addition, age of partner preferences are not dynamically updated. This implies that changes in the relative sizes of different age groups (as a result of demographic change and the effect of AIDS mortality) do not change the distribution of partner ages over time, in any given age group. More sophisticated approaches to modelling dependency between age mixing and risk group mixing, allowing for dynamic updating, have been proposed in several modelling studies (Garnett and Anderson 1993; Hallett *et al*, 2007; Pourbohloul *et al*, 2003). However, model results are generally not very sensitive to the assumed form of age mixing (Hallett *et al*, 2007; Garnett and Anderson 1993), and it is therefore unlikely that a more sophisticated approach would change our results substantially.

In spite of the sophistication of the model of sexual behaviour, the modelling of STI transmission is fairly simple. For a susceptible individual in a given cohort, the probability of acquiring infection over a small time interval is assumed to depend on the prevalence of infection in the cohort of individuals of the opposite sex with the corresponding risk group, partnership type and partner risk group. This means that the infection probabilities of individuals and their partners are assumed to be independent, *conditional upon* the risk groups of both partners, the nature of the relationship and the numbers of other partners each partner has. This assumption may be unrealistic, particularly for STIs with high transmission probabilities, in the context of partnerships involving frequent unprotected sex. It has therefore been assumed that there is no transmission of bacterial/protozoan STIs in mutually monogamous spousal relationships (effectively, it is assumed that if transmission hasn't occurred in the interval between partnership formation and marriage, it wouldn't occur after marriage). The assumption of conditional independence could be justified in non-spousal relationships if these are characterized by relatively low coital frequency and high rates of condom usage (Meekers and Van Rossem 2005). Ultimately, though, the appropriateness of the conditional independence assumption needs to be tested by

comparing the deterministic model described here with a more realistic microsimulation model with the same parameter values.

As noted in section 3.1, STIs other than HIV are modelled independently of one another, so that in any given individual, the probability of infection with a particular STI is assumed to be independent of any other STIs they may have, after controlling for the individual's age, sex, sexual activity state and HIV stage. This is achieved by modelling the change in the proportion of individuals in each infection state, for a given demographic/behavioural/HIV cohort, separately for each STI. This assumption of independence is made in order to reduce the amount of computation and memory required. For example, if one was to model interactions between syphilis, genital herpes and chancroid (seven-state, five-state and four-state processes respectively), it would be necessary to consider all possible permutations of infection states – a total of $7 \times 5 \times 4 = 140$ calculations. Modelling the three STIs independently would require only $7 + 5 + 4 = 16$ calculations. However, the assumption of independence is not completely realistic. For example, many studies have noted the strong positive associations that exist between bacterial vaginosis and trichomoniasis, even after adjusting for confounding behavioural factors (Bukusi *et al*, 2006; Jamieson *et al*, 2001; Cu-Uvin *et al*, 2002). This may be due to their common treatment (metronidazole) or the effect of bacterial vaginosis-associated changes in lactobacilli on susceptibility to trichomoniasis (Hillier *et al*, 1992a; Martin *et al*, 1999; Hesselstine *et al*, 1942). Studies have also noted significant *negative* associations between vaginal candidiasis and bacterial vaginosis (Eckert *et al*, 1998; Jamieson *et al*, 2001; Hillier *et al*, 1992b). These interactions are not allowed for in the model, but could be considered in future modelling work.

There exists much uncertainty regarding the STI natural history parameters. In addition to the problem of lack of evidence, there is much uncertainty regarding the applicability of the available evidence. For example, most of the published studies on the natural history of genital herpes are from Seattle, U.S.A., and there are relatively few studies from developing countries. Infection with HSV-1 appears to provide some protection against symptoms in incident HSV-2 (Stanberry *et al*, 2002) and chronic HSV-2 (Koutsky *et al*, 1990), and since the prevalence of HSV-1 is substantially

higher in Africa than in industrialized nations, HSV-2 symptoms may tend to be milder in the African setting than the available evidence suggests. Another example is primary syphilis: the experience in industrialized nations is that primary syphilis is characterized by a single, painless ulcer. South African studies, however, have found that between 36 and 75% of primary syphilis cases involve multiple ulcers, many of which are painful (Coovadia *et al*, 1985; Duncan *et al*, 1984; Duncan *et al*, 1981; Crewe-Brown *et al*, 1982). In view of the uncertainty regarding the natural history parameters, Bayesian techniques that allow for *a priori* specification of uncertainty regarding model parameters are particularly appropriate.

The model has very substantial computational requirements. The sexually experienced population is divided into 16 age groups, with 17 sexual activity states for males and 18 sexual activity states for females, and 6 HIV states considered within each subgroup, i.e. a total of $16 \times (17 + 18) \times 6 = 3\,360$ possible states. Within each state, we calculate the proportion of individuals in each STI state, separately for 6 different infections in males and 8 different infections in females, at weekly intervals. This is clearly very computationally demanding. When the model was first programmed in Excel/VBA, it took approximately 10 hours to run a 20-year projection on a Pentium 4 with 2 GB of RAM and 2.8 GHz CPU. After reprogramming the model in Visual C++, the time taken to run a 20-year projection was reduced to approximately 10 seconds. However, even at 10 seconds per run, it is not feasible to conduct a Bayesian analysis of all sources of uncertainty simultaneously (the analysis in section 4.1, for example, shows that even when only 12 of the HIV and sexual behaviour parameters are considered, 100 000 simulations are required to achieve convergence). We therefore conduct separate Bayesian analyses of different groups of parameters, holding other parameters constant at their baseline level or at the levels estimated in previous analyses. It is possible to reduce run times by switching off the modelling of STIs other than HIV, or by modelling only one STI in addition to HIV, if the effect of STIs on HIV transmission probabilities is ignored. This is the approach taken in chapter 4, where we first conduct a Bayesian analysis of the HIV and sexual behaviour parameters, ignoring other STIs, and then conduct separate Bayesian analyses for each STI. The effect of STIs on HIV transmission probabilities is then considered in chapter 5.

Chapter 4: Estimation of HIV and STI prevalence levels in South Africa

This chapter describes the Bayesian techniques used to fit the previously described model to the South African HIV and STI prevalence data and sexual behaviour data. In addition to showing the resulting predictions of HIV and STI prevalence levels, this chapter compares prior and posterior estimates of parameters and assesses the correspondence between the model predictions and the survey estimates. Section 4.1 describes the method used to estimate HIV prevalence, while section 4.2 describes the method used in respect of other STIs. Section 4.3 considers alternative models of immunity to STIs, and this is followed by a discussion of the results.

4.1 Fitting the model to HIV prevalence data and sexual behaviour data

The objective of the initial Bayesian analysis is to identify the sexual behaviour parameters and HIV parameters that give the best fit to the HIV prevalence data and sexual behaviour data collected in South Africa, before allowing for the effects of other STIs on HIV transmission probabilities. Other STIs are initially excluded because the addition of other STIs into the model introduces many new sources of uncertainty, and it is not practical to consider all sources of uncertainty simultaneously. The sections below describe the method used to define the priors and the likelihood function and the method used to compute the posterior distribution. This is followed by the results of the Bayesian analysis: a comparison of the prior and posterior distributions, and a comparison of the model predictions with the corresponding survey estimates.

4.1.1 Prior distributions

Twelve parameters are included in the initial Bayesian analysis. With the exception of the initial HIV prevalence (discussed below), all of these parameters have been previously explained and the prior distributions assigned to these parameters have

been specified (see sections 3.2.2, 3.2.6 and 3.3.2.1). For ease of reference, the prior distributions for all 12 parameters are repeated in Table 4.1.1 below.

Table 4.1.1: Prior distributions for HIV and sexual behaviour parameters

Parameter	Prior distribution	Prior mean, std deviation
Male-to-female transmission probability in short-term relationships	Beta (5.68, 467.6)	0.012, 0.005
Male-to-female transmission probability in spousal relationships	Beta (3.99, 1991)	0.002, 0.001
Female-to-male transmission probability in short-term relationships	Beta (10.99, 1088)	0.01, 0.003
Female-to-male transmission probability in spousal relationships	Beta (3.99, 1991)	0.002, 0.001
Initial HIV prevalence in high risk group	Uniform (0, 0.002)	0.001, 0.00058
Degree of sexual mixing (ϵ)	Beta (5.8, 3.867)	0.6, 0.15
Ratio of desired partner acquisition rate in high risk males with 1 short-term partner to that in single high risk males	Uniform (0, 1)	0.50, 0.29
Ratio of desired partner acquisition rate in high risk females with 1 short-term partner to that in single high risk females	Uniform (0, 1)	0.50, 0.29
Ratio of desired partner acquisition rate in high risk males with 1 spousal partner to that in single high risk males	Uniform (0, 1)	0.50, 0.29
Ratio of desired partner acquisition rate in high risk females with 1 spousal partner to that in single high risk females	Uniform (0, 1)	0.50, 0.29
Ratio of desired partner acquisition rate in single low risk males to that in single high risk males	Uniform (0, 1)	0.50, 0.29
Ratio of desired partner acquisition rate in single low risk females to that in single high risk females	Uniform (0, 1)	0.50, 0.29

The HIV/AIDS epidemic in South Africa is ‘started’ by assuming a low initial prevalence of HIV in all individuals in the high risk group in the 15-49 age range in 1985 (in all other age groups and in the low risk group, the initial HIV prevalence is assumed to be 0). Surveys conducted between 1985 and 1987 found no evidence of HIV in the general population (Abdool Karim and Abdool Karim 1992; Hoosen *et al*, 1989; O’Farrell *et al*, 1989), and in an early survey of 56 sex workers and 195 STI clinic attenders, only one HIV case was identified (Schoub *et al*, 1987). Considering that the HIV prevalence in the first national antenatal clinic survey in 1990 was 0.76%

and this grew by a multiple of 1.8 in each of the next two years (Küstner *et al*, 1994), it is unlikely that HIV prevalence in pregnant women in 1985 would have been more than 0.04% (0.0076×1.8^{-5}), since the early antenatal surveys were biased towards urban areas in which HIV prevalence was relatively high. Assuming that 25% of pregnant women were in the high risk group (in line with the model assumption), the prevalence of HIV in these high risk women would therefore probably have been less than 0.16%. The initial HIV prevalence in the 15-49 high risk group has therefore been assigned a uniform (0, 0.002) prior.

4.1.2 Likelihood formulation

In the initial uncertainty analysis, three data sources are considered in defining the likelihood function: HIV prevalence data from the national antenatal clinic surveys, HIV prevalence data from the 2005 HSRC household survey, and sexual behaviour data from the 2005 HSRC household survey. The formulation of the likelihood in respect of each of these data sources is described in the sections that follow.

(a) Antenatal clinic data

Suppose that $H_{x,t}(\boldsymbol{\phi})$ represents the prevalence of HIV that we would expect to measure in pregnant women aged x to $x + 4$, in year t , based on the model predictions when the input parameters are represented by vector $\boldsymbol{\phi}$. Further suppose that the corresponding prevalence of HIV measured in the survey is $\zeta_{x,t}$. It is assumed that if $\boldsymbol{\phi}$ is the true set of parameter values, then the difference between the logit-transformed model prediction and the logit-transformed observed prevalence is normally distributed. The mean of this normal distribution represents the extent of antenatal bias. The variance of the distribution is assumed to be composed of a ‘survey error’ term, representing the uncertainty around the survey estimate due to binomial variation and cluster variation in the survey, and a ‘model error’ term. The latter term is included in many analyses (e.g. Sevcikova *et al* (2006) and Raftery *et al* (2003)) to represent differences between true population means and model predictions that can be attributed to sources of variation not allowed for in the model (as distinct

from differences due to choice of model parameters). More formally, it is assumed that

$$\log\left(\frac{\zeta_{x,t}}{1-\zeta_{x,t}}\right) = \log\left(\frac{H_{x,t}(\boldsymbol{\varphi})}{1-H_{x,t}(\boldsymbol{\varphi})}\right) + b + \varpi_{x,t} + \varepsilon_{x,t}, \quad (4.1)$$

where b is the antenatal bias parameter, $\varpi_{x,t} \sim N(0, \sigma_{\varpi}^2)$ and $\varepsilon_{x,t} \sim N(0, \sigma_{\varepsilon}^2)$. The latter two terms represent the model error and the survey error respectively. The logit transformations ensure that the error terms are closer to normality and the model error terms are roughly independent of the level of HIV prevalence. For a given parameter combination $\boldsymbol{\varphi}$, the antenatal bias parameter is estimated using the formula

$$\hat{b} = \frac{1}{Y} \sum_x \sum_t \left(\log\left(\frac{\zeta_{x,t}}{1-\zeta_{x,t}}\right) - \log\left(\frac{H_{x,t}(\boldsymbol{\varphi})}{1-H_{x,t}(\boldsymbol{\varphi})}\right) \right), \quad (4.2)$$

where Y is the number of antenatal prevalence estimates to which the model is calibrated. The σ_{ε}^2 values are estimated from the 95% confidence intervals that have been published for the various survey estimates. Once these have been obtained, the σ_{ϖ}^2 parameter is estimated using the formula

$$\hat{\sigma}_{\varpi}^2 = \frac{1}{Y} \sum_x \sum_t \left(\log\left(\frac{\zeta_{x,t}}{1-\zeta_{x,t}}\right) - \log\left(\frac{H_{x,t}(\boldsymbol{\varphi})}{1-H_{x,t}(\boldsymbol{\varphi})}\right) - \hat{b} \right)^2 - \sigma_{\varepsilon}^2. \quad (4.3)$$

The likelihood in respect of observation $\zeta_{x,t}$ is then calculated based on the assumption that the error terms are normally distributed:

$$L(\zeta_{x,t} | \boldsymbol{\varphi}) = \frac{\exp\left[-\frac{(\text{logit}(\zeta_{x,t}) - \text{logit}(H_{x,t}(\boldsymbol{\varphi})) - \hat{b})^2}{2(\hat{\sigma}_{\varpi}^2 + \sigma_{\varepsilon}^2)}\right]}{\sqrt{2\pi(\hat{\sigma}_{\varpi}^2 + \sigma_{\varepsilon}^2)}}. \quad (4.4)$$

The aggregate likelihood for the antenatal clinic data is then calculated by taking the product of the $L(\zeta_{x,t} | \phi)$ values across age bands 15-19 to 35-39, and across calendar years 1997 to 2005. Antenatal survey data collected prior to 1997 and after 2005 were not included, as these were obtained using different survey protocols, and are therefore (potentially) subject to different levels of antenatal bias. Prior to 1997, for example, the antenatal surveys were biased towards antenatal clinics in urban areas (Abdool Karim *et al*, 1997; Webb 1994), which may have led to some over-estimation of HIV prevalence in pregnant women generally. Confirmatory HIV testing was also discontinued after the 1996 survey (Department of Health 1997; Department of Health 1998), which may have led to a change in bias due to false positive reactions on ELISA tests. Another reason for excluding the antenatal data collected prior to 1997 is that the 95% confidence intervals around the published prevalence estimates did not take into account the clustering in the survey design (Department of Health 1997), and the $\sigma_{x,t}^2$ values therefore cannot be reliably determined from the published estimates.

(b) *HSRC prevalence data*

The approach to defining the likelihood function is the same as for the antenatal data, except that the bias term (b) and model error term (ϖ) are both omitted. The model error term is omitted because the 95% confidence intervals around the HIV prevalence estimates are very wide, and introducing a model error term therefore reduces the weight given to the HSRC data to unreasonably low levels. The omission of the bias term is consistent with the approach adopted in other uncertainty analyses of HIV data in developing countries (Morgan *et al*, 2006), in which it is assumed that household prevalence data provide an unbiased estimate of HIV prevalence in the general population. The plausibility of this assumption is questionable in the case of the 2002 HSRC household survey, which had a low response rate (71% of households visited were interviewed and 58% of eligible individuals agreed to be tested) and did not include confirmatory HIV testing (Human Sciences Research Council 2002). The 2005 HSRC survey, on the other hand, achieved a higher rate of response (84% of households visited were interviewed and 65% of eligible individuals agreed to be tested), and included confirmatory testing of all specimens that were initially reactive

(Shisana *et al*, 2005). The present analysis is therefore based only on the data collected in the 2005 household survey, and the 2002 data are not considered in defining the likelihood function. The likelihood is calculated separately for males and females, for each age band from 15-19 up to 55-59.

(c) *Sexual behaviour data*

Three types of sexual behaviour data are incorporated in the uncertainty analysis:

- Proportions of sexually experienced unmarried individuals who report more than one current sexual partner,
- Proportions of sexually experienced married individuals who report more than one current sexual partner, and
- Proportions of sexually experienced unmarried individuals who report no current partner.

The data were collected in face-to-face interviews (FTFIs) during the 2005 HSRC household survey, and the proportions (together with 95% confidence intervals) have been calculated separately for males and females, for each of five age groups (15-24, 25-34, 35-44, 45-59 and 60+)⁴. The method used to define the likelihood is similar to that used to define the antenatal likelihood function: the difference between the logit-transformed survey proportion and the logit-transformed model estimate is assumed to be comprised of a bias term and a survey error term. However, there is no model error term, as the 95% confidence intervals around the reported proportions are wide enough to include most model predictions, once adjusted for bias.

As with the other data sources, the variance of the survey error term is estimated from the 95% confidence interval around the reported proportion. The bias terms have been estimated separately for each sex and for each of the three types of sexual behaviour data, using a formula analogous to that in equation (4.2).

⁴ Data were kindly provided by Victoria Pillay-Van Wyk of the Human Sciences Research Council.

4.1.3 Posterior simulation

The posterior density cannot be evaluated analytically, since it is necessary to run the model in order to obtain the likelihood for a single set of ϕ values. The posterior density is therefore simulated numerically using the Metropolis algorithm, a Markov Chain Monte Carlo technique that is commonly used in Bayesian analysis (Gelman *et al.*, 2004). The steps listed below follow closely those recommended by Gelman and colleagues:

1. An initial sample of 1 000 parameter combinations was drawn from the prior distributions described in 4.1.1, the likelihood was calculated for each parameter combination, and ten parameter combinations were sampled (without replacement) from the initial set of 1 000 combinations, using the likelihood functions as weights. This sample of 10 parameter combinations was used to determine the starting points for ten sequences (Markov chains).
2. For each sequence and for each step of the iteration, an alternative parameter combination was proposed by sampling from a jumping distribution with the same mean as the previous parameter combination in the sequence. All parameters were logit-transformed so that the jumping distribution could be assumed to take the form of a multivariate normal distribution. The posterior value (the product of the likelihood and the prior) was calculated for the proposed parameter combination and compared to that of the previous parameter combination in the sequence. If the posterior value of the new parameter combination was greater than that of the old, it was accepted as the next parameter combination in the sequence. If not, it was accepted with probability proportional to the ratio of its posterior value to that of the posterior value of the previous parameter combination. If the proposed parameter combination was rejected, the parameter combination for the iteration was set equal to that for the previous iteration.
3. The covariance matrix of the jumping distribution was updated at regular intervals, (a) to ensure that the acceptance rate lay between 0.1 and 0.4, and (b) to ensure that correlations between parameters were adequately reflected. At every 25th iteration, all covariance terms were multiplied by 4 if the

acceptance rate (calculated for all ten sequences) was above 0.4, and were multiplied by 0.25 if the acceptance rate was below 0.1. This continued until the 2000th iteration. At every 200th iteration, the covariance matrix was recalculated from the latter half of the iterations up to that point (for all ten sequences combined), and multiplied by the covariance scaling factor of $2.4^2/12$. This continued until the 1400th iteration. These adjustments to the jumping distribution improve the efficiency of the algorithm and are acceptable as long as they are confined to the burn-in phase of the algorithm.

4. A total of 10 000 iterations were performed for each sequence, and convergence over the last half of the iterations was checked. The parameter combinations generated over the burn-in phase (the first 5 000 iterations of each sequence) were discarded, and the remaining iterations were thinned by drawing every 50th parameter combination. This yielded a posterior sample of 1 000 parameter combinations.

Convergence of the Metropolis algorithm is generally considered to have been reached when the scale reduction factor \hat{R} (a function of the ratio of the variation between sequences to the average variation within sequences) is below the threshold 1.1, for each of the parameters of interest (on the transformed scale) and for the log-transformed posterior values. Table 4.1.2 shows that this convergence criterion has been satisfied, and the parameter combinations sampled therefore provide a good approximation to the posterior distribution.

Table 4.1.2: Scale reduction factors calculated for the last 5 000 iterations

Parameter	\hat{R}
Posterior value	1.0313
Male-to-female transmission probability in short-term relationships	1.0072
Male-to-female transmission probability in mutually monogamous spousal relationships	1.0096
Female-to-male transmission probability in short-term relationships	1.0090
Female-to-male transmission probability in mutually monogamous spousal relationships	1.0038
Initial HIV prevalence in high risk group	1.0271
Degree of sexual mixing (ϵ)	1.0277
Ratio of partner acquisition rate in high risk males with 1 short-term partner to that in single high risk males	1.0122
Ratio of partner acquisition rate in high risk females with 1 short-term partner to that in single high risk females	1.0152
Ratio of partner acquisition rate in high risk males with 1 spousal partner to that in single high risk males	1.0105
Ratio of partner acquisition rate in high risk females with 1 spousal partner to that in single high risk females	1.0081
Ratio of partner acquisition rate in single low risk males to that in single high risk males	1.0105
Ratio of partner acquisition rate in single low risk females to that in single high risk females	1.0190

4.1.4 Comparison of prior and posterior distributions

Prior and posterior distributions for the probabilities of HIV transmission per sex act are compared in Figure 4.1.1. The prior and posterior distributions are reasonably similar in the case of the HIV transmission probabilities in spousal relationships, but are very different in the context of non-spousal relationships. For both male-to-female and female-to-male transmission, the posterior mean transmission probability in non-spousal relationships is substantially lower than the prior mean.

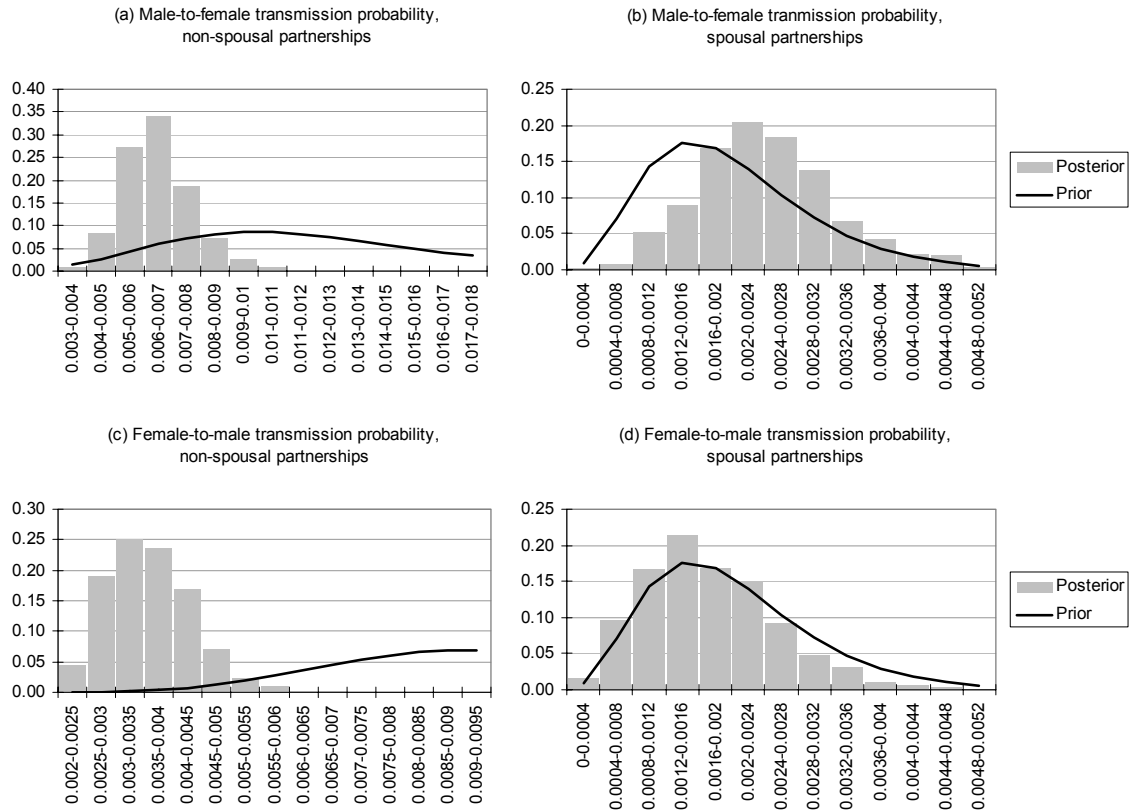


Figure 4.1.1: Prior and posterior distributions for HIV transmission probabilities (per sex act)

Prior distributions have been scaled to be comparable with posterior histogram plots.

The posterior distribution for the initial proportion of the high risk group that is HIV-positive is compared with the corresponding uniform prior in Figure 4.1.2(a). The data suggest that the initial prevalence of HIV in the high risk group is close to 0.2%. The posterior distribution for the sexual mixing parameter is similar to the prior distribution, as shown in Figure 4.1.2(b).

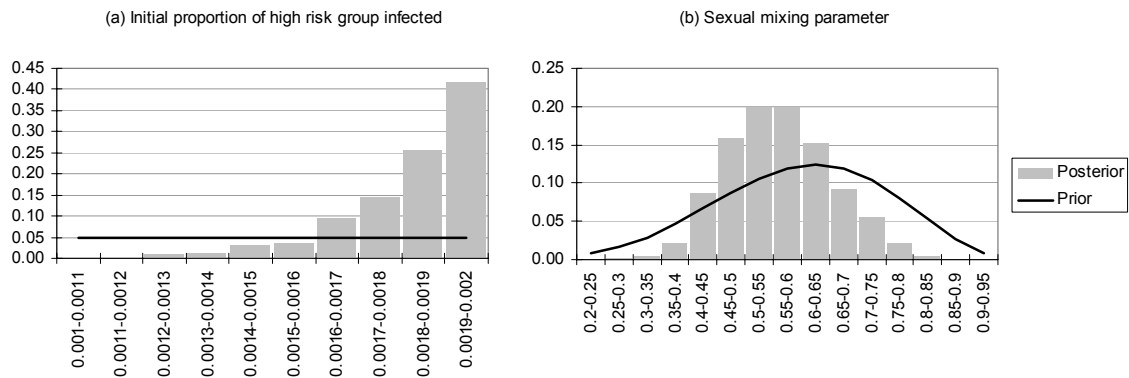


Figure 4.1.2: Prior and posterior distributions for initial HIV prevalence in high risk group and sexual mixing parameter

Prior distributions have been scaled to be comparable with posterior histogram plots.

Posterior distributions for the remaining sexual behaviour parameters are shown in Figure 4.1.3. The posterior distributions suggest that among high risk women, there is little reduction in the rate of partner acquisition if the woman is already in a non-spousal relationship, but there is a very substantial reduction in the rate of partner acquisition if the woman is in a spousal relationship. Women in the low risk group have a slightly lower rate of partner acquisition than their counterparts in the high risk group. Men in the low risk group, on the other hand, tend to have rates of partner acquisition substantially lower than those among men in the high risk group.

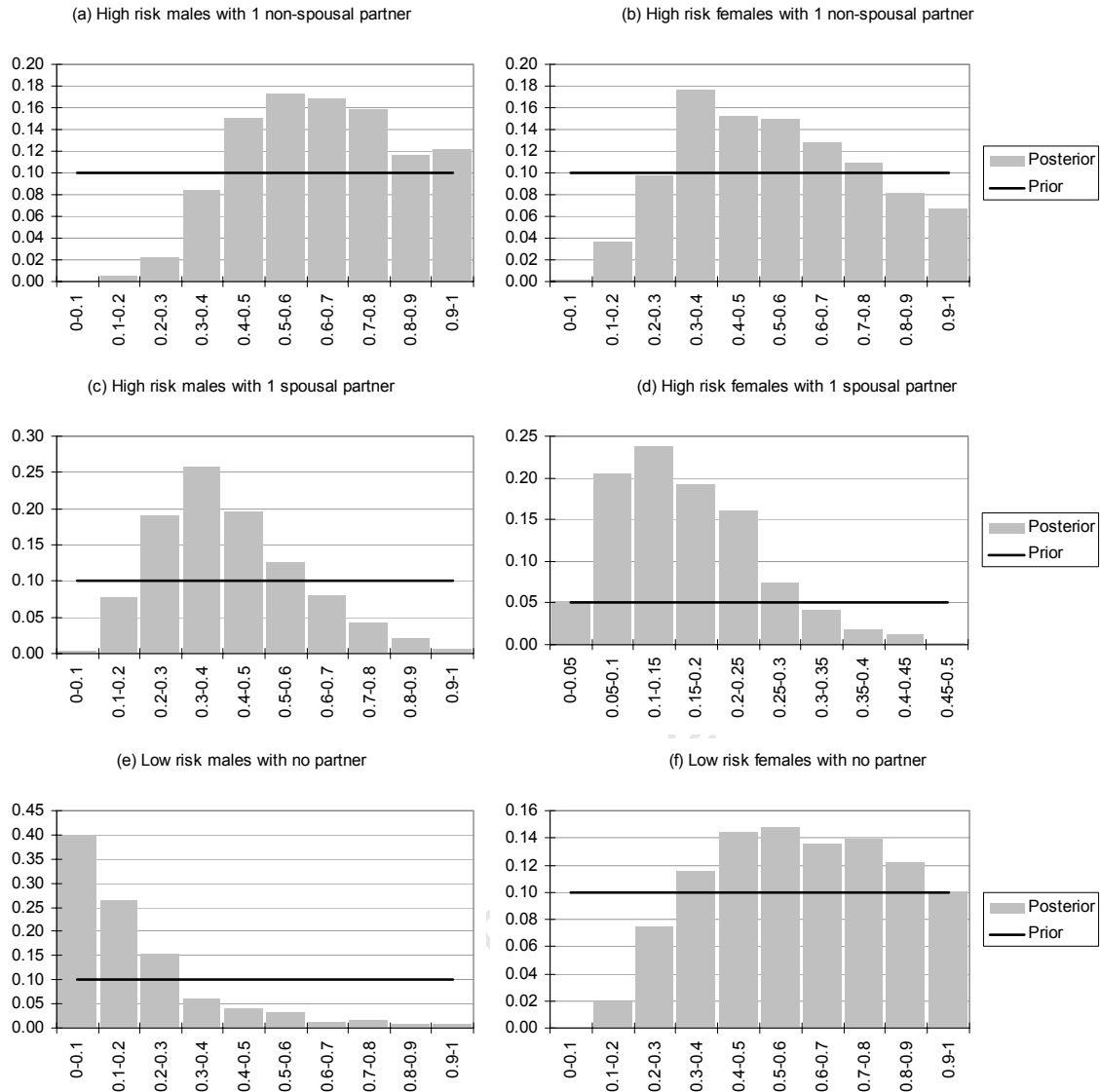


Figure 4.1.3: Prior and posterior distributions for rates of partner acquisition, expressed as a multiple of the corresponding rates in single high risk individuals. Prior distributions have been scaled to be comparable with posterior histogram plots.

4.1.5 Comparison of model predictions and survey estimates

Figure 4.1.4 compares the levels of HIV prevalence measured in the national antenatal clinic surveys with the corresponding posterior mean estimates of HIV prevalence in pregnant women. Following the approach of Sevcikova *et al* (2006), the posterior model estimates have been adjusted to reflect the antenatal bias. Although data from the 1990-1996 and 2006 surveys were not used in defining the likelihood function, they are compared with the corresponding posterior means in Figure 4.1.4(a). The

posterior means in 2006 and before 1997 should be interpreted as the antenatal prevalence that would be predicted *if* the antenatal bias in these years were the same as that over the 1997-2005 period. Although the change in antenatal bias is unknown, the model predictions are reasonably consistent with the survey estimates over these periods. Age-specific comparisons of posterior means and antenatal survey results (Figures 4.1.4(b)-(f)) show that a high proportion of model predictions lie outside of the published 95% confidence intervals, and it is for this reason that it is necessary to allow for model error terms when defining the likelihood function for the antenatal clinic data.

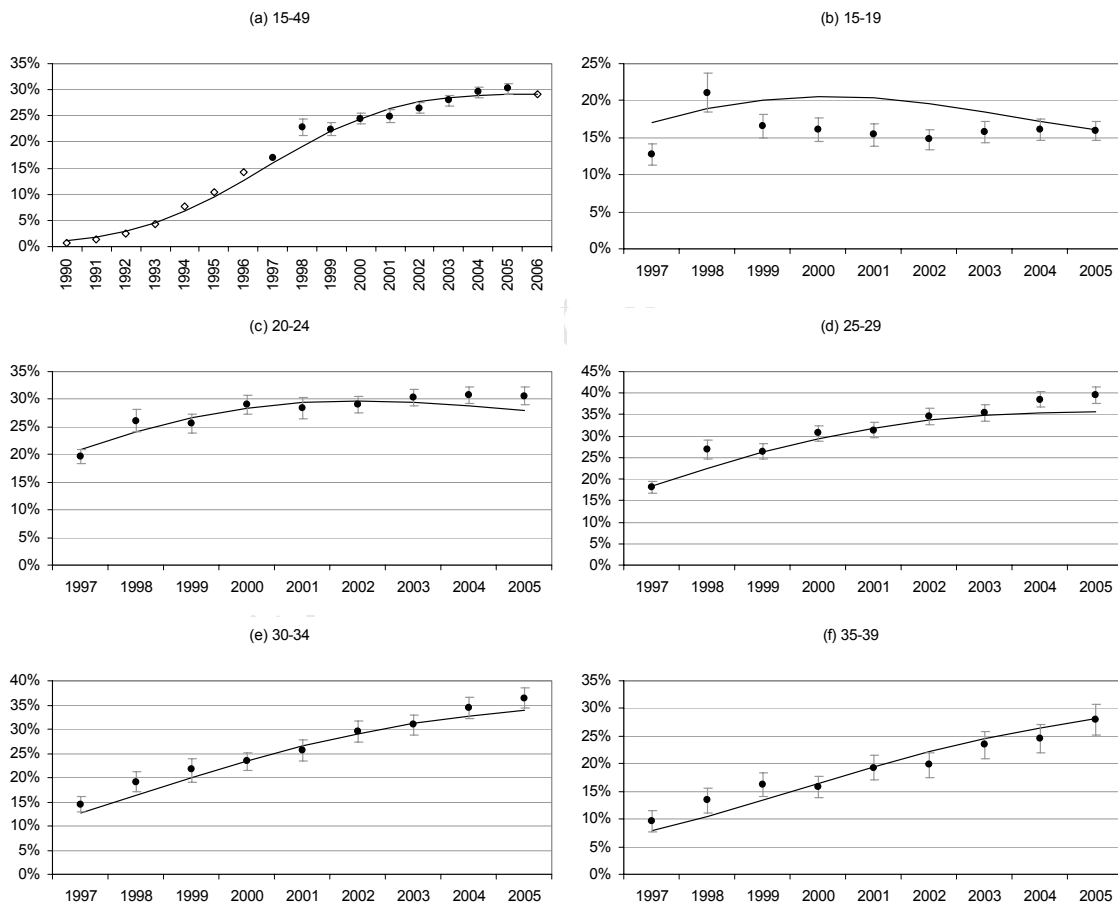


Figure 4.1.4: HIV prevalence in pregnant women attending public antenatal clinics

Reported prevalence levels represented by closed circles (with 95% confidence intervals) if used to define the likelihood function, or by open diamonds if not used in likelihood definition. Mean of posterior distribution represented by solid black line.

Figures 4.1.5(a) and (b) compare the HIV prevalence levels observed in the 2005 HSRC household survey with the corresponding 95% model predictions. The

posterior predictions are reasonably consistent with the survey results, both in males and females. Although the results of the 2002 HSRC household survey were not included in the definition of the likelihood, the posterior estimates for 2002 are compared with the 2002 survey results in Figures 4.1.5(c) and (d). The model predictions are reasonably consistent with the 2002 survey results. However, in both the 2002 and 2005 surveys, the prevalence of HIV among males aged 15 to 19 was estimated to be much higher than that predicted by the model.

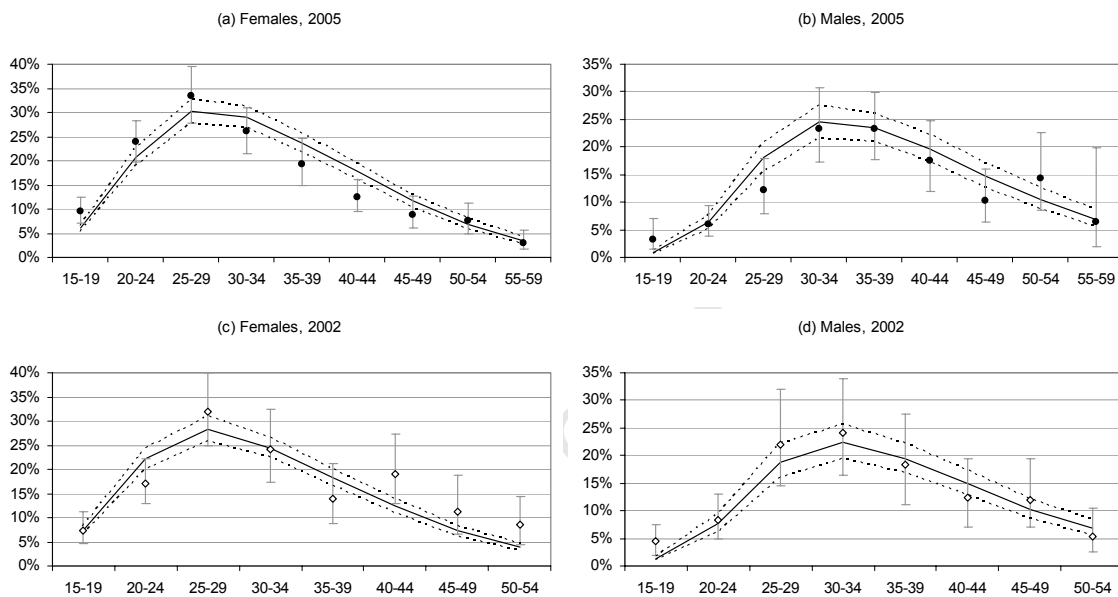


Figure 4.1.5: HIV prevalence in the general population

Reported prevalence levels represented by closed circles (with 95% confidence intervals) if used to define the likelihood function, or by open diamonds if not used in likelihood definition. Mean of posterior distribution represented by solid black line. 2.5 and 97.5 percentiles of posterior distribution (95% prediction intervals) represented by dashed lines.

The model HIV prevalence estimates are also validated by comparison with HIV prevalence estimates from the 2003 Reproductive Health Research Unit/loveLife youth survey (Fig 4.1.6(a)) and estimates of HIV prevalence in studies of commercial sex workers (Fig 4.1.6(b)). As with the 2002 and 2005 HSRC surveys, the RHRU survey measured a higher HIV prevalence among males aged 15 to 19 than predicted by the model. Model estimates of HIV prevalence in sex workers tend to be slightly higher than those measured in surveys, but most survey estimates are roughly consistent with the model predictions. The relatively low HIV prevalence in sex

workers measured by Leggett (2001), 43%, may be due to over-representation of non-African sex workers in this study.

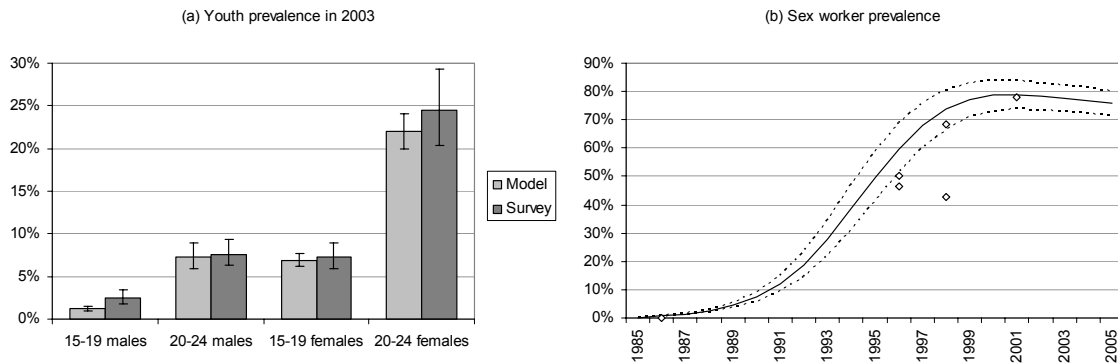


Figure 4.1.6: HIV prevalence among youth and sex workers

Survey estimates in panel (a) are from the 2003 RHRU/loveLife youth survey (Pettifor *et al*, 2005b), and survey estimates in panel (b) are from studies of sex workers (Schoub *et al*, 1987; Ramjee *et al*, 2005; Dunkle *et al*, 2005; Leggett 2001; Williams *et al*, 2000; Ndhlovu *et al*, 2005). In the second panel, posterior means are represented by the solid black line and 95% prediction intervals are represented by dashed lines. Open diamonds represent survey estimates.

Model predictions of proportions of individuals with more than one current partner or no current partner are compared with the corresponding results from the 2005 HSRC household survey in Figure 4.1.7. Only the means of the posterior distributions are shown, as the 95% prediction intervals are very narrow. The average posterior model estimates of proportions of individuals with different numbers of partners are reasonably consistent with the survey results, after adjusting for bias.

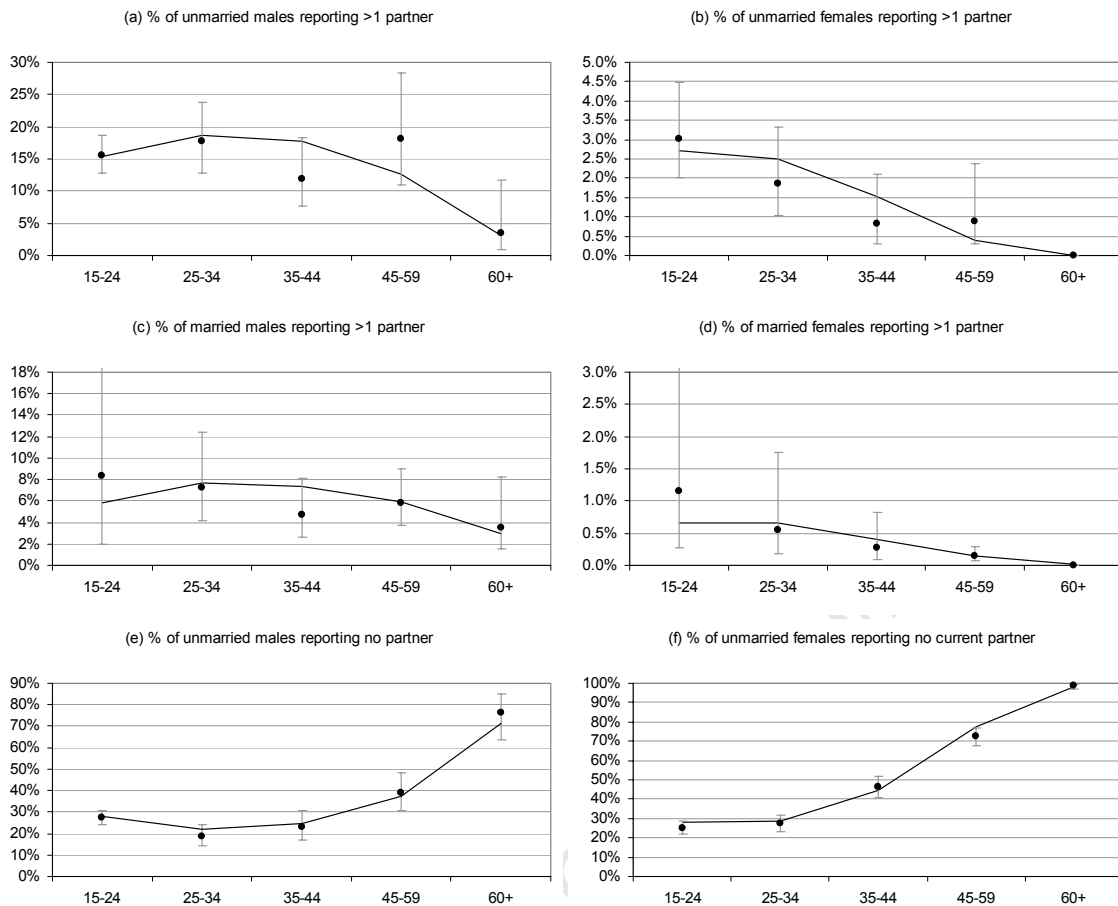


Figure 4.1.7: Sexual behaviour of sexually experienced individuals

Reported proportions represented by closed circles (with 95% confidence intervals). Mean of posterior distribution represented by solid black line.

Although marriage data have not been used in defining the likelihood function, it is useful to validate the model against survey estimates of proportions of individuals who are married or in cohabiting relationships. Figure 4.1.8 compares the model estimates of the proportions of the population in long-term relationships with the results from the 1996 census, 2001 census and 2007 community survey⁵. In all cases, the proportions compared are the proportions of individuals who are married *or* in cohabiting relationships. These posterior means are reasonably consistent with the proportions reported in the three surveys, although in the 1996 census the proportions of older women who reported being in spousal relationships were higher than estimated by the model. In addition, the proportions of individuals in spousal relationships in the 2007 community survey are lower than those predicted by the

⁵ Data were extracted from the survey datasets by Rob Dorrington of the Centre for Actuarial Research.

model. This may be due to declining rates of entry into marriage over time (Garenne 2004), which are not allowed for in the model.

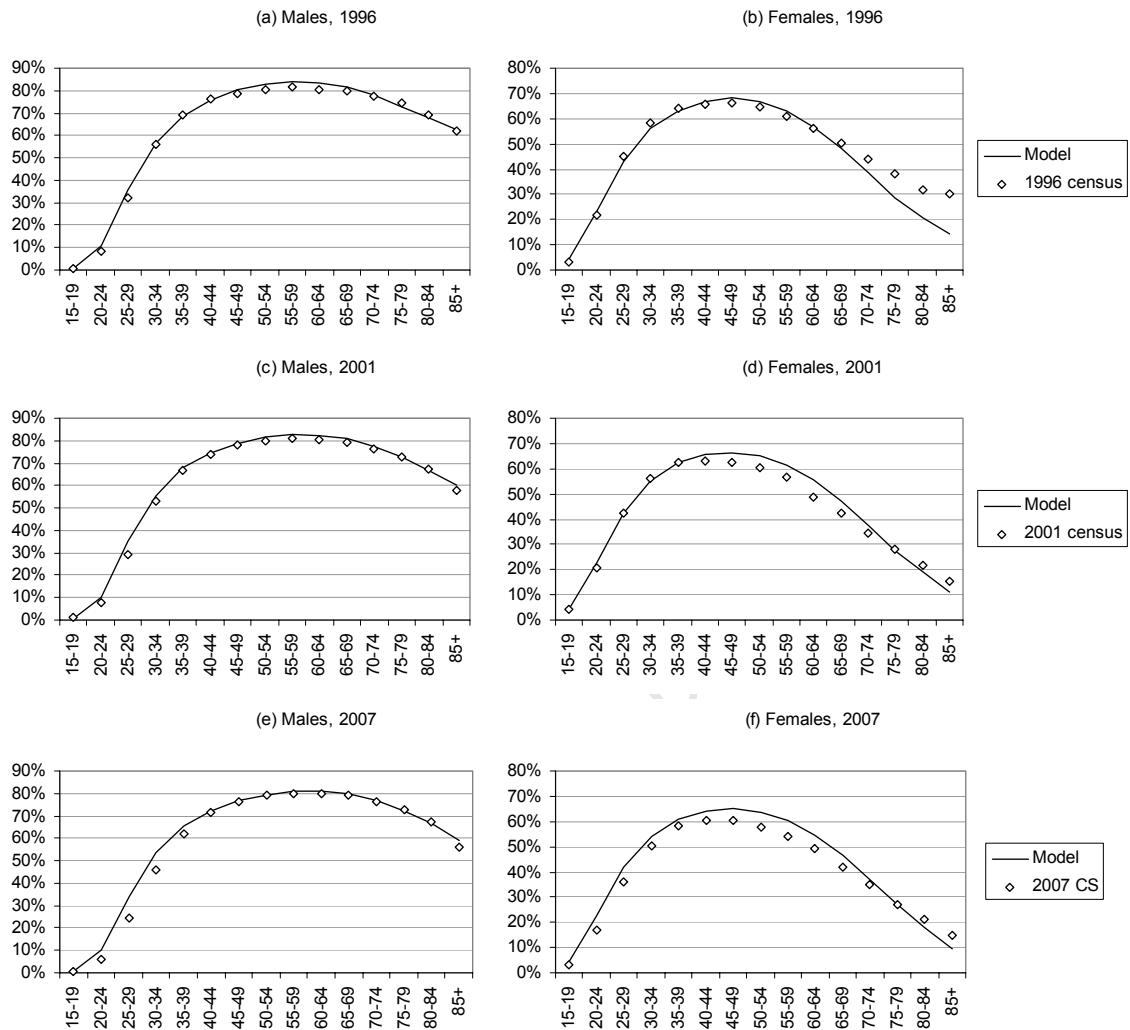


Figure 4.1.8: Proportions of individuals who are married or in cohabiting relationships. Mean of posterior distribution represented by solid black line. Reported proportions married or in cohabiting relationships represented by open diamonds.

4.1.6 Posterior model estimates of the impact of HIV/AIDS in South Africa

Having fitted the model and validated the model against various data sources, we now present summary outputs of the model. Figure 4.1.9(a) shows that HIV prevalence levels in South Africa have risen rapidly over the last two decades, with an estimated 10.1% (95% prediction interval: 9.4-10.9%) of the population infected in 2005. HIV prevalence levels in 2005 are estimated to be particularly high in the 15 to 49 age range, at 16.9% (95% interval: 15.7-18.1%). HIV prevalence is estimated to be

substantially higher in adult women than in adult men in 2005, at 19.8% and 14.0% respectively (Figures 4.1.9(c) and (d)). Although HIV prevalence levels have risen steadily up to 2005, HIV incidence appears to have been on the decline since 1999, partly due to the rising levels of condom use assumed in the model and partly due to the natural course of the HIV/AIDS epidemic. Figure 4.1.9(e) shows that by 2005, HIV incidence rates had dropped to 1.2% of the uninfected population per annum. AIDS mortality rates in South Africa appear to be levelling off, mainly as a result of the rapid rollout of antiretroviral treatment in the public health sector (Figure 4.1.9(f)).

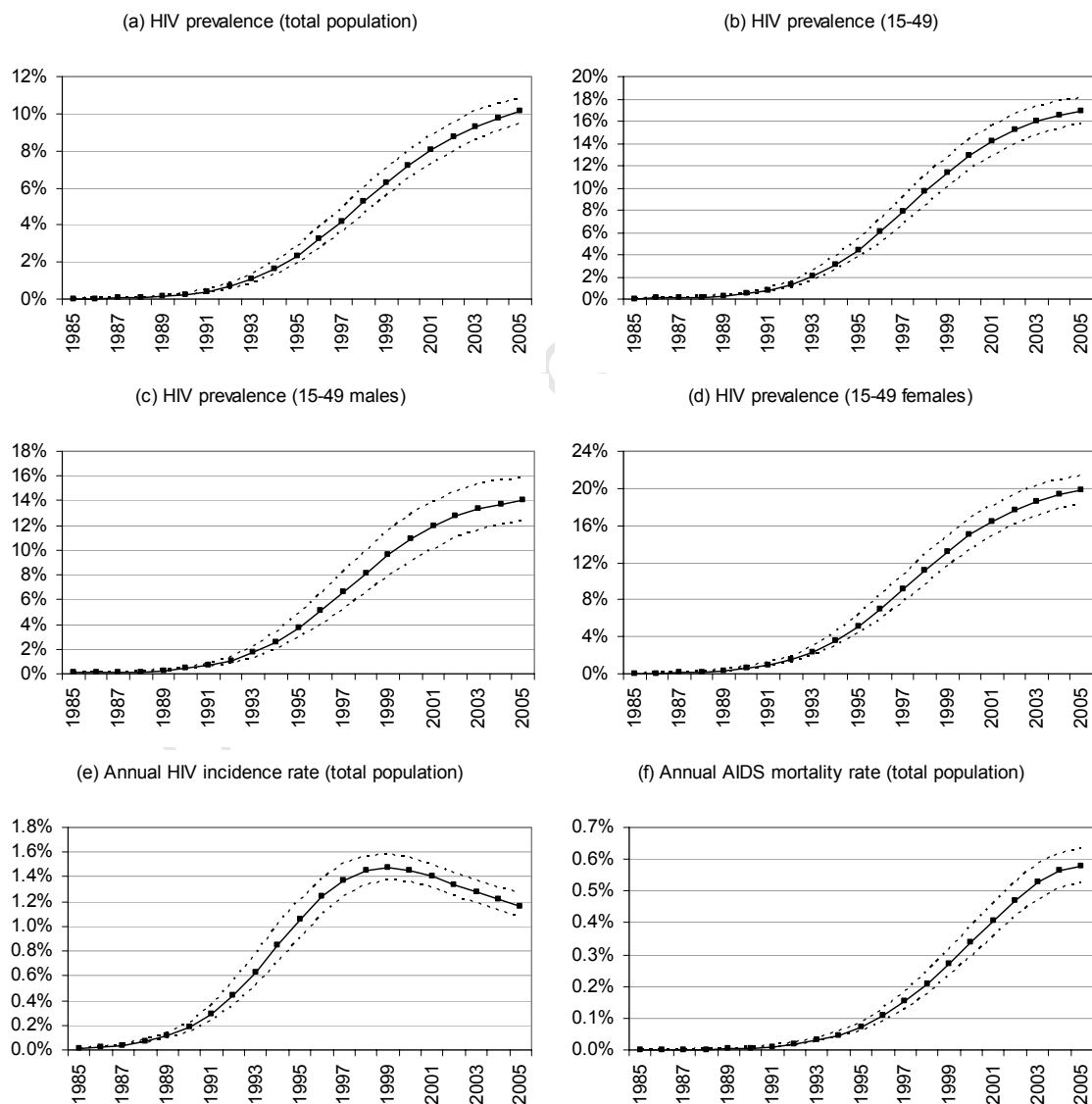


Figure 4.1.9: Trends in HIV prevalence, HIV incidence and AIDS mortality

Mean of posterior sample is represented by solid black line and 95% prediction intervals are represented by dashed lines.

4.2 Fitting the model to STI prevalence data

Having fitted the model to HIV prevalence data and sexual behaviour data, we now have reasonable estimates of the sexual behaviour and HIV parameters in the model. The next step is to estimate trends in STI prevalence over time, given the previous estimates of sexual behaviour and HIV parameters. The approach adopted in fitting the model to STI prevalence data is again Bayesian. The sources of uncertainty are the STI natural history, STI transmission and STI treatment parameters (the prior distributions for these parameters are specified in Tables 3.3.1-3.3.9 and 3.3.14). The sexual behaviour and HIV parameters are fixed at the posterior means estimated in section 4.1. As in section 4.1, the effects of STIs on HIV transmission probabilities are ignored, and the projected HIV and demographic outcomes are thus the same across all the scenarios considered. The sections that follow describe the STI prevalence data sources, the method used to define the likelihood, and the method used to simulate the posterior distribution. This is followed by a presentation of the results: a comparison of the prior and posterior distributions for each STI, and a comparison of the model predictions with the levels of STI prevalence measured in various surveys.

4.2.1 Data sources

Unlike HIV, other STIs are seldom monitored in nationally representative surveys. Except in the case of syphilis, which is monitored together with HIV in the annual national survey of women attending public antenatal clinics, the only STI prevalence data available are the data collected in sentinel surveys of individual communities (Johnson *et al*, 2005). For the purpose of the analysis that follows, five types of data are considered:

- STI prevalence data from surveys of women attending antenatal clinics
- STI prevalence data from surveys of women attending family planning clinics
- STI prevalence data from surveys of sex workers
- STI prevalence data from household surveys
- Proportions of genital ulcer disease (GUD) patients with ulcers of different aetiologies

The first three data sources relate only to women, while for the last two sources, data are usually published for men and women separately. GUD data are included because almost all GUD is due to either herpes, syphilis or chancroid, while data in respect of other STI syndromes are excluded because non-ulcerative symptoms are relatively non-specific indicators of infection, and discharges can often be caused by organisms other than those considered in this analysis (e.g. *Mycoplasma genitalium* and *Ureaplasma urealyticum*).

South African STI prevalence data were identified through a Medline search, through a hand search of the *Southern African Journal of Epidemiology and Infection*, through searches of abstracts of relevant conferences and through an earlier review of STI prevalence data in South Africa (Pham-Kanter *et al*, 1996). This search was conducted in 2004 and subsequently published (Johnson *et al*, 2005). The database of STI sentinel surveillance studies has been augmented as new studies were identified, and details of the data used in the present analysis appear in Appendix C. In cases in which the year of the survey was not stated, the year of the survey was imputed to be three years prior to the date of publication if published in a peer-reviewed journal, or one year prior to the date of publication if presented at a conference (based on the median publication lags for those studies in which the year of the survey was stated).

4.2.2 Likelihood formulation

The objective of this section is to derive an expression for the likelihood of measuring a particular STI prevalence level in a particular community, conditional upon a set of model estimates that are assumed to represent the true population prevalence of that STI at a national level. Suppose that there are J admissible studies in which the prevalence of the STI has been measured. For the i^{th} study, available information includes the number of individuals tested (n_i), the number of individuals who test positive (y_i) and covariate information (x_i). Included in the covariate information is:

- the year in which the study was conducted (t_i),
- the location in which the study was conducted,
- the nature of the sample, s_i (antenatal clinic, family planning clinic, households etc.),

- the number of individuals tested (n_i), and
- the method used to detect the STI.

Suppose that $M_i(\boldsymbol{\phi})$ represents the model estimate of the prevalence of the STI in year t_i in sub-population s_i , given a set of assumptions represented by the parameter vector $\boldsymbol{\phi}$. This represents the prevalence of the STI that might be expected in a randomly selected sentinel site.

A number of technical points regarding the calculation of $M_i(\boldsymbol{\phi})$ should be noted. In deriving $M_i(\boldsymbol{\phi})$ estimates for health facilities, it is necessary to make assumptions about relative rates of health facility usage in different groups. Model estimates of STI prevalence in antenatal clinic attenders are calculated as a weighted average of the age- and HIV stage-specific STI prevalence levels in women, where the weights are the numbers of women multiplied by their age- and HIV stage-specific fertility rates. Similarly, model estimates of STI prevalence in family planning clinic attenders are calculated as a weighted average of the age-specific STI prevalence levels in women, where the weights are the numbers of women multiplied by their age-specific rates of modern contraceptive usage, as reported in the 1998 DHS (Department of Health 1999). Model estimates of ulcerative STI prevalence in GUD patients are calculated as the number of individuals with symptoms of the ulcerative STI divided by the model estimate of the total number of individuals with GUD, on the assumption that individuals would seek treatment at the same rate for all ulcers, regardless of their aetiology.

A simple approach to defining the likelihood function would be to assume that for the i^{th} study, the number of individuals found to be infected with the STI is binomially distributed with parameters n_i and $M_i(\boldsymbol{\phi})$. This approach has two major limitations. Firstly, STI prevalence levels are unlikely to be the same in all communities, and thus the prevalence of the STI estimated at a national level, $M_i(\boldsymbol{\phi})$, is unlikely to be the same as the STI prevalence in the sampled community. Variation in STI prevalence levels between different communities is therefore likely to be greater than binomial variation alone suggests. Secondly, the methods used to detect STIs are seldom 100%

sensitive or 100% specific, and hence the number of individuals testing positive in a particular sample is not necessarily the number of people who are actually infected. Not only do different studies use different diagnostic techniques, but the same diagnostic technique can have different sensitivity and specificity profiles in the hands of different investigators, depending on their experience, their sample collection procedures and their subjective interpretation of the test results. There is thus substantial variation in STI prevalence levels between surveys that can be attributed to differences in testing procedures.

A better approach to formulating the likelihood would therefore be to specify the STI prevalence one expects to *measure* in study i , θ_i , as follows:

$$\theta_i = (M_i(\varphi) + b_i)Se_i + (1 - M_i(\varphi) - b_i)(1 - Sp_i). \quad (4.5)$$

Here b_i represents the difference between the actual prevalence in the subpopulation from which study i has sampled and the national average. Se_i represents the sensitivity of the test used in study i , and Sp_i represents the specificity of the test used in study i . Parameter b_i accounts for geographical variation in STI prevalence mainly, but it could also represent differences in sampling methods between studies and differences in sub-populations within the same location. The ‘study effect’ b_i is unknown *a priori*, but it might be assumed that it has 0 mean and variance σ_b^2 . Se_i and Sp_i are also random variables, but the mean and variance of these variables can be estimated from various studies. Estimates of the expectation and variance of the sensitivity and specificity parameters used in this analysis are given for each STI and for each STI diagnostic technique in Appendix D.

A limitation of the model represented by equation (4.5) is that the variance in θ_i due to the b_i term is the same at all STI prevalence levels. In reality, one might expect less variation if the model estimate of prevalence, $M_i(\varphi)$, is close to 0 or 1. In addition, it is possible that the addition of b_i to $M_i(\varphi)$ could result in a prevalence less than zero or greater than one. To avoid both of these problems, a logit transformation is applied to the model estimates of STI prevalence:

$$\begin{aligned}
\theta_i &= \text{logit}^{-1}(\text{logit}(M_i(\boldsymbol{\varphi})) + b_i)Se_i + (1 - \text{logit}^{-1}(\text{logit}(M_i(\boldsymbol{\varphi})) + b_i))(1 - Sp_i) \\
&= \frac{Se_i + Sp_i - 1}{1 + \left(\frac{1 - M_i(\boldsymbol{\varphi})}{M_i(\boldsymbol{\varphi})}\right)e^{-b_i}} + (1 - Sp_i) \\
&= (Se_i + Sp_i - 1)f(b_i) + (1 - Sp_i)
\end{aligned} \tag{4.6}$$

where b_i , as before, is assumed to have 0 mean and variance σ_b^2 . The function $f(b_i)$ is defined as

$$f(b_i) = \left(1 + \left(\frac{1 - M_i(\boldsymbol{\varphi})}{M_i(\boldsymbol{\varphi})}\right)e^{-b_i}\right)^{-1}. \tag{4.7}$$

In order to determine the mean and variance of θ_i , it is necessary to estimate the mean and variance of $f(b_i)$. These can best be approximated using the delta method (Rice 1995). The third-order Taylor approximation to (4.7) about the mean $E[b_i]$ is

$$\begin{aligned}
f(b_i) &\approx M_i(\boldsymbol{\varphi}) + b_i M_i(\boldsymbol{\varphi})(1 - M_i(\boldsymbol{\varphi})) \\
&\quad + b_i^2 M_i(\boldsymbol{\varphi})(1 - M_i(\boldsymbol{\varphi}))(0.5 - M_i(\boldsymbol{\varphi})) \\
&\quad + b_i^3 M_i(\boldsymbol{\varphi})(1 - M_i(\boldsymbol{\varphi}))(1/6 - M_i(\boldsymbol{\varphi}) + M_i(\boldsymbol{\varphi})^2)
\end{aligned} \tag{4.8}$$

and from this it follows that

$$E[f(b_i)] \approx M_i(\boldsymbol{\varphi}) + \sigma_b^2 M_i(\boldsymbol{\varphi})(1 - M_i(\boldsymbol{\varphi}))(0.5 - M_i(\boldsymbol{\varphi})), \tag{4.9}$$

if it is assumed that b_i is normally distributed. The expectation of θ_i is then

$$\begin{aligned}
E[\theta_i] &\approx \left(M_i(\boldsymbol{\varphi}) + \sigma_b^2 M_i(\boldsymbol{\varphi})(1 - M_i(\boldsymbol{\varphi}))(0.5 - M_i(\boldsymbol{\varphi}))\right) \\
&\quad \times (E[Se_i] + E[Sp_i] - 1) + 1 - E[Sp_i]
\end{aligned} \tag{4.10}$$

Using the formulas for the moments of the normal distribution with zero mean (Rice 1995), and the approximate formulas for $f(b_i)$ and $E[f(b_i)]$ in equations (4.8) and (4.9), the variance of $f(b_i)$ can then be estimated as

$$\begin{aligned} \text{Var}[f(b_i)] \approx & M_i(\Phi)^2(1 - M_i(\Phi))^2 \left[\sigma^2 + (1.5 - 8M_i(\Phi) + 8M_i(\Phi)^2) \right. \\ & \left. \times \sigma^4 + 15(1/6 - M_i(\Phi) + M_i(\Phi)^2)^2 \sigma^6 \right] \end{aligned} \quad (4.11)$$

The variance of θ_i is obtained by noting that

$$\text{Var}[\theta_i] = E[\text{Var}[\theta_i | b_i]] + \text{Var}[E[\theta_i | b_i]]. \quad (4.12)$$

From equation (4.6),

$$\begin{aligned} E[\text{Var}[\theta_i | b_i]] = & \text{Var}[Se_i] \left(\text{Var}[f(b_i)] + E[f(b_i)]^2 \right) \\ & + \text{Var}[Sp_i] \left(\text{Var}[f(b_i)] + (1 - E[f(b_i)])^2 \right) \end{aligned} \quad (4.13)$$

$$\text{Var}[E[\theta_i | b_i]] = (E(Se_i) + E(Sp_i) - 1)^2 \text{Var}[f(b_i)] \quad (4.14)$$

These results are obtained by assuming that b_i , Se_i and Sp_i are mutually independent. Substituting the approximate values of $E[f(b_i)]$ and $\text{Var}[f(b_i)]$ into equations (4.13) and (4.14), and substituting these results into equation (4.12) gives an approximation to the variance of θ_i . This approximation appears to be reasonable across a range of different scenarios, as Table 4.2.1 shows. For each scenario, 10 000 values of Se_i and Sp_i were sampled from beta distributions (with means and variances that differed by scenario) and 10 000 values of b_i were sampled from a normal distribution (with standard deviation that differed by scenario). In all cases, the difference between the estimate obtained using equation (4.12) and the simulated variance is less than 5%.

Table 4.2.1: Difference between approximate variance and simulated variance (as a percentage of the simulated variance)

$M_i(\varphi)$	$E[Se_i]$	$SD[Se_i]$	$E[Sp_i]$	$SD[Sp_i]$	$\sigma_b = 0.2$	$\sigma_b = 0.4$	$\sigma_b = 0.6$
5%	0.75	0.10	0.99	0.008	-1.5%	-0.8%	-0.4%
5%	0.95	0.03	0.98	0.016	1.3%	0.4%	3.9%
5%	0.95	0.03	0.99	0.008	-2.4%	1.2%	-0.7%
15%	0.75	0.10	0.99	0.008	0.5%	2.4%	4.4%
15%	0.95	0.03	0.98	0.016	0.3%	-1.4%	4.6%
15%	0.75	0.03	0.99	0.008	0.6%	0.0%	3.3%
25%	0.75	0.10	0.99	0.008	-1.2%	0.0%	0.1%
25%	0.95	0.03	0.98	0.016	1.4%	3.0%	4.4%
25%	0.75	0.03	0.99	0.008	0.3%	2.5%	3.2%
40%	0.75	0.10	0.99	0.008	-0.5%	0.8%	-1.9%
40%	0.95	0.03	0.98	0.016	-0.7%	-2.7%	-0.8%
40%	0.75	0.03	0.99	0.008	-2.1%	3.8%	-3.3%
70%	0.75	0.10	0.99	0.008	1.9%	-0.4%	1.1%
70%	0.95	0.03	0.98	0.016	-1.3%	1.7%	3.1%
70%	0.75	0.03	0.99	0.008	-2.5%	0.7%	-0.2%

SD = standard deviation

Having determined the mean and variance of θ_i , one can set a beta prior distribution on parameter θ_i , with parameters α_i and β_i calculated from the above mean and variance:

$$\alpha_i = E[\theta_i] \left(\frac{E[\theta_i](1 - E[\theta_i])}{Var[\theta_i]} - 1 \right)$$

$$\beta_i = (1 - E[\theta_i]) \left(\frac{E[\theta_i](1 - E[\theta_i])}{Var[\theta_i]} - 1 \right)$$
(4.15)

The prior distribution for θ_i is then:

$$p(\theta_i | \varphi^*, x_i) = \frac{\Gamma(\alpha_i + \beta_i)}{\Gamma(\alpha_i)\Gamma(\beta_i)} \theta_i^{\alpha_i-1} (1 - \theta_i)^{\beta_i-1}$$
(4.16)

where $\boldsymbol{\phi}^*$ is the combination of the vector $\boldsymbol{\phi}$ and the parameter σ_b . This is a hierarchical Bayesian approach, as the prior distributions on the θ_i parameters are conditional upon the parameter vector $\boldsymbol{\phi}^*$, which has a prior distribution of its own (Gelman *et al*, 2004).

To determine the prior distribution on σ_b , it is helpful to examine the total variation in logit-transformed study prevalence levels for each of six STIs, noting that the total variation is likely to be an upper bound on the variance σ_b^2 , since much of the total variation is attributable to variation in study diagnostics, variation in sample types, changes in prevalence over time and binomial variation. The standard deviations of the logit-transformed prevalence levels are 0.69 for gonorrhoea, 0.55 for chlamydial infection, 0.64 for trichomoniasis, 0.86 for syphilis, 0.68 for bacterial vaginosis, and 0.61 for candidiasis. (Herpes and chancroid are not included, since most of the prevalence data for these STIs are from GUD patients, and it will be shown that these GUD data cannot be incorporated in the specification of the likelihood.) The prior chosen for σ_b is a gamma distribution with mean of 0.3 and standard deviation of 0.15, as the 97.5 percentile of this distribution is 0.66, which conforms with the upper limits of around 0.7 estimated from the data (see Figure 4.2.1).

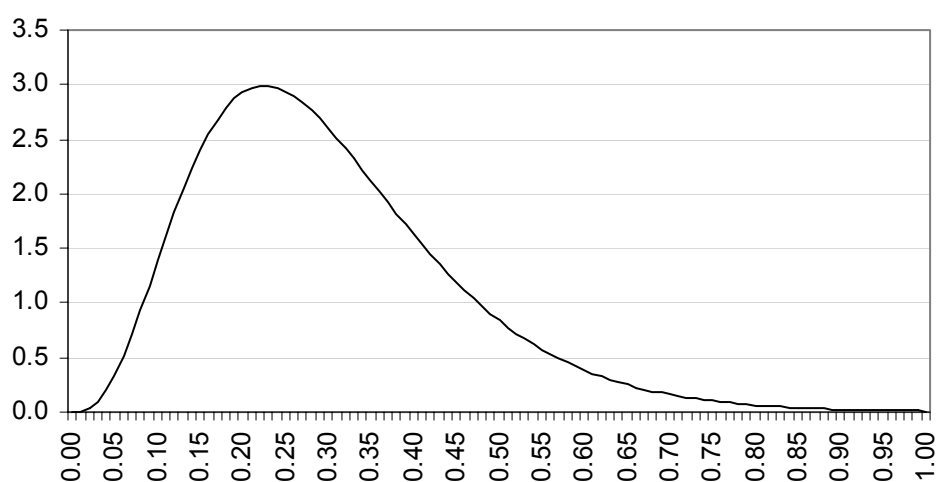


Figure 4.2.1: Prior distribution on σ_b , the standard deviation of the study effects

The number of individuals testing positive in study i , y_i , is assumed to be binomially distributed, and thus the likelihood function is

$$p(y_i | \theta_i, x_i) = \binom{n_i}{y_i} \theta_i^{y_i} (1 - \theta_i)^{n_i - y_i}, \quad (4.17)$$

supposing that the θ_i value is known. However, since the θ_i value is unknown *a priori*, the likelihood function should be conditional upon only the parameter vector $\boldsymbol{\varphi}^*$ and the covariate information (the x_i values), i.e.

$$p(y_i | \boldsymbol{\varphi}^*, x_i) = \int_0^1 p(y_i | \theta_i, x_i) p(\theta_i | \boldsymbol{\varphi}^*, x_i) d\theta_i. \quad (4.18)$$

(Note that the likelihood for y_i is independent of $\boldsymbol{\varphi}^*$, conditional upon θ_i being known.) By substituting equations (4.16) and (4.17) into equation (4.18), we find:

$$\begin{aligned} p(y_i | \boldsymbol{\varphi}^*, x_i) &= \binom{n_i}{y_i} \int_0^1 \frac{\Gamma(\alpha_i + \beta_i)}{\Gamma(\alpha_i)\Gamma(\beta_i)} \theta_i^{\alpha_i + y_i - 1} (1 - \theta_i)^{\beta_i + n_i - y_i - 1} d\theta_i \\ &\propto \frac{\Gamma(\alpha_i + \beta_i)}{\Gamma(\alpha_i)\Gamma(\beta_i)} \times \frac{\Gamma(\alpha_i + y_i)\Gamma(\beta_i + n_i - y_i)}{\Gamma(\alpha_i + \beta_i + n_i)} \end{aligned} \quad (4.19)$$

The likelihood for all the STI prevalence data is thus

$$p(\mathbf{y} | \boldsymbol{\varphi}^*, \mathbf{x}) \propto \prod_{i=1}^J \frac{\Gamma(\alpha_i + \beta_i)}{\Gamma(\alpha_i)\Gamma(\beta_i)} \times \frac{\Gamma(\alpha_i + y_i)\Gamma(\beta_i + n_i - y_i)}{\Gamma(\alpha_i + \beta_i + n_i)}, \quad (4.20)^*$$

where \mathbf{x} and \mathbf{y} represent the vectors of x_i and y_i values respectively. The likelihood is thus a function of the numbers tested and the numbers testing positive in each study, as well as the α_i and β_i parameters (calculated from equations (4.15) and (4.16)), which are the parameters of the beta priors on the θ_i parameters. The parameters of the beta priors are in turn a function of the level of prevalence predicted by the model

* A similar formula for the likelihood function is derived by Gelman *et al* (2004, p. 128).

$(M_i(\boldsymbol{\phi}))$, the assumed variance of the study effects, and the assumed means and variances of the diagnostic performance characteristics.

The approach to defining the likelihood is modified slightly in the case of bacterial vaginosis, as this condition is usually diagnosed using Nugent's scoring method (Nugent *et al*, 1991), and there is no objective benchmark against which the sensitivity or specificity of this technique can be assessed. The scoring method is nevertheless subjective, and there is variation between raters' assessments of Nugent scores (Nugent *et al*, 1991; Joesoef *et al*, 1991; Nelson *et al*, 2003). Equation (4.6) can therefore be reformulated as

$$\theta_i = \text{logit}^{-1}(\text{logit}(M_i(\boldsymbol{\phi})) + b_i)NS_i, \quad (4.21)$$

where NS_i is the factor by which the Nugent score prevalence in study i differs from the average Nugent score prevalence that would be obtained if a large number of investigators were to examine independently the same specimens. The mean of NS_i is 1, and its standard deviation is estimated to be 0.087, based on empirical estimates of variation between clinicians (Nugent *et al*, 1991; Joesoef *et al*, 1991; Nelson *et al*, 2003). The approach adopted is therefore the same as before, but with $\text{Var}[NS_i]$ taking the place of $\text{Var}[Se_i]$, and $E[Se_i]$, $E[Sp_i]$ and $\text{Var}[Sp_i]$ being replaced by 1, 1 and 0 respectively.

The method used to define the likelihood is not applicable to GUD data, since the proportion of GUD cases attributable to the STI of interest is a function of both the study effect in respect of that STI (in the numerator and denominator) and the study effects in respect of other ulcerative STIs (in the denominator), which complicates the calculation of the variance of the proportion. GUD data are therefore not used in defining the likelihood function, though they are used in validating the model. Because the only data available for chancroid are those collected from GUD patients, it is not possible to conduct a formal Bayesian analysis for chancroid, and the default values assumed for the chancroid parameters are therefore used throughout this analysis. Most HSV-2 data are also data from GUD patients, though there are sufficient HSV-2 seroprevalence data from other settings to allow a Bayesian

analysis. Syphilis data from GUD patients are not considered at all, either in defining the likelihood function or in validating the model, due to the absence of any consistent diagnostic method across studies.

4.2.3 Posterior simulation

The posterior density $p(\boldsymbol{\varphi}^* | \mathbf{x}, \mathbf{y})$ is proportional to the product of the prior distribution on the $\boldsymbol{\varphi}^*$ parameters, $p(\boldsymbol{\varphi}^*)$, and the likelihood function, as represented in equation (4.20). As in section 4.1.3, however, the posterior density cannot be evaluated analytically, since it is necessary to run the model in order to obtain the likelihood for a single set of $\boldsymbol{\varphi}^*$ values. The posterior density is therefore evaluated numerically, using Sampling Importance Resampling (Smith and Gelfand 1992). This involves randomly sampling parameter combinations from $p(\boldsymbol{\varphi}^*)$, calculating the likelihood for each parameter combination, and then resampling from the generated set of parameter combinations using the likelihood values as sample weights. In each of the analyses presented here, an initial sample of 20 000 parameter combinations was drawn and a ‘resample’ of 500 parameter combinations was drawn from the initial sample. The sample of 500 parameter combinations thus represents a sample from the posterior distribution. The procedure was carried out separately for each STI.

Table 4.2.2 shows the numbers of distinct parameter combinations in each posterior sample, and the greatest number of times that any single parameter combination was sampled. For all eight analyses, more than half of the posterior sample was composed of distinct parameter combinations, and no single parameter combination accounted for more than 3% of the posterior sample. The Sampling Importance Resampling approach therefore yields a reasonable approximation to the posterior distribution, and the chosen sample size appears to be acceptable. However, it would probably be necessary to increase the sizes of the initial sample and resample in order to estimate the 95% prediction interval accurately.

Table 4.2.2: Number of distinct parameter combinations and frequency of most frequently sampled parameter combination in posterior sample of 500 parameter combinations

STI	Distinct parameter combinations		Most frequently sampled parameter combination	
	n	%	n	%
Syphilis	257	51.4%	15	3.0%
Gonorrhoea	313	62.6%	9	1.8%
Chlamydial infection	350	70.0%	14	2.8%
Trichomoniasis	385	77.0%	5	1.0%
Bacterial vaginosis	439	87.8%	3	0.6%
Vaginal candidiasis	491	98.2%	2	0.4%
Genital herpes	308	61.6%	7	1.4%

4.2.4 Comparison of prior and posterior distributions

The prior distributions and posteriors distributions for gonorrhoea, chlamydial infection and trichomoniasis are summarized in Table 4.2.3. In general, there is a fair degree of consistency between the prior and posterior distributions. In the case of trichomoniasis, however, the posterior mean of the study effect standard deviation (0.51) is substantially greater than the prior mean (0.30), indicating that there is a relatively high degree of variation in trichomoniasis prevalence between settings.

Table 4.2.3: Comparison of prior and posterior distributions for gonorrhoea, chlamydial infection and trichomoniasis

Parameter	Gonorrhoea		Chlamydial infection		Trichomoniasis	
	Prior (mean, 95% CI)	Posterior (mean, 95% CI)	Prior (mean, 95% CI)	Posterior (mean, 95% CI)	Prior (mean, 95% CI)	Posterior (mean, 95% CI)
Male-to-female transmission probability	0.40 (0.21-0.60)	0.46 (0.30-0.62)	0.16 (0.02-0.40)	0.18 (0.08-0.31)	0.15 (0.03-0.34)	0.22 (0.10-0.40)
Female-to-male transmission probability	0.20 (0.11-0.31)	0.23 (0.16-0.32)	0.12 (0.03-0.26)	0.11 (0.03-0.31)	0.04 (0.01-0.09)	0.05 (0.02-0.10)
Proportion of cases becoming symptomatic:						
Males	0.90 (0.78-0.97)	0.88 (0.78-0.96)	0.30 (0.06-0.63)	0.33 (0.07-0.60)	0.40 (0.21-0.60)	0.38 (0.20-0.58)
Females	0.40 (0.13-0.71)	0.35 (0.12-0.64)	0.15 (0.03-0.34)	0.17 (0.04-0.31)	0.30 (0.13-0.51)	0.29 (0.12-0.48)
Average duration of untreated infection (weeks):						
Symptomatic males	15.0 (6.9-26.3) ^a	17.8 (10.0-27.3) ^a	16.0 (4.4-35.1) ^b	17.0 (4.5-35.1) ^b	2.0 (0.9-3.6)	2.0 (0.8-3.7)
Symptomatic females	15.0 (6.9-26.3) ^a	14.8 (10.1-21.2) ^a	-	-	15.0 (6.9-26.3)	14.9 (6.7-26.7)
Asymptomatic males	-	-	90 (63-122) ^b	89 (66-117) ^b	20.0 (8.7-35.9)	21.2 (11.2-34.4)
Asymptomatic females	-	-	-	-	150 (69-263)	157 (87-247)
Average duration of immunity (weeks)	52 (14-114)	68 (40-113)	520 (205-979)	490 (277-773)	52 (14-114)	63 (22-121)
Proportion of cases immune after treatment	0	-	0.50 (0.03-0.98)	0.72 (0.21-0.99)	0	-
Proportion of cases correctly treated prior to						
introduction of syndromic management	0.70 (0.49-0.87)	0.71 (0.53-0.86)	0.70 (0.49-0.87)	0.71 (0.51-0.88)	0.40 (0.13-0.71)	0.41 (0.14-0.68)
Standard deviation of study effects	0.30 (0.08-0.66)	0.30 (0.17-0.44)	0.30 (0.08-0.66)	0.33 (0.21-0.47)	0.30 (0.08-0.66)	0.53 (0.33-0.75)

^a Distribution applies to both symptomatic and asymptomatic cases. ^b Distribution applies to both males and females.

The prior and posterior distributions for syphilis are compared in Table 4.2.4. The posterior distributions suggest a shorter duration of infectious syphilis (primary and secondary syphilis) and a longer average duration of latent syphilis. In addition, for the inter-study variation in syphilis prevalence, the female-to-male transmission probability and the proportion of syphilis cases treated correctly prior to syndromic management, the posterior mean is considerably greater than the prior mean.

Table 4.2.4: Comparison of prior and posterior distributions for syphilis

Parameter	Prior (mean, 95% CI)	Posterior (mean, 95% CI)
Male-to-female transmission probability	0.18 (0.09-0.29)	0.17 (0.12-0.23)
Female-to-male transmission probability	0.15 (0.07-0.26)	0.19 (0.13-0.27)
Average time (in weeks) from		
Primary to secondary	6.6 (3.3-11.1)	6.1 (3.0-10.7)
Secondary to latent	15.6 (8.8-24.4)	14.9 (9.1-22.1)
Latent to spontaneous resolution	520 (269-853)	572 (355-883)
Recovery in early disease to seronegativity	26.0 (12.8-43.9)	23.0 (12.8-42.6)
Recovery in latent infection to seronegativity	52.0 (25.5-87.7)	51.5 (25.5-84.4)
Proportion of primary cases seronegative		
immediately after successful treatment	0.40 (0.21-0.60)	0.42 (0.24-0.60)
Proportion of cases correctly treated prior to syndromic		
management	0.70 (0.49-0.87)	0.76 (0.62-0.90)
Standard deviation of study effects	0.30 (0.08-0.66)	0.38 (0.28-0.50)

Table 4.2.5 summarizes the prior and posterior distributions for bacterial vaginosis. The posterior distributions suggest a more rapid progression from normal flora to bacterial vaginosis, and a slower recovery from bacterial vaginosis to normal flora, than the prior assumptions indicate. In addition, the posterior mean of the standard deviation of the study effects is substantially greater than the prior mean (0.48 vs 0.30), indicating that there is substantial variation in bacterial vaginosis prevalence between settings that is not accounted for by the model.

Table 4.2.5: Comparison of prior and posterior distributions for bacterial vaginosis

Parameter	Prior (mean, 95% CI)	Posterior (mean, 95% CI)
Proportion of cases that are initially symptomatic	0.25 (0.08-0.47)	0.22 (0.06-0.44)
Weekly rates of transition (in absence of treatment)		
Intermediate flora to bacterial vaginosis	0.100 (0.050-0.167)	0.117 (0.073-0.174)
Bacterial vaginosis to normal flora	0.008 (0.003-0.015)	0.008 (0.003-0.014)
Bacterial vaginosis to intermediate flora	0.051 (0.026-0.084)	0.044 (0.024-0.072)
Normal flora to intermediate flora	0.030 (0.014-0.053)	0.035 (0.022-0.055)
Intermediate flora to normal flora	0.069 (0.036-0.113)	0.064 (0.034-0.104)
Standard deviation of study effects	0.30 (0.08-0.66)	0.48 (0.28-0.72)

The prior and posterior distributions for the vulvovaginal candidiasis natural history parameters are quite similar, as shown in Table 4.2.6. However, the posterior distributions suggest a higher incidence of asymptomatic yeast infection and a slower rate of clearance of asymptomatic yeast infection in the absence of treatment.

Table 4.2.6: Comparison of prior and posterior distributions for vulvovaginal candidiasis

Parameter	Prior (mean, 95% CI)	Posterior (mean, 95% CI)
Average duration of symptoms (weeks)	12.0 (6.9-18.6)	12.0 (7.2-18.5)
Average time to clearance of asymptomatic infection in weeks (in absence of treatment)	26.0 (15.6-39.0)	28.9 (19.3-40.9)
Annual incidence of yeast infection	0.80 (0.46-1.24)	0.94 (0.63-1.34)
Annual incidence of symptoms (in women with asymptomatic yeast infection)	0.15 (0.07-0.26)	0.15 (0.06-0.26)
Standard deviation of study effects	0.30 (0.08-0.66)	0.30 (0.09-0.66)

Table 4.2.7 compares the prior and posterior distributions for the genital herpes (HSV-2) natural history and transmission parameters. Although the prior and posterior distributions are similar in respect of most parameters, the standard deviation of the study effects has a high posterior mean (0.69). This should be seen in the context of the high standard deviation of the logit-transformed HSV-2 seroprevalence survey estimates (0.98). The posterior distributions also suggest higher

probabilities of HSV-2 transmission in non-spousal relationships than the prior distributions indicate.

Table 4.2.7: Comparison for prior and posterior distributions for genital herpes

Parameter	Prior (mean, 95% CI)	Posterior (mean, 95% CI)
HSV-2 transmission probability		
Male-to-female, non-spousal partnership	0.0075 (0.0057-0.0096)	0.0083 (0.0065-0.0106)
Female-to-male, non-spousal partnership	0.0025 (0.0016-0.0036)	0.0029 (0.0021-0.0039)
Male-to-female, spousal partnership	0.00090 (0.00063-0.00122)	0.00088 (0.00064-0.00118)
Female-to-male, spousal partnership	0.00015 (0.00010-0.00021)	0.00015 (0.00010-0.00021)
Male-to-female, client-sex worker	0.0020 (0.0011-0.0031)	0.0018 (0.0010-0.0027)
Proportion of cases becoming symptomatic	0.15 (0.07-0.26)	0.18 (0.09-0.29)
Annual incidence of symptomatic recurrences		
in the transiently asymptomatic state: Male	6.0 (4.2-8.1)	6.2 (4.3-8.3)
Female	3.0 (2.1-4.1)	3.1 (2.3-4.1)
Factor by which infectiousness increases if symptomatic	15.0 (6.9-26.3)	17.4 (9.0-27.4)
Annual rate of transition from transiently asymptomatic to permanently asymptomatic	0.100 (0.065-0.143)	0.099 (0.062-0.141)
Standard deviation of study effects	0.30 (0.08-0.66)	0.69 (0.44-0.96)

Since the differences between the prior and posterior distributions tend to be greatest in the case of the standard deviation of the study effects, the prior and posterior distributions in respect of this model parameter are compared in Figure 4.2.2, for six of the analyses. (Results for vulvovaginal candidiasis have not been included, since the prior and posterior distributions of the standard deviation of study effects are very similar.) The variance of the posterior distribution is lower in the case of syphilis than for other STIs, partly because there is relatively more syphilis prevalence data, and partly because the variability in diagnostic accuracy is lower than for most other STIs, which makes it possible to quantify the inter-study variation more precisely.

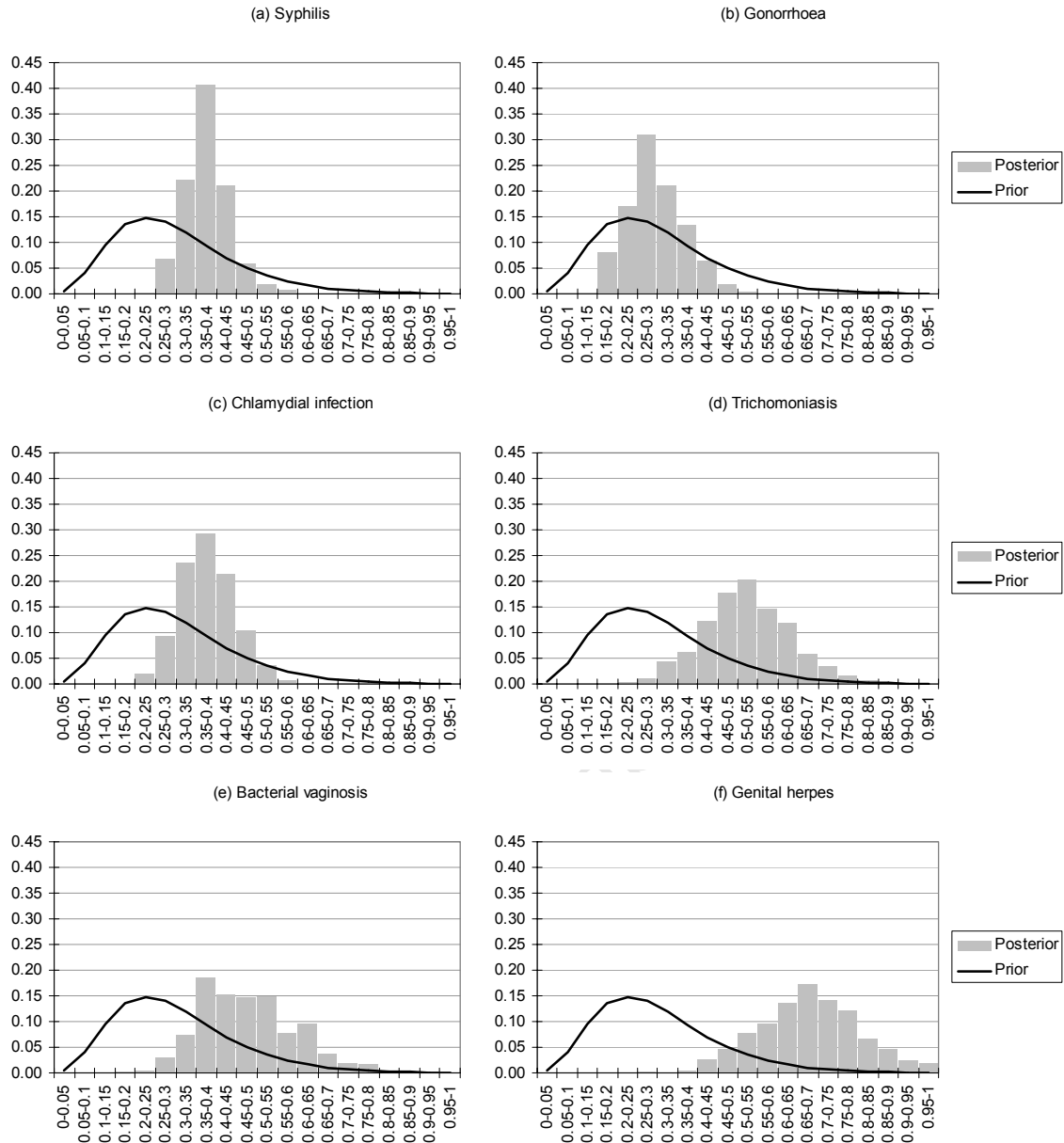


Figure 4.2.2: Comparison of prior and posterior distributions for the standard deviation of study effects

Prior distributions have been scaled to be comparable with posterior histogram plots.

4.2.5 Comparison of model predictions and survey estimates

Figure 4.2.3 compares the predicted seroprevalence of syphilis with the measured seroprevalence of syphilis in various studies. The 95% prediction intervals represent the ranges of uncertainty around the population mean and are thus narrower than the ranges of prevalence measurements in surveys, because they do not reflect variation attributable to study effects. In general there is fair consistency between survey

estimates and model estimates. Although the syphilis seroprevalence estimates from the national antenatal surveys were not included in the definition of the likelihood function, they are compared with the model estimates in Figure 4.2.3(a), and appear to validate the model. Household survey estimates shown in Figures 4.2.2(c) and (d) are not strictly comparable with the model predictions because a number of the surveys sampled over age ranges other than 15 to 49, but the comparisons nevertheless give a crude sense of the extent of consistency between model predictions and survey estimates.

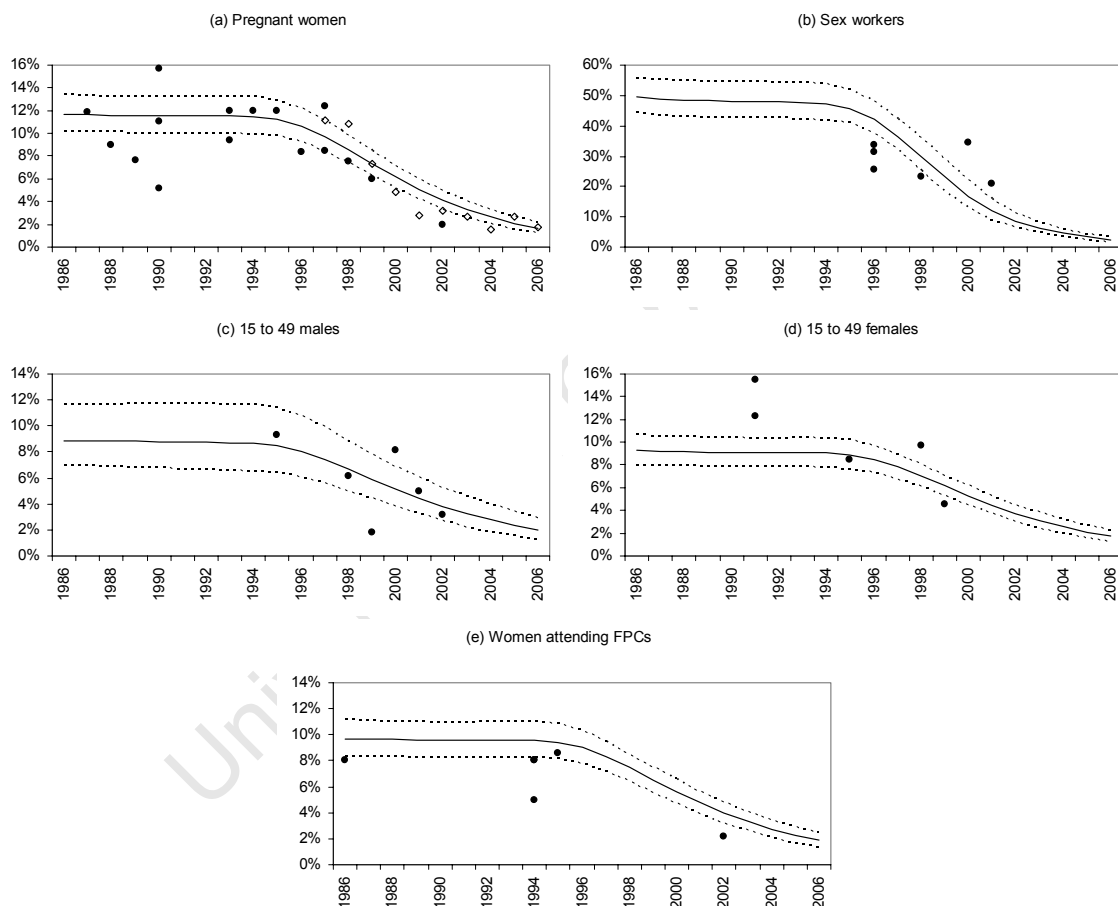


Figure 4.2.3: Syphilis seroprevalence in different sub-populations

Dots represent measurements from sentinel surveys. Open diamonds represent measurements from national surveys (not included in the definition of the likelihood). Mean of posterior distribution represented by solid black line. 2.5 and 97.5 percentiles of posterior distribution (95% prediction intervals) represented by dashed lines.

Figure 4.2.4 compares model predictions of the prevalence of gonorrhoea with observations. The observations have been adjusted to take into account the sensitivity

and specificity of the diagnostics used. Measurements of gonorrhoea prevalence in women attending antenatal and family planning clinics tend to be below the levels predicted by the model, but measurements of gonorrhoea prevalence in women in households tend to be above the levels predicted by the model. The data do not suggest any clear trend in the prevalence of gonorrhoea over time.

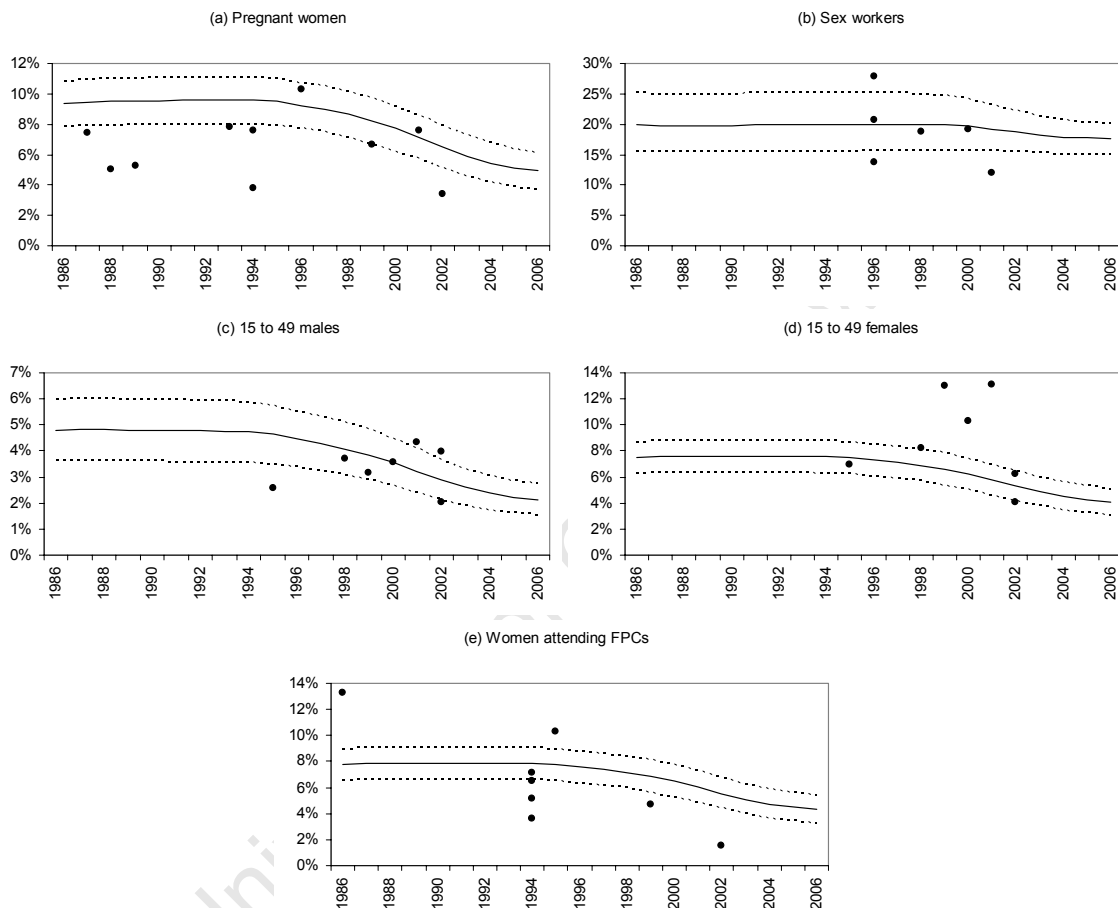


Figure 4.2.4: Gonorrhoea prevalence in different sub-populations

Dots represent measurements from sentinel surveys, after adjustment for sensitivity and specificity of diagnostic used. Mean of posterior distribution represented by solid black line. 2.5 and 97.5 percentiles of posterior distribution (95% prediction intervals) represented by dashed lines.

Figure 4.2.5 compares the observed prevalence of chlamydial infection in various studies (after adjustment for diagnostic sensitivity and specificity) with the corresponding model predictions. The prevalence of chlamydial infection measured in surveys of family planning clinic attenders tends to be greater than that predicted by the model, while the prevalence measured in studies of sex workers tends to be lower

than that predicted by the model. As with gonorrhoea, the data do not suggest any clear trend in the prevalence of chlamydial infection.

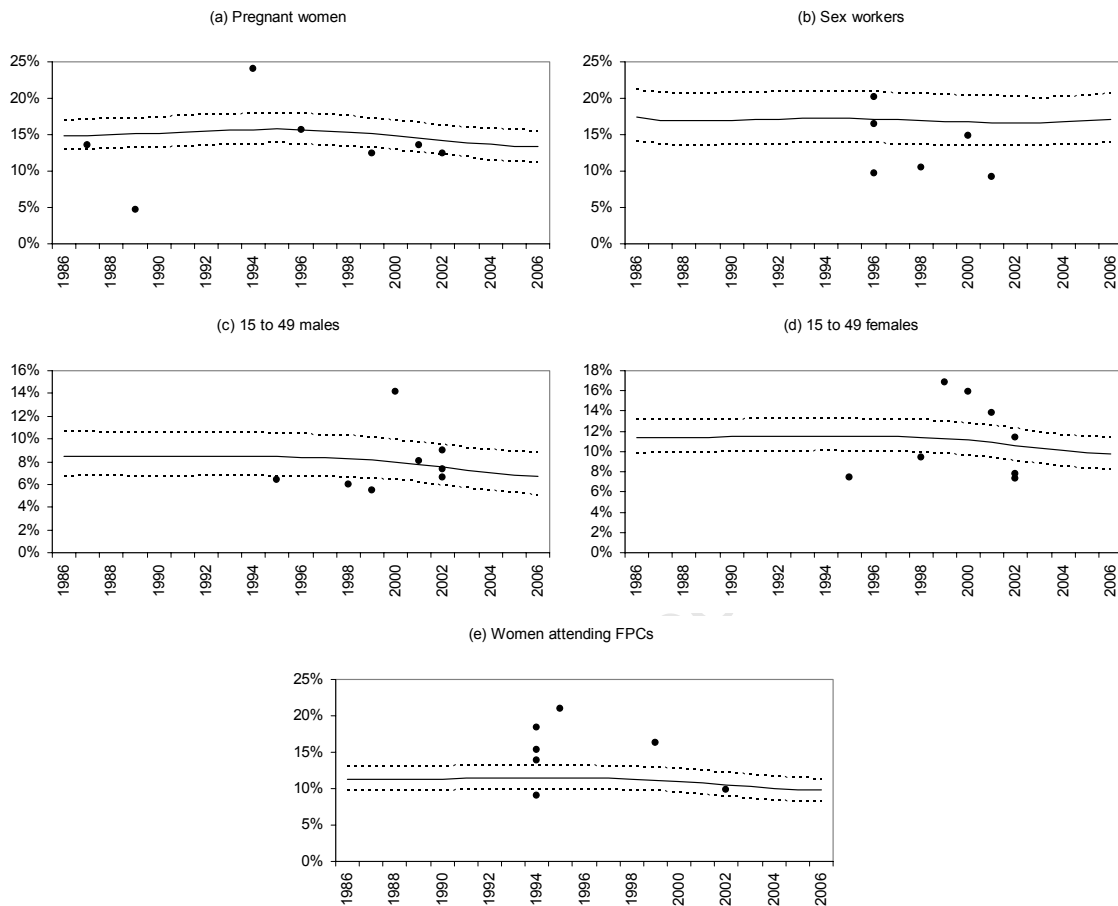


Figure 4.2.5: Prevalence of chlamydial infection in different sub-populations

Dots represent measurements from sentinel surveys, after adjustment for sensitivity and specificity of diagnostic used. Mean of posterior distribution represented by solid black line. 2.5 and 97.5 percentiles of posterior distribution (95% prediction intervals) represented by dashed lines.

Figure 4.2.6 compares the posterior estimates of trichomoniasis prevalence with those measured in surveys, after adjusting the latter for the sensitivity and specificity of the diagnostic used. The prevalence of trichomoniasis measured in surveys of pregnant women tends to be greater than the posterior model prediction, while the prevalence levels measured in women attending family planning clinics tends to be below that predicted by the model. In many cases the differences between the observations and the model predictions are extreme, thus accounting for the large standard deviation of study effects estimated in section 4.2.4. The posterior prediction intervals are very wide in the case of males, due to the lack of male trichomoniasis prevalence data.

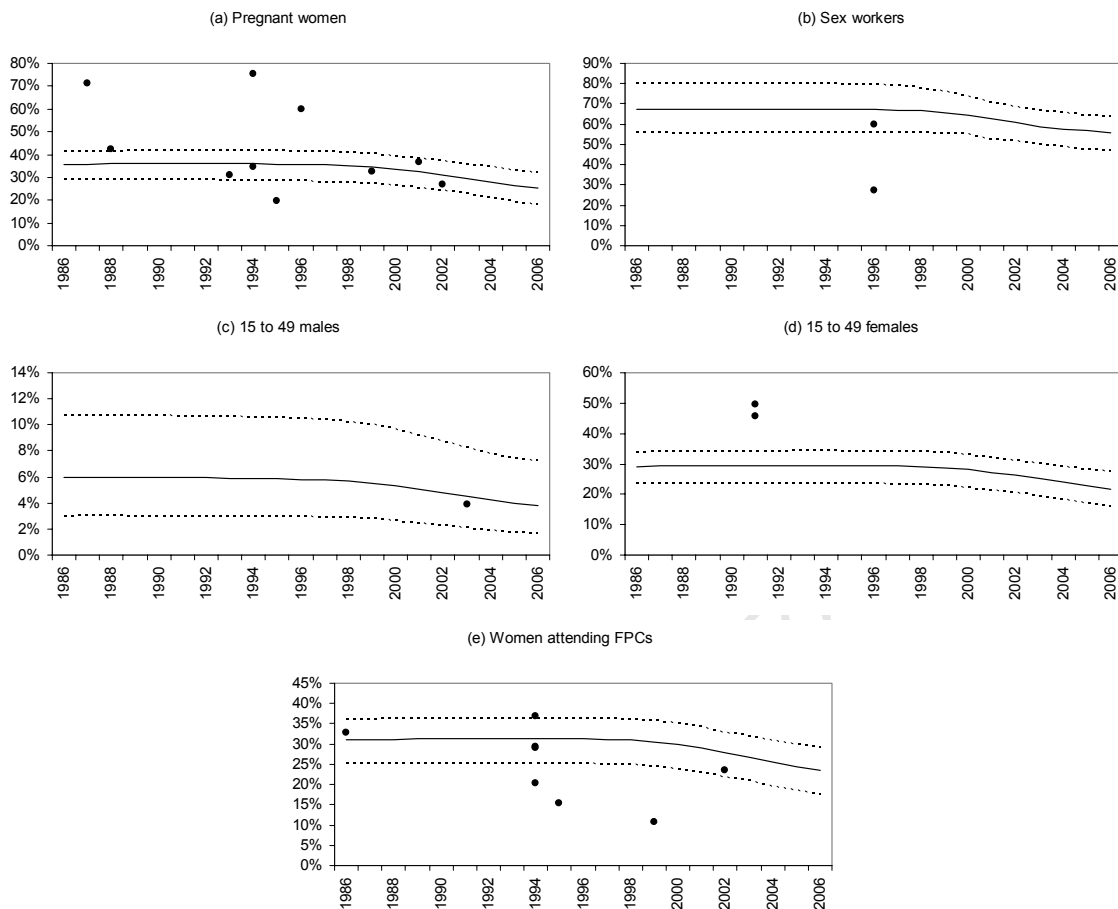


Figure 4.2.6: Trichomoniasis prevalence in different sub-populations

Dots represent measurements from sentinel surveys, after adjustment for sensitivity and specificity of diagnostic used. Mean of posterior distribution represented by solid black line. 2.5 and 97.5 percentiles of posterior distribution (95% prediction intervals) represented by dashed lines.

Figure 4.2.7 compares model estimates of the prevalence of bacterial vaginosis (defined according to Nugent's scoring method) with survey estimates. Although there are relatively few studies in which bacterial vaginosis was measured using Nugent's scoring method, the model predictions and observations are reasonably consistent.

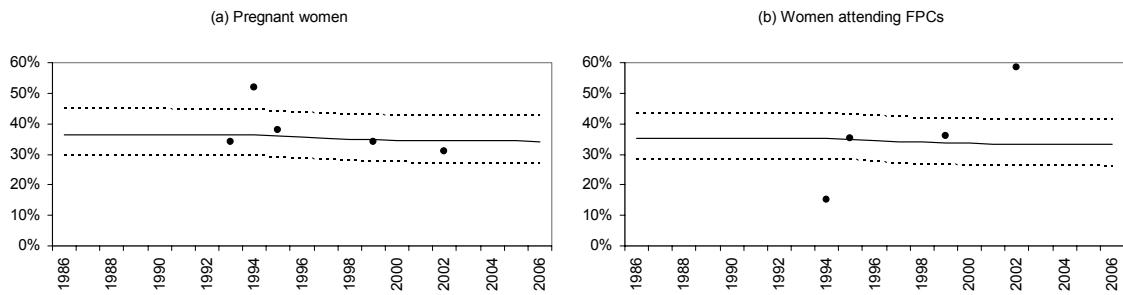


Figure 4.2.7: Bacterial vaginosis prevalence in different sub-populations

Dots represent measurements from sentinel surveys. Mean of posterior distribution represented by solid black line. 2.5 and 97.5 percentiles of posterior distribution (95% prediction intervals) represented by dashed lines.

Figure 4.2.8 compares survey estimates of the prevalence of vulvovaginal candidiasis (including asymptomatic yeast infection) with the model posterior prediction intervals. As with bacterial vaginosis, there are relatively few studies, but model predictions appear to be reasonably consistent with survey estimates.

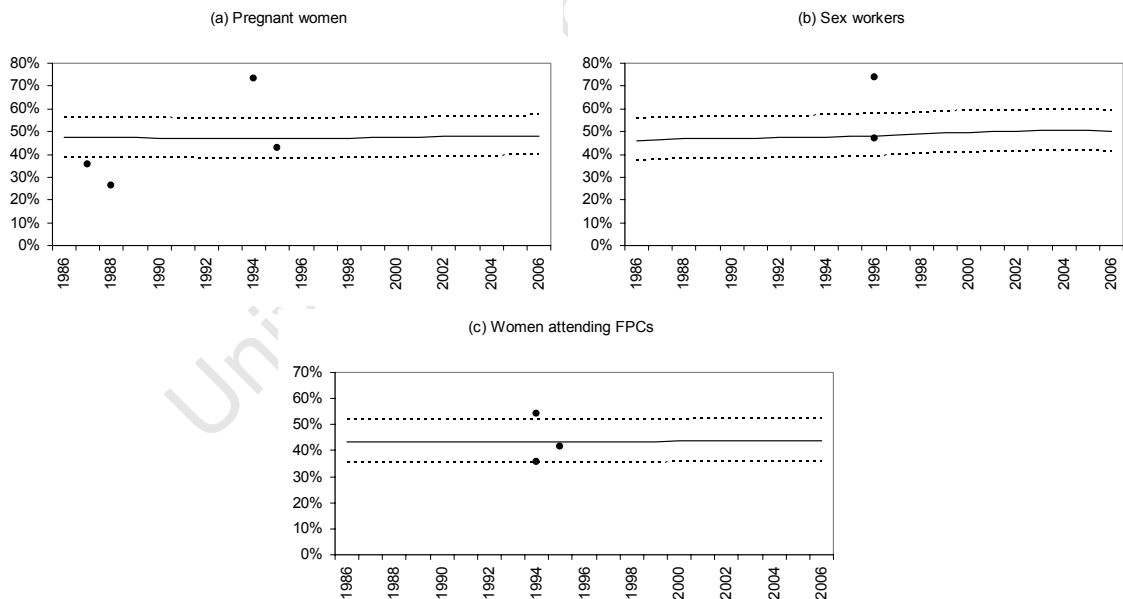


Figure 4.2.8: Vulvovaginal candidiasis prevalence in different sub-populations

Dots represent measurements from sentinel surveys, after adjustment for sensitivity and specificity of diagnostic used. Mean of posterior distribution represented by solid black line. 2.5 and 97.5 percentiles of posterior distribution (95% prediction intervals) represented by dashed lines.

Data are particularly sparse in the case of genital herpes, after the exclusion of the GUD data. Figure 4.2.9 compares the posterior prediction intervals with the few

seroprevalence survey estimates that have been published (adjusted for the sensitivity and specificity of the diagnostics used). As in previous figures, the model estimates of HSV-2 prevalence in the 15 to 49-year old population are not strictly comparable with the household survey estimates for different age groups, particularly in the case of the 1999 survey, which was conducted among 14 to 24-year olds (the prevalence of HSV-2 in 14 to 24-year olds would be expected to be lower than that in the population aged 15 to 49). The differences between the model predictions of the national average and the survey proportions are in many cases extreme, and the standard deviation of the study effects estimated in section 4.2.4 is therefore very high.

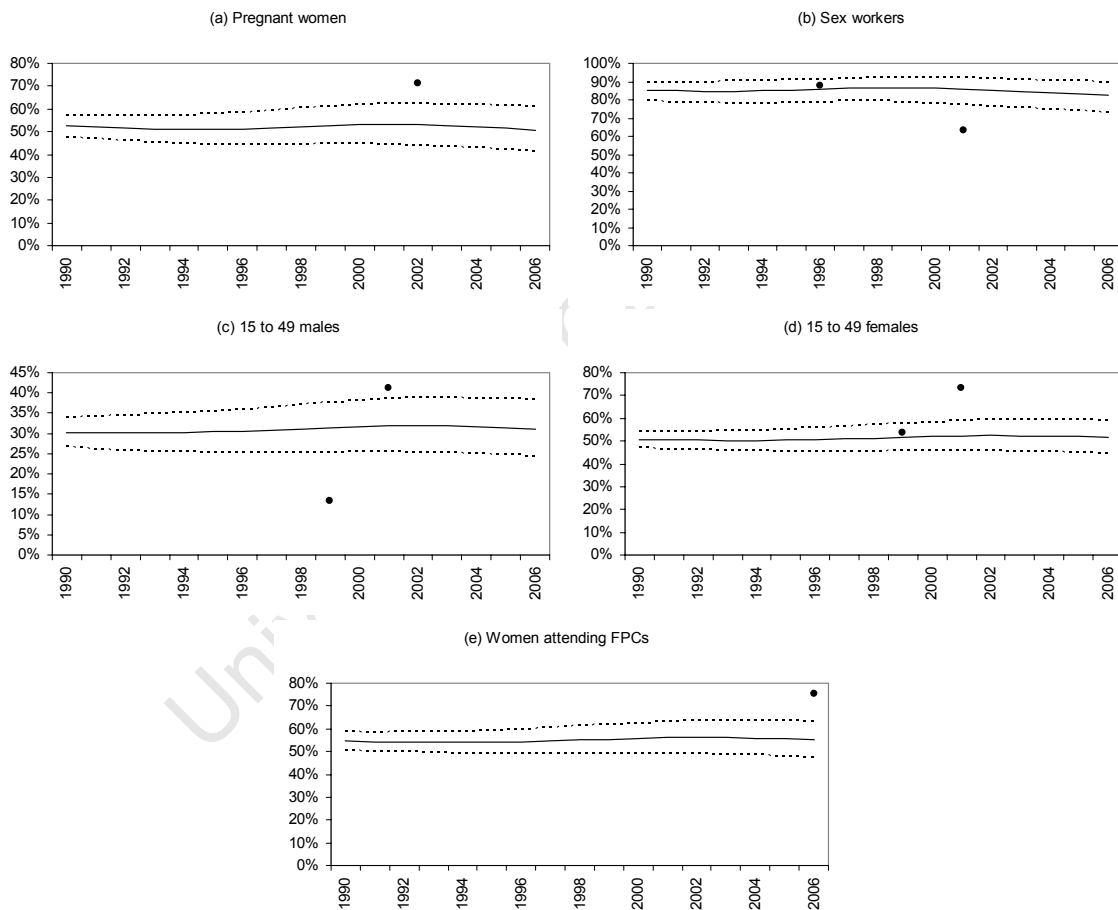


Figure 4.2.9: HSV-2 seroprevalence in different sub-populations

Dots represent measurements from sentinel surveys, after adjustment for sensitivity and specificity of diagnostic used. Mean of posterior distribution represented by solid black line. 2.5 and 97.5 percentiles of posterior distribution (95% prediction intervals) represented by dashed lines.

Although not included in the definition of the likelihood function, the GUD data are compared with model predictions of the proportion of GUD cases attributable to

genital herpes and chancroid in Figure 4.2.10. For the purpose of calculating the model estimates of the proportion of GUD attributable to genital herpes and chancroid, it is assumed that 25% of all GUD cases are attributable to causes other than herpes, syphilis and chancroid, based on findings of studies that used highly sensitive PCR tests to investigate GUD aetiology (Chen *et al*, 2000; Moodley *et al*, 2003a; Lai *et al*, 2003; Kharsany *et al*, 2000; Muller *et al*, 2007b; Muller *et al*, 2007a). Syphilis parameter combinations were randomly paired with HSV-2 parameter combinations to generate the prediction intervals, but because the chancroid parameters are not included in the Bayesian analysis, the 95% prediction intervals understate the true extent of the uncertainty surrounding the GUD estimates.

Figure 4.2.10 shows that the model predictions are reasonably consistent with empirical findings, after taking into account the limited sensitivity of the culture methods used to test for chancroid and herpes in the studies conducted prior to 1993. Although the predicted proportion of female GUD cases attributable to chancroid appears to be implausibly high prior to 2000, these predictions are consistent with an earlier study that estimated the proportion to be 46% (Duncan *et al*, 1984), and the 0 observation for 1997 is based on a small sample of only 23 GUD cases.

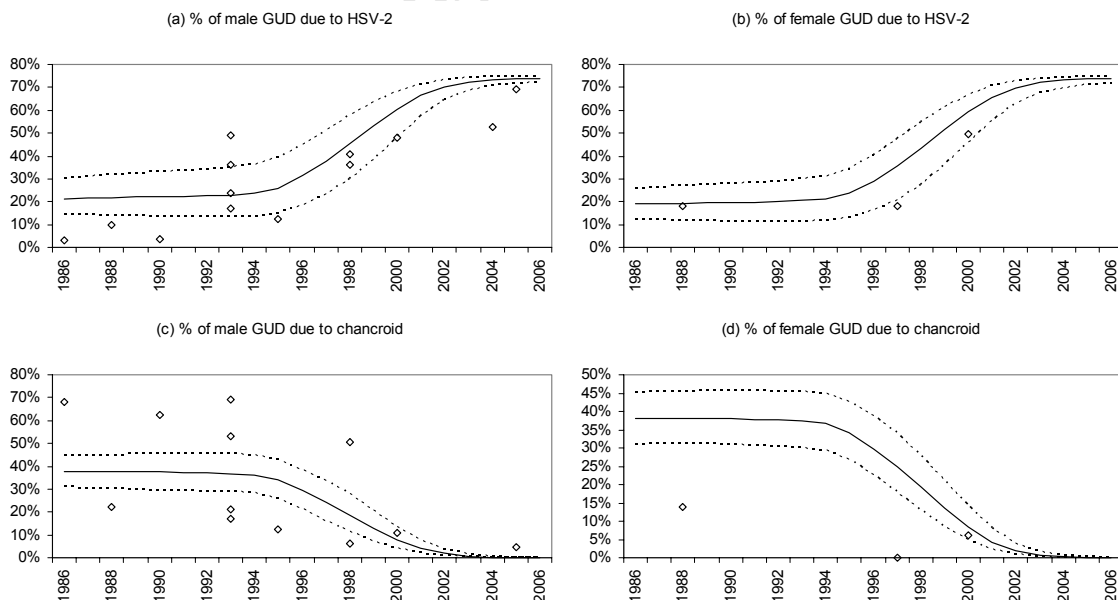


Figure 4.2.10: Proportion of GUD cases attributable to genital herpes and chancroid
Open diamonds represent measurements from sentinel surveys (not included in the definition of the likelihood). Posterior means and 95% prediction intervals are represented by solid and dashed lines.

The model also predicts an overall prevalence of GUD in females consistent with levels measured in surveys of women attending family planning clinics (Wilkinson *et al*, 1997; Kleinschmidt *et al*, 2007) and antenatal clinics (O'Farrell *et al*, 1989). Figure 4.2.11 shows that the model estimates of the GUD prevalence in women between the ages of 15 and 49 are roughly consistent with survey estimates of the prevalence of GUD in women of reproductive age, after taking into account the variability of the study effects estimated for ulcerative STIs. The model also predicts that the prevalence of GUD in sex workers in 1996 was 8.8% (95% CI: 7.4-10.3%), which is roughly consistent with the observed prevalence of GUD in sex workers at this time: 12.7% among sex workers in KwaZulu-Natal (Ramjee *et al*, 1998), 9.7% among sex workers in Virginia (Steen *et al*, 2000) and 3.8% among sex workers in Johannesburg (Dunkle *et al*, 2005).

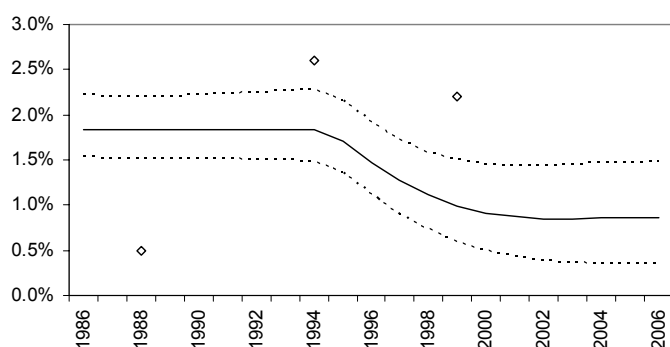


Figure 4.2.11: Prevalence of GUD among women aged 15 to 49

Open diamonds represent measurements from sentinel surveys (not included in the definition of the likelihood). Mean of posterior distribution represented by solid black line. 2.5 and 97.5 percentiles of posterior distribution (95% prediction intervals) represented by dashed lines.

The model is also validated against age-specific STI prevalence data, where available. Figure 4.2.12 shows that the modelled seroprevalence of syphilis follows a similar age pattern to the national antenatal survey (Department of Health 2000), with the seroprevalence of syphilis being highest in the 20 to 34 age group. Few other reliable age-specific STI prevalence estimates are available in South Africa, as sample sizes are generally too small to allow meaningful age-specific comparisons. However, it is useful to compare the age-specific seroprevalence of HSV-2 in Zambia (Weiss *et al*, 2001) with the model prediction for South Africa in 2000 (Figure 4.2.13), as a check

on the plausibility of the HSV-2 assumptions. The Zambian survey, as well as other HSV-2 prevalence surveys in other southern and eastern African countries (Smith and Robinson 2002), suggest that male HSV-2 prevalence peaks at over 50% after the age of 40, and that female HSV-2 prevalence peaks at over 75% after the age of 35. The model results are consistent with these age-specific HSV-2 prevalence trends in other African countries, although the modelled estimate of HSV-2 prevalence in young females is significantly lower than the corresponding prevalence in Zambia.

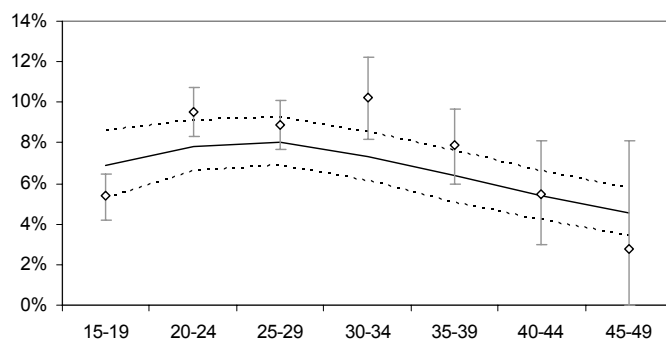


Figure 4.2.12: Age-specific seroprevalence of syphilis in pregnant women in 1999

Open diamonds (with 95% CI) represent measurements from national antenatal survey. Mean of posterior distribution for South Africa represented by solid black line. 2.5 and 97.5 percentiles of posterior distribution (95% prediction intervals) represented by dashed lines.

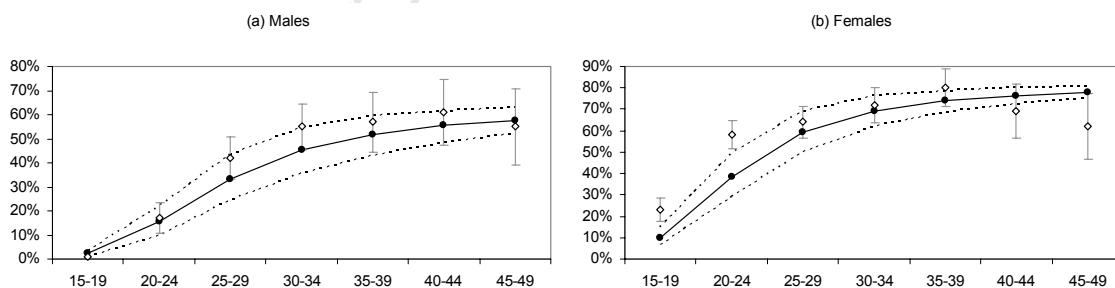


Figure 4.2.13: Age-specific seroprevalence of HSV-2 in 2000, compared with that in Ndola (Zambia)

Open diamonds (with 95% CI) represent measurements from survey in Ndola. Mean of posterior distribution for South Africa represented by solid black line. 2.5 and 97.5 percentiles of posterior distribution (95% prediction intervals) represented by dashed lines.

4.2.6 Comparison of STI prevalence estimates

Figure 4.2.14 summarizes the posterior predictions shown in the previous section, comparing the relative prevalence levels of different infections. HSV-2, bacterial vaginosis and vulvovaginal candidiasis are highly prevalent in South African women, and the prevalence of these infections has remained relatively constant over the 1995-2005 period. Trichomoniasis is the most common curable STI in women, infecting approximately 29% (95% prediction interval: 24-34%) of women aged 15 to 49 in 1995. However, trichomoniasis is relatively uncommon in men. The prevalence of gonorrhoea and chlamydial infection is also substantially lower in men than in women, while the prevalence of syphilis⁶ is similar in men and women. The model predicts substantial declines in the prevalence of syphilis and chancroid over the 1995 to 2005 period, consistent with those observed in the antenatal clinic surveys and in studies of GUD patients. The model also predicts moderate declines in the prevalence of gonorrhoea, trichomoniasis and chlamydial infection.

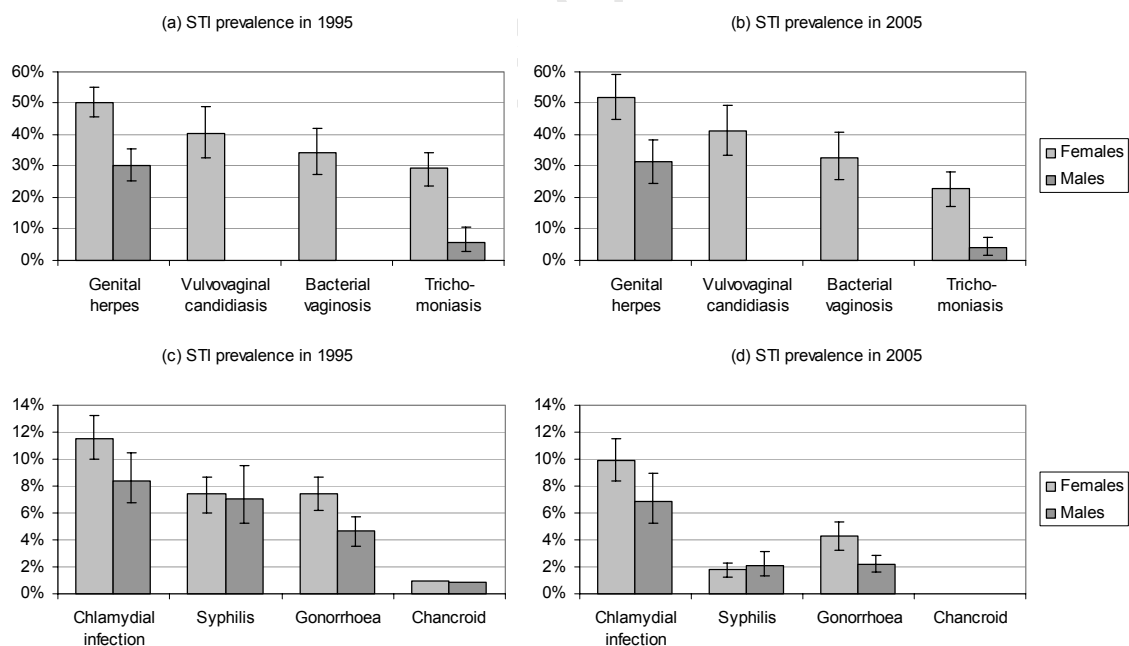


Figure 4.2.14: Comparison of STI prevalence in males and females aged 15 to 49

Error bars represent 95% prediction intervals.

⁶ The prevalence of syphilis presented here is the actual prevalence of syphilis predicted by the model, not the seroprevalence shown in section 4.2.5. The seroprevalence is adjusted to take into account absence of syphilis antibodies during the incubation phase of syphilis and the presence of syphilis antibodies in the months following the resolution of infection.

4.3 Alternative models of STI immunology

STI models have not traditionally allowed for immunity after STI recovery, although the existence of temporary immunity after recovery from syphilis is well accepted (Korenromp *et al*, 2000b; Garnett *et al*, 1997; Pourbohloul *et al*, 2003), and a few models have also allowed for immunity after recovery from chlamydial infection (White *et al*, 2004; Garnett and Anderson 1996). The model described in chapter 3 differs from most other STI models in that it allows for temporary immune protection after recovery from syphilis, chlamydial infection, gonorrhoea, trichomoniasis and chancroid. Although there is empirical evidence suggesting that this approach may be valid (as discussed in section 3.3.1), it is important to examine whether allowing for immunity to STIs significantly improves the fit of the model to the available STI prevalence data. If there is an improvement in fit, this would support the view that partial immunity is significant in STI epidemiology. This section therefore compares the fit of the model to the available gonorrhoea, chlamydial infection and trichomoniasis prevalence data, under various assumptions about STI immunology. (Syphilis is not included because the existence of partial immunity is already well accepted, and chancroid is not included because we have not been able to define a likelihood function to represent the ‘goodness of fit’ to the chancroid prevalence data.)

4.3.1 Method

For each of the three STIs, three different models are fitted:

- Model A: There is assumed to be no immunity, i.e. individuals return to the susceptible state as soon as they recover from their STI.
- Model B: Spontaneous resolution of STIs is assumed to be the result of a successful immune response to the infection, and hence all individuals are assumed to be temporarily immune to reinfection after spontaneous resolution. Individuals who are successfully treated are assumed not to develop immunity, and therefore return immediately to the susceptible state.

- Model C: As for model B, all individuals who experience spontaneous resolution are temporarily immune to reinfection. In addition, a proportion of those who are successfully treated are immune to reinfection.

Model B is thus the model used for gonorrhoea and trichomoniasis in section 4.2, while model C is the model used for chlamydial infection in section 4.2.

All three models are fitted using the method described in section 4.2, i.e. using a sampling importance resampling (SIR) approach that yields an approximation to the posterior distribution of model outputs. Model B is the same as model A, but with one additional parameter (the average duration of immunity), and model C is the same as model B, except for the parameter that determines the proportion of successfully treated individuals who are immune to reinfection. Model A is thus nested in model B, which in turn is nested in model C. The prior distribution on the average duration of immunity is gamma with mean 52 weeks and standard deviation 26 weeks for gonorrhoea and trichomoniasis, and gamma with mean 520 weeks and standard deviation 200 weeks for chlamydial infection (since there is stronger evidence of immunity for chlamydial infection than for gonorrhoea and trichomoniasis). This prior is the same in models B and C. In model C, the prior distribution on the proportion of individuals who are immune after treatment is uniform on the interval $(0, 1)$ for all three STIs. Prior distributions on other parameters are the same as those described in previous sections.

In comparing the different models, three sets of statistics are examined:

1. The distribution of likelihood values in the posterior sample. The greater the difference in distributions, when comparing two nested models, the more significant is the improvement in the ‘goodness of fit’ to the STI prevalence data that is achieved through the additional parameter. Although it does not appear to be possible to conduct a formal statistical test to establish significance, it is worth noting that when comparing nested models that have been fitted by maximum likelihood, where the two models differ by a single parameter, a difference in log likelihood values of 1.9 would be considered significant at the 5% level, and a difference of 6.1 would be considered significant at the 0.05% level.

2. The number of distinct parameter combinations in the posterior sample. The more efficient the SIR technique is in simulating the posterior distribution, the greater one would expect the number of distinct parameter combinations to be. The SIR posterior simulation technique is most efficient when the prior and posterior distributions are similar, i.e. when the STI prevalence data support the *a priori* assumptions. Hence, if the number of distinct parameter combinations in the posterior sample is large, this is an indication that our prior beliefs about model parameters are consistent with the STI prevalence data, for a given model structure.
3. The estimated standard deviation of the study effects. The lower the variance of the study effects, the greater is the proportion of the total variation in STI prevalence levels that is accounted for by the model. Models that provide a better fit to the STI prevalence data therefore tend to have lower posterior estimates of the standard deviation of study effects.

In addition, the correspondence between the means of the posterior distributions and the observed STI prevalence levels (after adjustment for the expected sensitivity and specificity of diagnostics) is examined visually for both ‘low risk’ females (women in households and women attending antenatal and family planning clinics) and ‘high risk’ females (commercial sex workers), for all three models. This shows the particular features of the data that most significantly determine the differences in ‘goodness of fit’ between the models. For the sake of convenience, antenatal, family planning and household prevalence data are combined in this comparison, since the simulations in section 4.2 suggest that they would be expected to be roughly similar. Male STI prevalence data are not included in the comparison since there are relatively few male prevalence estimates.

4.3.2 Results

Table 4.3.1 compares the parameter estimates for each of the three models and for each of the three STIs. In the case of gonorrhoea, model B provides a significantly better fit than model A. The difference in likelihood values between models A and B is highly significant. The fact that there are relatively few distinct parameter combinations in the posterior sample for model A is also an indication that model A

does not conform with our prior beliefs about the gonorrhoea parameters. The estimated standard deviation of the study effects in model B is also substantially smaller than that in model A. Models B and C, however, have similar likelihood values and similar study effect standard deviations, which suggests that allowing for immunity after successful treatment does not significantly improve the model in the case of gonorrhoea.

In the case of chlamydial infection, the differences between models A and B are again very significant. Only one parameter combination is sampled in the posterior sample for model A. The likelihood values for model B are significantly greater than those for model A, and the standard deviation of the study effects is significantly lower for model B than for model A. The difference between model B and model C is of borderline significance (a difference in log likelihood values of 1.9 would normally be considered significant at the 5% level), and the standard deviation of study effects in model C is slightly lower than that in model B. Allowing for immunity after successful treatment therefore improves the fit of the model, though it is questionable whether the improvement is significant enough to justify the additional model parameter.

In the case of trichomoniasis, there appears to be a significant difference between models A and B in terms of their likelihood values, but there is relatively little difference in either the number of distinct parameter combinations or the standard deviation of the study effects. When comparing models B and C, however, there is no significant difference in likelihood values, numbers of distinct parameter combinations or standard deviations of study effects. Allowing for partial immunity following successful treatment of trichomoniasis therefore does not improve the fit of the model.

Figure 4.3.1 compares the model predictions with the observed STI prevalence levels, after adjusting the latter for expected levels of sensitivity and specificity (the results for model B are not shown because they are barely distinguishable from the results for model C on the scale presented). For all three STIs, model A provides a poor fit to the observed levels of STI prevalence in sex workers, but models B and C provide a

Table 4.3.1: Comparison of models A, B and C in terms of ‘goodness of fit’ statistics and posterior parameter estimates

	Model A	Model B	Model C
Gonorrhoea			
Log likelihood values from posterior sample			
Median	-3875.0	-3850.0	-3850.0
Maximum	-3874.0	-3848.1	-3848.3
Minimum	-3885.7	-3857.5	-3858.0
# distinct parameter combinations in posterior sample	52	313	285
Standard deviation of study effects*	0.58 (0.42-0.74)	0.30 (0.17-0.44)	0.31 (0.17-0.46)
Average duration of immunity (weeks)*	-	68 (40-113)	58 (29-105)
Proportion of cases immune after treatment*	-	-	0.41 (0.02-0.91)
Chlamydial infection			
Log likelihood values from posterior sample			
Median	-6184.5	-6144.7	-6142.3
Maximum	-6184.5	-6142.6	-6139.5
Minimum	-6184.5	-6152.6	-6148.0
# distinct parameter combinations in posterior sample	1	364	350
Standard deviation of study effects*	1.07	0.36 (0.24-0.49)	0.33 (0.21-0.47)
Average duration of immunity (weeks)*	-	558 (338-894)	490 (277-773)
Proportion of cases immune after treatment*	-	-	0.72 (0.21-0.99)
Trichomoniasis			
Log likelihood values from posterior sample			
Median	-3352.6	-3348.9	-3348.2
Maximum	-3351.4	-3347.2	-3346.5
Minimum	-3357.9	-3354.6	-3353.5
# distinct parameter combinations in posterior sample	397	385	382
Standard deviation of study effects*	0.51 (0.31-0.77)	0.53 (0.33-0.75)	0.52 (0.33-0.75)
Average duration of immunity (weeks)*	-	63 (22-121)	56 (21-114)
Proportion of cases immune after treatment*	-	-	0.58 (0.05-0.98)

* Numbers reported are the mean of the posterior distribution and the 95% prediction interval (in brackets).

substantially better fit. Models A, B and C all provide reasonable fits to the STI prevalence data in ‘low risk’ women, though model A predicts a more rapid decline in the prevalence of gonorrhoea after 1995 than the gonorrhoea prevalence data suggest. Models A, B and C also all provide reasonable fits to the STI prevalence data for men sampled in household surveys, except in the case of model A, which substantially overestimates the prevalence of chlamydial infection (results not shown). Most of the differences between models, in terms of distributions of likelihood values, therefore appear to be explained by differences in the fit to the observed STI prevalence levels in ‘high risk’ women, though differences in fit also appear to be significant in ‘low risk’ women in the case of gonorrhoea, and in ‘low risk’ men in the case of chlamydial infection.

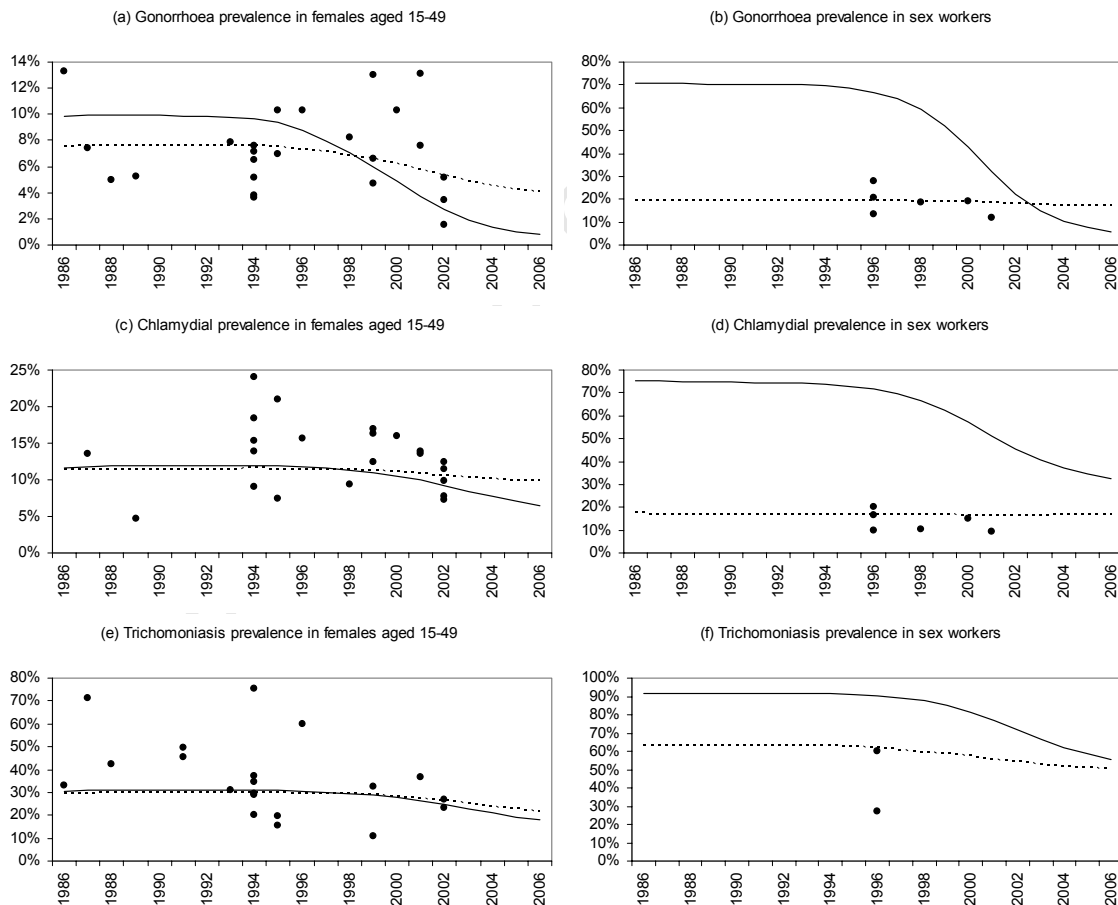


Figure 4.3.1: Comparison of predicted and observed STI prevalence levels, for models A and C

Posterior means are represented by solid black line for model A and dashed line for model C. Observed STI prevalence levels, adjusted for expected sensitivity and specificity levels, are represented by closed circles.

4.4 Discussion

4.4.1 The impact of HIV/AIDS in South Africa

This analysis confirms that HIV/AIDS is having a major demographic impact in South Africa, with the crude mortality rate attributable to AIDS reaching approximately 6 per 1000 person years in 2005, and the proportion of the 15 to 49-year old population infected with HIV rising to roughly 17% in 2005. Although HIV incidence rates appear to have declined since 1999, they remain high, and there is thus still an urgent need for advances in HIV prevention.

The model has been fitted to HIV prevalence data and sexual behaviour data from the antenatal clinic surveys conducted between 1997 and 2005 and the HSRC household survey that was conducted in 2005. In addition, the model has been validated against several data sources that were not used in defining the likelihood function: antenatal HIV prevalence estimates from surveys conducted prior to 1997, HIV prevalence estimates from national household surveys conducted in 2002 and 2003, HIV prevalence estimates from studies of sex workers, and proportions of the population in spousal relationships (as reported in two censuses and a national community survey). Although there were a few instances in which this validation process revealed significant discrepancies between model predictions and survey measurements, there was good overall agreement between the posterior model estimates and the survey results. The fact that this agreement was achieved in spite of these data not being incorporated into the likelihood definition increases our confidence in the results of the model.

The model is also in broad agreement with other HIV/AIDS models that have been developed for South Africa. Table 4.4.1 compares the posterior estimates from the current model with estimates from uncertainty analyses of the ASSA2002 AIDS and Demographic model (Johnson *et al*, 2007) and the EPP/Spectrum model (UNAIDS 2006), and estimates from the ASSA2003 model (Dorrington *et al*, 2006). HIV prevalence estimates in the STI-HIV interaction model are slightly lower than those obtained using other models, probably because greater weight is given to the HIV

prevalence estimates from the 2005 HSRC household survey in the current analysis than in the fitting of the ASSA2002 and ASSA2003 models (the 2005 HSRC household survey measured a lower male HIV prevalence than that predicted by the ASSA2002 and ASSA2003 models). The models produce similar estimates of HIV incidence in 2005, but very different estimates of the effect of AIDS on the crude mortality rate. The lower AIDS mortality rate predicted by the STI-HIV interaction model can probably be explained by (a) the lower HIV prevalence in the current model, (b) the greater assumed effectiveness of antiretroviral treatment in the current model, and (c) the more gradual increase in AIDS mortality in the current model, as a result of HIV survival times being modelled as a sum of exponentially-distributed random variables rather than a sum of Weibull-distributed random variables. Since the modelling of the effect of AIDS on mortality is not as sophisticated in the STI-HIV interaction model as in the ASSA2002 and ASSA2003 models, the ASSA AIDS and Demographic model estimates of the impact of AIDS on mortality should be regarded as more reliable.

Table 4.4.1: Comparison of HIV/AIDS indicators for South Africa, as estimated by different models

Indicator	Model	Estimate (95% range)
HIV prevalence in 2005 (total population)	STI-HIV interaction model	10.1% (9.4-10.9%)
	ASSA2002	11.1% (9.1-13.1%)
	ASSA2003	11.0%
HIV prevalence in 2005 (15 to 49-year olds)	STI-HIV interaction model	16.9% (15.7-18.1%)
	EPP/Spectrum	18.8% (16.8-20.7%)
	ASSA2003	18.0%
HIV incidence rate in 2005 (total population)	STI-HIV interaction model	1.2% (1.1-1.3%)
	ASSA2002	1.2% (0.9-1.5%)
	ASSA2003	1.3%
Increase in crude death rate due to AIDS in 2005 (per 1 000 person years)	STI-HIV interaction model	5.8 (5.3-6.3)
	ASSA2002	7.4 (6.2-8.9)
	ASSA2003	7.1

Table 4.4.1 also shows that the 95% prediction intervals estimated in the ASSA2002 uncertainty analysis are wider than those obtained in the current uncertainty analysis. This is because the likelihood function in the ASSA2002 uncertainty analysis was adjusted subjectively to obtain 95% prediction intervals wide enough to include 95% of observations. The 95% prediction intervals in the current analysis reflect the uncertainty around key model parameters, but they do not take into account uncertainty regarding many other behavioural and biological parameters in the model, and they do not reflect the uncertainty regarding the choice of model structure. Taking these factors into account would widen the prediction intervals.

A possible criticism of the method used to estimate HIV prevalence is that it does not allow for the possibility that HIV prevalence levels measured in household surveys may be biased. Some under-estimation of HIV prevalence may occur due to the exclusion from the sampling frame of the population in institutions (prisons, military bases, hospitals, etc), in which the prevalence of HIV might be expected to be relatively high. It is also possible that non-responders and respondents who refuse to be HIV-tested may be at a higher risk of HIV infection than those survey respondents who are HIV-tested (Boerma *et al*, 2003). However, analyses of household HIV prevalence surveys in other African countries show that allowing for non-response bias does not substantially change overall estimates of HIV prevalence (Mishra *et al*, 2006; McNaghten *et al*, 2007). In the 2005 HSRC household survey, the source of the household prevalence data in the current analysis, the only significant differences between individuals who agreed to be tested and those who refused testing were that those who agreed to be tested were more likely to report STI symptoms in the last three months, more likely to be female, and more likely to consider themselves not at risk of HIV infection (Shisana *et al*, 2005). It is therefore not clear in which direction the bias would lie, but in the absence of better information, the observed HIV prevalence is treated as an unbiased estimate of the true population prevalence of HIV.

4.4.2 Assessing uncertainty in HIV/AIDS projection models

Much research has recently been conducted to assess uncertainty in HIV/AIDS projection models. Early work focussed on assessing uncertainty in models that were

not constrained to produce outputs consistent with observed HIV prevalence levels, through the use of techniques such as Latin hypercube sampling and Monte Carlo simulation (Blower and Dowlatabadi 1994; Boily *et al*, 2004; Davenport *et al*, 2004; Law *et al*, 2001). More recent work has focussed on the assessment of uncertainty in HIV/AIDS projections models that are calibrated to observed HIV prevalence levels using ‘goodness of fit’ or ‘likelihood’ measures (Alkema *et al*, 2007; Morgan *et al*, 2006; Grassly *et al*, 2004; Salomon and Murray 2001; Hsieh *et al*, 2006). These HIV prevalence data are usually obtained from particular clinics or sentinel sites, which are usually not systematically sampled to give nationally representative HIV prevalence estimates. In South Africa, however, antenatal and household surveys of HIV prevalence are based on nationally representative samples, and this requires a different approach to defining the ‘goodness of fit’ to the survey data.

Relatively few assessments of uncertainty in HIV/AIDS models follow Bayesian approaches (Alkema *et al*, 2007; Goubar *et al*, 2008; Gilks *et al*, 1999; Tan and Ye 2000). The fundamental advantage of adopting the Bayesian approach is that it allows the modeller to incorporate prior knowledge about epidemiological parameters and to make inferences about these parameters, in addition to assessing the range of uncertainty around the model predictions. In earlier work based on the ASSA2002 model, a generalized likelihood uncertainty estimation (GLUE) technique was used, as a means of integrating data from multiple data sources (Johnson *et al*, 2007). This approach might be considered ‘pseudo-Bayesian’ insofar as it allows for the specification of prior distributions to represent prior knowledge, but it falls short of being truly Bayesian because the likelihood function is an arbitrarily defined ‘goodness of fit’ measure and not a likelihood function in the true statistical sense. In this analysis, we adopt a more rigorous approach to defining the likelihood function, including bias terms and model error terms to represent different components of the differences between observations and model predictions (Sevcikova *et al*, 2006).

The antenatal bias parameters that have been estimated on a logit scale can be exponentiated to obtain an odds ratio relating the observed HIV prevalence to the true HIV prevalence (as predicted by the model). The average value of this odds ratio is 1.48 (95% prediction interval: 1.30-1.69). This difference between the observed and modelled HIV prevalence in pregnant women could be attributed to a number of

factors. Firstly, the antenatal clinic surveys represent only women seeking antenatal care in public health facilities, and women who seek private antenatal care (who are generally believed to be at a lower risk of HIV infection) are not included. Secondly, false positive reactions on standard antibody tests may lead to an exaggeration of HIV prevalence levels in pregnant women; ELISA specificities in African populations tend to be lower than those in the developed world (Van Kerckhoven *et al*, 1991), and in many African studies specificities of 98% or lower have been recorded (Nkengasong *et al*, 1999; Meda *et al*, 1999a; Urassa *et al*, 1999). Lastly, it is possible that the model may under-estimate the true prevalence of HIV in pregnant women because it assumes that in sexually experienced women, fertility rates depend only on age and HIV stage. Since fertility rates probably also depend on the amount of unprotected sex that women have, and since the frequency of unprotected sex is also likely to be associated with HIV risk, the model may fail to capture some of the association between pregnancy and HIV risk. Alternative fertility assumptions will need to be explored in future analyses of the model.

Bias parameters have also been estimated for the sexual behaviour data. These parameters can be exponentiated to obtain odds ratios relating the true prevalence of a particular sexual behaviour to the reported prevalence of that behaviour. The odds ratios that have been estimated in this way are represented in Table 4.4.2. The results suggest that there is substantial under-reporting of concurrent partnerships, particularly among women and among married individuals. The magnitude of this under-reporting is perhaps not surprising, considering that self-reported sexual behaviour data were obtained in face-to-face interviews (FTFIs) conducted by retired nurses. Social desirability bias can be expected to lead to the under-reporting of certain risk behaviours in FTFIs, especially when those administering the questionnaires are considerably older than the respondents (Mensch *et al*, 2003). Several alternative interview formats have been tested in an attempt to reduce this bias, including audio-computer-assisted self-interviews (ACASI), informal confidential voting interviews (ICVI) and self-administered questionnaires (SAQ). Using these more impersonal interview techniques, it has been found that the women's odds of reporting multiple sexual partners are between 1.0 and 5.2 times those reported in FTFIs (Ghanem *et al*, 2005; Kissinger *et al*, 1999; Rogers *et al*, 2005; Gregson *et al*, 2004; Gregson *et al*, 2002b), with this multiple being

considerably higher in married women than in unmarried women (Gregson *et al*, 2002b). Men’s odds of reporting multiple partners in the more impersonal interview formats are between 1.1 and 1.7 times those in FTFIs (Ghanem *et al*, 2005; Rogers *et al*, 2005; Gregson *et al*, 2004; Gregson *et al*, 2002b). The odds ratios that are shown in Table 4.4.2 are roughly consistent with the empirical estimates of bias, though the latter tend to be closer to one. It is likely that the alternative interview formats only partially reveal the extent of social desirability bias, since subjects will tend to worry about the confidentiality of their responses even when impersonal interview formats are used, and individuals who have had limited contact with computer technology are likely to be distrustful and fearful of computer-assisted methods (Mensch *et al*, 2003).

Table 4.4.2: Posterior estimates of the ratio of the odds of engaging in a particular behaviour to the odds of reporting that behaviour

Behaviour	Odds ratio (95% prediction interval)	
	Males	Females
More than one current partner (unmarried individuals)	1.26 (0.87-1.54)	6.3 (3.9-8.2)
More than one current partner (married individuals)	3.3 (2.0-4.3)	20.6 (9.5-31.0)
No current partner (unmarried individuals)	1.16 (0.60-2.00)	0.66 (0.46-1.06)

Model error terms have been included in the likelihood function definition for the antenatal clinic data, but not for the HSRC household survey data. This is because the 95% confidence intervals around the levels of HIV prevalence measured in the antenatal clinic surveys are too narrow to include most model estimates, and there is thus a need to allow for differences between model predictions and survey estimates in excess of what can be attributed to sampling variation alone. The 95% confidence intervals around the HSRC household survey data, on the other hand, are wide enough to include most model estimates, and there is thus less of a need for model error terms when specifying the likelihood function for the HSRC data. Initial attempts to include model error terms in the likelihood function for the HSRC survey data resulted in poor fits to the HSRC HIV prevalence data; the Metropolis algorithm converged on

parameter combinations that gave good fits to the large antenatal HIV prevalence dataset, at the expense of the fit to the smaller HSRC dataset, the significance of which was diminished to low levels by imputing large model error terms. Model error terms should therefore be used with discretion in likelihood specification.

Most previous Bayesian analyses of HIV/AIDS models have been based on only one source of data, typically HIV prevalence data or reported numbers of AIDS cases. Goubar *et al* (2008) note that it is ideal to incorporate a number of data sources in the Bayesian analysis, as this helps to validate the model structure and can also yield important insights into biases that might not be apparent when considering one data set in isolation of others. In the analysis presented in section 4.1, HIV prevalence data from antenatal clinic surveys, HIV prevalence data from household surveys and sexual behaviour data have all been used in defining the likelihood function. All data are sex- and age-specific, which helps to improve confidence in the modelling of age and gender differences in sexual behaviour. It would also be possible to include reported death data in the definition of the likelihood function, as in our previous analysis (Johnson *et al*, 2007), but since the STI-HIV interaction model is not designed to be a demographic model, and since the HIV survival assumptions are not included in the present Bayesian analysis, there would probably be little benefit from doing so.

4.4.3 Estimating STI prevalence levels from sentinel surveillance data

Relatively little work has been published on appropriate methodologies for calibrating models of STIs other than HIV. Past attempts to calibrate STI models to STI prevalence data have involved subjectively selecting a single set of model parameters in such a way that the model produces estimates of STI prevalence close to the levels of STI prevalence observed (Korenromp *et al*, 2002c; Boily *et al*, 2002; White *et al*, 2004; Turner *et al*, 2004). In some cases this fitting process has implicitly recognized the imperfect sensitivity and/or specificity of the STI diagnostics used. However, modellers have not explicitly taken into account the potential variability in diagnostic performance and the potential binomial variation in STI prevalence, and as a result have not identified ranges of plausible model predictions or quantified the relative likelihood of different model predictions.

The more formal statistical approach that we have proposed has several advantages. Firstly, it allows one to judge the plausibility of a particular model prediction according to an objective likelihood function, which takes into consideration both the potential binomial variation and the potential variation in diagnostic performance, in the data to which the model is calibrated. This in turn is important in uncertainty analysis. Considering that there is substantial uncertainty regarding many of the STI transmission and natural history parameters, it is desirable that STI model conclusions be tested across a range of different plausible parameter combinations, and that conclusions not be based on a single parameter combination. The Bayesian approach provides a natural means of identifying a plausible set of parameter combinations that can be used to make model predictions.

The hierarchical Bayesian approach that we have proposed also takes into account variation in STI prevalence between locations, which is important when attempting to estimate national or regional STI prevalence levels on the basis of STI prevalence data collected in selected communities. In estimating the prevalence of STIs in different global regions, the WHO appears to have used a subjective method to weight the STI prevalence estimates from various studies (Gerbase *et al*, 1998; Rowley and Berkley 1998). The hierarchical Bayesian approach is effectively a random effects weighting method that allows the weights given to different prevalence estimates to vary in relation to the estimated variability in STI prevalence between studies. A similar hierarchical Bayesian approach has been applied by Alkema *et al* (2007), to HIV prevalence data from antenatal sites in African countries. However, Alkema *et al* model a ‘clinic effect’ rather than a ‘study effect’, effectively assuming that all variation between different prevalence measurements (after controlling for the year of measurement) can be explained by the location of the clinic sampled. A potential criticism of the approach that we have adopted is that there is no allowance for correlation between b_i terms for studies conducted in the same location (see equation (4.6) in section 4.2.2), as there is in the analysis of Alkema *et al*. However, when the empirical STI prevalence estimates were adjusted for sensitivity and specificity, logit-transformed and then regressed on time and sample type, the residuals did not appear to differ significantly between locations. This suggests that the inclusion of location effects in the model would probably not change the model results substantially.

The posterior distribution in this Bayesian analysis has been approximated using the Sampling Importance Resampling (SIR) technique. This technique differs from the Metropolis algorithm used to approximate the posterior distribution in section 4.1; while the Metropolis algorithm involves sampling successive parameter combinations based on the posterior densities of the preceding parameter combinations, the parameter combinations that are sampled under the SIR approach are all sampled independently of one another. Although the SIR approach was initially applied to the analysis in section 4.1, it was found that the posterior sample consisted of only a few distinct parameter combinations, even when the initial sample consisted of 100 000 parameter combinations. It is likely that the inefficiency of the SIR approach is due to the extreme differences between the prior and posterior distributions in section 4.1; parameter combinations randomly sampled from the prior distribution tend to have very low posterior densities. In this situation, the Metropolis algorithm performs better because the sampling is adaptive, and the sampling algorithm will therefore avoid the parts of the posterior distribution that have low posterior density. The SIR approach works reasonably well in section 4.2 because the prior and posterior distributions are similar in most cases, and it is therefore not necessary to resort to using the Metropolis algorithm. The initial sample size of 20 000 parameter combinations is the same as that used by Smith and Gelfand (1992), but is smaller than that used in other SIR applications, which have used samples of 100 000 to 200 000 parameter combinations (Johnson *et al*, 2007; Alkema *et al*, 2007). Table 4.2.2 shows that the sample size of 20 000 is sufficient to yield a posterior sample with a large proportion of distinct parameter combinations, and no single parameter combination influencing the posterior sample excessively. However, in cases in which the model fits the data poorly (for example, the model of chlamydial infection in which there is no immunity), the posterior sample may consist of only a single unique parameter combination, and in such cases the SIR approach is clearly not appropriate.

A limitation of the hierarchical Bayesian approach we have described is that it does not allow for systematic bias in the sampling of sentinel surveillance sites. Far from being randomly selected, sentinel sites appear to be disproportionately selected from urban areas and from the Gauteng and KwaZulu-Natal provinces, and the few studies that have been conducted in rural areas are mostly from the Hlabisa district in

KwaZulu-Natal. In addition, a significant number of STI prevalence estimates are from the Khutsong community, which is located close to the world's largest gold mining complex, with extremely high HIV prevalence levels (Ndhlovu *et al*, 2005). It is therefore possible that the STI sentinel surveillance data may provide a very biased picture of STI prevalence levels in the general population of South Africa. The direction of this bias, however, is unclear. In their review of STI prevalence data in Sub-Saharan Africa, Rowley and Berkeley (1998) note that the prevalence of syphilis and chlamydial infection tends to be higher in rural areas than in urban areas, while the prevalence of gonorrhoea tends to be similar in urban and rural areas. The significance of the bias towards surveillance in settings with high HIV prevalence is also not clear; although one might expect a strong positive correlation between HIV prevalence and STI prevalence at a community level, there is little evidence to support this. In fact, a number of African surveys have found weak *negative* correlation between HIV and syphilis prevalence at a regional level (Swai *et al*, 2006; Department of Health 2006; Department of Health 2005; Department of Health 2004a). For other STIs, there are too few data to estimate correlations between STI and HIV prevalence at a regional level, and it is important that such data be collected in order to judge the reliability of estimates derived from sentinel surveillance data.

Another potential limitation of the approach we have proposed is that it does not take into account biases specific to women attending antenatal clinics and family planning clinics. Pregnancy and the use of hormonal contraception are both associated with hormonal and immunological changes (Sonnex 1998; Witkin 1987), and these factors could affect women's susceptibility to STIs. The following associations have been noted in the epidemiological literature:

- Symptomatic vulvovaginal candidiasis has been found to be more prevalent in pregnant women (Ohmit *et al*, 2003; Daus and Hafez 1975) and women using oral contraceptives (Spinillo *et al*, 1993; Geiger and Foxman 1996). However, culture-confirmed yeast infection is not significantly associated with pregnancy (Duerr *et al*, 1997) or oral contraceptive use (Goldacre *et al*, 1979; Hilton and Warnock 1975; Rashid *et al*, 1991; Eckert *et al*, 1998), and it is therefore unlikely that studies of the prevalence of *Candida* in antenatal and family planning clinics would be substantially biased.

- There is substantial evidence suggesting that the use of hormonal contraceptives reduces the risk of bacterial vaginosis (Yen *et al*, 2003; Holzman *et al*, 2001; Smart *et al*, 2004; Nagot *et al*, 2007a). Studies of women attending family planning clinics could therefore be biased towards understating the true prevalence of bacterial vaginosis.
- Oral contraceptive use has been found to increase significantly the risk of chlamydial infection (Cottingham and Hunter 1992), and prospective studies also suggest that injectable contraceptives increase the risk of chlamydial infection (Mohllajee *et al*, 2006). Studies of women attending family planning clinics could therefore exaggerate the average prevalence of chlamydial infection in the female population.
- Mohllajee *et al* (2006) note that several studies have found negative associations between trichomoniasis and use of oral contraceptives, though few have adjusted for likely confounding factors such as bacterial vaginosis and socioeconomic status. If there is indeed a negative association between trichomoniasis and hormonal contraceptive use, it could explain the relatively poor fit of the model to the trichomoniasis prevalence levels observed in women attending family planning clinics (see Figure 4.2.6).

The model also does not take into account potential differences in sexual behaviour and socioeconomic status between women attending these public clinics and women in the general population. It may therefore be necessary, in future, to adapt the method used to calculate antenatal and family planning clinic STI prevalence levels, by adjusting in some way for hormonal contraceptive use, sexual behaviour and socioeconomic factors.

The hierarchical Bayesian method that we have proposed does not take into account data from GUD patients, and as a result it has not been possible to apply the method to chancroid. This is an unfortunate limitation, as chancroid is estimated to be one of the most significant STIs promoting the spread of HIV in the early stages of the HIV/AIDS epidemic (Orroth *et al*, 2006; Freeman *et al*, 2007), and it therefore deserves special attention. A possible approach to calculating the proportion of genital ulcers attributable to chancroid in study *i* (say), would be to calculate it as

$$f_C^*(c_i, h_i, s_i) = \frac{f_C(c_i)}{f_C(c_i) + f_H(h_i) + f_S(s_i)}, \quad (4.22)$$

where $f_C(c_i)$, $f_H(h_i)$ and $f_S(s_i)$ are the model estimates of the prevalence of symptomatic chancroid, symptomatic genital herpes and primary syphilis respectively, after addition of study effects (c_i , h_i and s_i) through a logit transformation (see equation (4.7) in section 4.2.2). For the purpose of calculating the likelihood in respect of the i^{th} study estimate, it is necessary to calculate the mean and variance of $f_C^*(c_i, h_i, s_i)$. This was attempted using both first and second order Taylor series approximations, but neither approximation was found to be sufficiently accurate in the case of the variance (differences of up to 25% of the simulated variance were obtained). In addition to the difficulties associated with obtaining a reasonable approximation to the variance, there are several complications to consider: the formula for $f_C^*(c_i, h_i, s_i)$ does not take into account the possibility of ulcers of mixed aetiology, nor does it take into account ulcers due to causes other than chancroid, syphilis and herpes. More significantly, it is not possible to conduct the Bayesian analysis using chancroid data from GUD patients independently of the Bayesian analysis for syphilis and genital herpes, unless it is assumed that the syphilis and genital herpes parameters are known with certainty. For these reasons, it has not been feasible to include the GUD data in the present analysis. Future research should consider the feasibility of alternative approaches to incorporating the GUD data.

4.4.4 STI prevalence levels in South Africa

This analysis confirms that South Africa has an exceptionally high prevalence of STIs. Table 4.4.3 compares levels of STI prevalence in 15 to 49 year olds in 1995, as estimated by our model for South Africa, with those estimated by the WHO for Sub-Saharan Africa (Gerbase *et al*, 1998). In most cases, the STI prevalence predicted for South Africa is more than double that estimated for the Sub-Saharan African region. The WHO estimates that levels of STI prevalence are higher in Sub-Saharan Africa than in any other region, and South Africa's STI prevalence levels thus appear even more alarming when compared with levels of STI prevalence observed beyond the African continent.

Table 4.4.3: STI prevalence levels in males and females aged 15 to 49 in 1995

Sex	Region	Syphilis	Gonorrhoea	Chlamydial infection	Trichomoniasis
Males	Sub-Saharan Africa ¹	3.1%	2.0%	4.8%	1.4%
	South Africa	7.0%	4.6%	8.4%	5.9%
	(mean, 95% CI)	(5.2-9.5%)	(3.5-5.8%)	(6.8-10.5%)	(3.0-10.5%)
Females	Sub-Saharan Africa ¹	3.9%	2.8%	7.1%	14.1%
	South Africa	7.4%	7.5%	11.5%	29.4%
	(mean, 95% CI)	(6.0-8.6%)	(6.2-8.6%)	(10.0-13.2%)	(23.6-34.3%)

¹ World Health Organization estimates (see Gerbase *et al* (1998)).

Although the differences between our estimates for South Africa and the WHO estimates for Sub-Saharan Africa may be partly due to differences in methodology, it is likely that they reflect real differences in STI prevalence. South Africa has a relatively low prevalence of male circumcision when compared with most of Sub-Saharan Africa (Williams *et al*, 2006a), and since male circumcision has been found to be protective against a number of STIs (Weiss *et al*, 2006; Moses *et al*, 1998), the low prevalence of male circumcision in South Africa could be a significant factor explaining the high STI burden in South Africa. Other possible explanations for the relatively high STI prevalence in South Africa include the high levels of migrant labour (Lurie 2000), and the relatively high prevalence of commercial sex activity in southern Africa (Caraël *et al*, 2006). It is also possible that the relatively high STI prevalence levels in South Africa in 1995 may be a consequence of the relatively late start to the South African HIV/AIDS epidemic. This analysis has shown that AIDS mortality and behaviour change in response to HIV/AIDS can bring about substantial reductions in STI prevalence, but since these changes occurred later in South Africa than in other African countries, a higher STI prevalence in South Africa would be expected. Our model estimates of STI prevalence in South Africa in 2005 are certainly closer to those estimated by the WHO for Sub-Saharan Africa in 1995, though still tending to be higher (see Figure 4.2.14).

4.4.5 Modelling immunity to STIs

Traditionally, mathematical models of STI transmission dynamics have assumed that there is no immunity following recovery (Lena *et al*, 2005). This assumption is supported by evidence showing that many individuals become reinfected with STIs shortly after successful treatment (Moodley *et al*, 2002; Lyng and Christensen 1981). However, such evidence does not disprove the possible existence of either (a) partial protection against reinfection, or (b) the gradual development of immunity, with individuals treated in early infection being less likely to acquire immunity than those who are treated later in infection or those who experience spontaneous resolution of infection.

The latter possibility has been described as the “arrested immunity hypothesis” by Brunham *et al* (2008), who have used this hypothesis to explain the observed failure of chlamydial control programmes to reduce the incidence of chlamydial infection over the long term (Rekart and Brunham 2008; Brunham *et al*, 2005). Evidence that individuals treated in early infection are more susceptible to reinfection than those treated in late infection is available in the case of syphilis (Magnuson *et al*, 1956) and gonorrhoea (Schmidt *et al*, 2001), and in a murine model of chlamydial infection (Su *et al*, 1999). There is also evidence to suggest that immune responses may be relatively slow to develop in the case of syphilis (Lewinski *et al*, 1999; Salazar *et al*, 2002) and chancroid (Chen *et al*, 1997).

Our results suggest that there is indeed immune protection following recovery from gonorrhoea, trichomoniasis and chlamydial infection. Our model produces significantly better fits to the South African STI prevalence data than the “no immunity” model when it is assumed that individuals who experience spontaneous resolution are temporarily immune following recovery. Although our model also allows for temporary immunity following successful treatment, this was not found to improve the fit of the model in the case of gonorrhoea and trichomoniasis, and in the case of chlamydial infection, the improvement in fit was only of borderline significance. This is consistent with the arrested immunity hypothesis. Although it was not possible to compare formally different models of immunity to chancroid, it was found that the model was easier to fit to the limited chancroid prevalence data

when it was assumed that there was immunity following spontaneous resolution; when no immunity was assumed, the decline in chancroid prevalence in the mid-1990s was found to be too rapid relative to that observed (results not shown).

It may seem surprising that the assumptions about immunity should so significantly influence the fitting of the model, especially in the cases of gonorrhoea and trichomoniasis, for which the average duration of protection is fairly short (less than two years). However, in groups that are highly exposed to STIs, such as commercial sex workers, even immunity of short duration can significantly reduce the prevalence of the STI. In addition, immunity tends to lessen the impact of changes in sexual behaviour and improvements in STI treatment, since the direct effect of such interventions, in terms of reduced transmission risk or reduced duration of infection, is partially offset by the effect of reduced prevalence of immunity. The model therefore predicts a more gradual decline in the prevalence of gonorrhoea, trichomoniasis and chlamydial infection, following the behavioural and STI treatment changes in the mid-1990s, when it is assumed that there is immunity. Similar dynamics affect other infections such as malaria; mathematical models suggest that even when there is only partial immunity to malaria, interventions may fail to have a significant impact in the long term because of reducing levels of acquired immunity following the introduction of the intervention (Anderson and May 1992).

Although there has been a recent tendency to allow for immunity in models of chlamydial infection (Brunham *et al*, 2005; White *et al*, 2004), there do not appear to have been any previously published models of gonorrhoea or trichomoniasis that allow for immunity. Garnett *et al* (1999) acknowledge that the standard model of gonorrhoea produces estimates of gonorrhoea prevalence that are “unrealistically sensitive to small changes in parameter values” in a U.S. population, but argue against extending the model to allow for immunity on the basis that this would make it even more difficult to simulate the persistence of gonorrhoea in the population modelled. In contrast, our results suggest that extending the standard model of gonorrhoea to allow for immunity makes the overall prevalence of gonorrhoea significantly less sensitive to changes in behavioural parameters and treatment parameters, thus increasing the likelihood of long-term persistence of gonorrhoea in the South African population.

The fact that the “no immunity” model provides a poor fit to the South African STI prevalence data is largely due to the implausibly high STI prevalence in sex workers, predicted by the model when there is no immunity assumed. A possible criticism of this analysis is that the implausibly high STI prevalence levels in sex workers may be due to unrealistic assumptions about (a) sexual activity among sex workers or (b) health-seeking behaviour in sex workers, rather than unrealistic assumptions about immunity. The first possibility seems unlikely, since the assumptions about sex worker sexual behaviour are by and large based on the same studies from which sex worker STI prevalence levels are obtained, and the assumed levels of risk behaviour would thus only be inconsistent with the observed STI prevalence levels if sex workers were systematically exaggerating their risk behaviours. The second possibility also seems unlikely, since the model already allows for a higher rate of health seeking among sex workers than among women in the general population, for both symptomatic and asymptomatic STIs (at rates of 0.90 per week and 0.025 per week respectively). Antibiotic treatment is tightly controlled in South Africa (Hudson 1999), and there is little evidence to suggest that South African sex workers self-treat with antibiotics (Abdool Karim *et al*, 1995). The assumed treatment frequency of 0.025 per week in asymptomatic sex workers is based on treatment frequencies observed among sex workers in other African countries (Morison *et al*, 2001), though treatment frequencies among South African sex workers may be lower than this (Abdool Karim *et al*, 1995).

Although this analysis supports the arrested immunity hypothesis, the hypothesis still requires further testing. It is important that other mathematical models of STI transmission dynamics examine which models of immunity give the best fit to STI prevalence data from other settings. It may also be necessary to generalize the fairly simple models of immunity that have been considered here by allowing for partial protection (rather than complete protection) in the immune phase, by allowing for reinfected individuals to have a shorter average duration of infection, and by allowing for stronger protection following a second episode of infection than that following the first episode. If models are extended to allow for multiple strains, it may also be necessary to consider strain-specific immunity, which is likely to be particularly significant in the case of gonorrhoea (Plummer *et al*, 1989). Models could also examine the potential effects of immunity that is acquired as a result of exposure to an

infected partner, in the absence of transmission (Rowland-Jones *et al*, 1998; Mazzoli *et al*, 1999; Lo Caputo *et al*, 2003; Posavad *et al*, 2003). Mathematical assessments of these different models of immunity are unlikely to be helpful if they are not complemented by further empirical work, and there is clearly a need for a better understanding of the ways in which immune responses alter the transmission and natural history of STIs.

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Chapter 5: The contribution of STIs to the transmission of HIV

The objective of this chapter is to assess the extent to which STIs are contributing to the spread of HIV in South Africa. The chapter begins with a review of studies that have quantified the increase in the HIV transmission probability in the presence of STIs, and this review is then used as the basis for the assumptions made in section 5.2. The model described in chapters 3 and 4 is extended to allow for the effect of STIs on HIV transmission, and the model is then used to determine population attributable fractions (PAFs) that represent the proportion of incident HIV infections attributable to other STIs. These PAFs are then compared with empirical PAF estimates and PAFs estimated by other models of HIV-STI interactions in section 5.3, and results are discussed in section 5.4.

5.1 STIs as cofactors in HIV transmission: a review of cofactor estimates

There is substantial evidence to suggest that STIs in HIV-negative individuals increase their susceptibility to HIV infection. In addition, HIV-infected individuals are more likely to transmit HIV if they are co-infected with STIs. This section reviews evidence of the effect of STIs on both HIV susceptibility and HIV infectiousness, and aims to determine the factor by which HIV transmission probabilities are multiplied in the presence of STIs (the ‘STI cofactor effect’).

5.1.1 Effect of STIs on susceptibility to HIV

STIs may increase susceptibility to HIV through a number of biological mechanisms. STIs often lead to a disruption of the mucous membranes in the reproductive tract, which act as a barrier to HIV infection. STIs also result in the recruitment of leucocytes to the reproductive tract, as has been shown in the cases of gonorrhoea, chlamydial infection and trichomoniasis (Krieger *et al*, 1993; Hobbs *et al*, 1999; Bump *et al*, 1986; Cohen *et al*, 1999). Many of these leucocytes and associated immune cells are targets for HIV infection, and their increased presence in the

reproductive tract therefore makes transmission more probable. In addition, certain non-ulcerative STIs have been shown to increase the production of interleukin-10, a cytokine that increases the susceptibility of macrophages to HIV infection and that may suppress the HIV-specific cellular immune response (Cohen *et al*, 1999). Bacterial vaginosis is also associated with reduced production of lactic acid and hydrogen peroxide, both of which are thought to protect against HIV (Martin *et al*, 1999).

A large number of studies have estimated the extent to which STIs increase susceptibility to HIV. Cross-sectional studies are usually not considered to be reliable in estimating the effect of STIs on HIV susceptibility, as they are not able to determine whether current STIs were present at the time of HIV acquisition. Longitudinal studies, which track initially HIV-negative individuals and determine the effect of STIs on their risk of HIV acquisition, are more useful. However, these studies estimate the effect of an STI, identified at some point in a time interval, on the *cumulative* probability of HIV transmission over that time interval. The modeller is concerned primarily with the effect of the STI on the *per contact* probability of HIV transmission. The STI cofactor effect is therefore difficult to determine from longitudinal studies, for a number of reasons:

- The most obvious problem is that the probabilities of HIV infection and STI infection are both related to the amount of sex and condom usage occurring over the time interval. Although most studies attempt to overcome this problem by controlling for reported sexual behaviour in a multivariate analysis (Røttingen *et al*, 2001), the sexual behaviour variables are usually defined categorically, often with only two levels. To the extent that there is residual variation in sexual behaviour after these variables are controlled for, and to the extent that sexual behaviour is misreported, the problem of confounding remains.
- It is often implicitly assumed that the HIV prevalence and STI prevalence are the same in all partners of HIV-negative subjects. However, having an STI may indicate that one's partner has multiple partners, and is thus more likely to be HIV positive. Ignoring likely sexual mixing patterns may therefore also exaggerate the true STI cofactor effect (Korenromp *et al*, 2001).

- A related problem is that STI cofactor effects estimated in these studies are often taken as evidence of increased susceptibility to HIV infection in the presence of an STI (Hayes *et al*, 1995b), though the cofactor effect may in fact represent the effect of the same STI in the HIV-infected partner.
- The time of HIV infection is known only approximately, which makes it difficult to determine whether the HIV infection came before, after or at the same time as the STI infection.

Table 5.1.1 summarizes the results of two meta-analyses of longitudinal studies (Sexton *et al*, 2005; Røttingen *et al*, 2001). The earlier meta-analysis employed a fixed effects model, and noted that there was significant publication bias (smaller studies tended to report larger STI cofactor effects). The more recent meta-analysis employed a random effects model, which gives relatively more weight to smaller studies and thus produces slightly higher STI cofactor estimates in most cases. A further meta-analysis (Wald and Link 2002) examined the relationship between herpes and HIV incidence, and also found that herpes significantly increased HIV incidence (OR 2.1, 95% CI: 1.4-3.2). Another more recent HSV-2 meta-analysis (Freeman *et al*, 2006) found that combined odds ratios differed substantially between high-risk females (OR 1.0, 95% CI: 0.5-2.0), females in the general population (OR 3.1, 95% CI: 1.7-5.6), males in the general population (OR 2.7, 95% CI: 1.9-3.9) and men who have sex with men (OR 1.7, 95% CI: 1.2-2.4).

Effect estimates tend to be higher in HIV-susceptible males than in HIV-susceptible females. This is demonstrated in a meta-regression by Sexton *et al*, who found that effect estimates tended to be higher in studies of men than in studies of women, though the difference was not statistically significant (OR 1.27, 95% CI: 0.9-1.8). A possible explanation for this is that STI effects on HIV incidence may ‘saturate’ when there are multiple STIs present. If this were the case, the greater prevalence of multiple STIs in females could account for the sex differential in STI effects. Alternatively, STIs may affect male susceptibility to HIV to a greater extent than female susceptibility, due to STIs in males being more frequently symptomatic and inducing stronger immune responses in the genital tract.

Table 5.1.1: Combined estimates of effect of STIs on HIV susceptibility

Source	All studies	All studies	Females	Males
	(OR, 95% CI)	(OR, 95% CI)	(OR, 95% CI)	(OR, 95% CI)
	Sexton	Røttingen	Røttingen	Røttingen
Any STI	3.7 (2.5-5.4)	3.7 (2.7-5.0)	5.6 (3.2-9.7)	3.1 (2.1-4.5)
GUD	3.8 (2.5-5.7)	2.7 (2.2-3.3)	2.8 (2.0-4.0)	4.4 (2.9-6.6)
Herpes	2.3 (1.2-4.2)	2.7 (1.5-4.8)		2.7 (1.5-4.8)
Syphilis	2.4 (1.8-4.2)	2.5 (2.1-3.1)	2.1 (1.4-3.1)	2.5 (1.4-4.4)
Chancroid	2.4 (1.4-4.2)	2.1 (1.2-3.4)		2.1 (1.2-3.5)
NUD	1.8 (1.3-2.6)	1.7 (1.5-2.1)	1.6 (1.3-2.0)	2.6 (1.8-4.0)
Gonorrhoea	3.4 (2.1-5.4)	2.1 (1.7-2.5)	2.6 (1.9-3.4)	
Chlamydia	2.9 (1.7-4.8)	2.2 (1.4-3.3)	2.8 (1.8-4.4)	
Trichomoniasis	2.0 (1.4-2.8)	1.5 (1.2-2.0)	1.5 (1.2-1.9)	
Candidiasis	2.7 (1.1-6.3)		2.2 (1.6-2.8)	
Bacterial vaginosis			1.4 (1.0-2.0)	

Source: Sexton *et al* (2005), Røttingen *et al* (2001)

GUD = genital ulcer disease, NUD = non-ulcerative disease (symptoms of discharge, urethritis or PID)

There is much uncertainty regarding the relative significance of symptomatic and asymptomatic infections in determining susceptibility to HIV. To the extent that symptomatic infections are more likely to lead to disruption of mucosal membranes in the reproductive tract, and to the extent that symptomatic infections are associated with higher concentrations of immune cells in the reproductive tract, symptomatic STIs might be expected to increase HIV susceptibility to a greater extent than asymptomatic STIs. This appears to be true in the case of ulcerative STIs; Table 5.1.1 shows that the average effect of GUD symptoms is greater than the average effects of herpes and syphilis (both of which are mostly asymptomatic). However, the same is not true for non-ulcerative STIs; the combined estimate for discharge/urethritis/PID symptoms tends to be similar to or lower than the combined effects for the corresponding STIs. This may be due to these non-ulcerative symptoms being relatively non-specific and thus poor indicators of actual STI infection. Both in males and females, GUD symptoms appear to influence HIV susceptibility to a greater extent than symptoms of non-ulcerative STIs.

Longitudinal studies do not indicate the true STI cofactor effect, but the STI cofactor effect can be approximated from these studies by using mathematical modelling. Three studies have used mathematical models to determine the likely magnitude of the STI cofactor effect. The first, by Boily and Anderson (1996), assumed that the HIV transmission probability per partnership increased by a factor of 4 in the presence of an STI, and simulated the various conditions under which STI cofactors might be measured empirically. It was found that when STI exposure was treated as a time-varying covariate in the regression model, the measured STI cofactor was around 2.5. When STI exposure was not treated as a time-varying covariate, the STI cofactor was typically less than 1.5 if the follow-up time was greater than 6 months, but closer to 2.5 if the follow-up time was less than 6 months. This suggests that the measures of association between STIs and HIV incidence, computed in longitudinal studies, are likely to under-estimate substantially the true STI cofactors. The potential for bias is particularly significant when it is considered that in 15 of the 31 studies included in the meta-analysis of Sexton *et al* (2005), STI exposure was not treated as a time-varying covariate, and in 13 of these 15 studies, the length of follow-up was greater than 6 months. A limitation of Boily and Anderson's analysis, however, is that the model assumes STIs affect the probability of HIV transmission *per partnership*, and it is not clear to what extent the findings would hold if it were instead assumed that STIs affect the probability of HIV transmission *per act of sex*.

The second attempt to estimate the STI cofactor effect using mathematical modelling is that of Hayes *et al* (1995b). Using detailed data from a longitudinal study of HIV incidence in Kenyan sex workers (Plummer *et al*, 1991), Hayes *et al* estimated that GUD increased the probability of male-to-female transmission of HIV by a factor of between 12 and 49, with the midpoint estimate being a factor of 23. This was substantially greater than the odds ratio of 3.3 (95% CI: 1.2-10.1) for the association between HIV incidence and GUD that had been estimated by Plummer *et al*. However, the analysis of Hayes *et al* has a number of limitations, illustrated by the model developed by Korenromp *et al* (2001). Korenromp *et al* refined the model of Hayes *et al* to allow for:

- a) greater exposure to HIV-positive clients in women experiencing GUD;

- b) lower rates of male circumcision in male partners of women with GUD (the model assumes that male-to-female HIV transmission probabilities are three times greater when male partners are uncircumcised than when male partners are circumcised); and
- c) greater exposure to partners with GUD in women with GUD (the model assumes that male GUD increases the efficiency of male-to-female transmission five-fold).

When all three refinements were allowed for simultaneously, it was found that the cofactor effect reduced from 23 to 3, similar to the level that had been reported by Plummer *et al.* Although there is some arbitrariness in the assumptions made by Korenromp *et al.*, and although the assumed effect of male circumcision on male-to-female transmission appears implausible (Wawer *et al.*, 2008), the analysis does nevertheless demonstrate that the STI cofactor effect can be substantially over-estimated if certain sources of bias are not taken into account.

Hayes *et al.* (1995b) have also estimated the GUD cofactor effect in the case of female-to-male transmission. This is based on a study of Kenyan men with GUD, who reported a single act of sex with a commercial sex worker (Cameron *et al.*, 1989). Hayes *et al.* estimate that the HIV transmission probability in this study was 0.16 (95% CI: 0.06-0.32). Assuming the female-to-male HIV transmission probability is 0.001 in the absence of GUD, they thus calculate that the GUD cofactor effect is likely to be 160 (with a range of 60 to 320). However, 0.001 is likely to underestimate significantly the probability of HIV transmission in a once-off encounter with an HIV-positive sex worker, even if it is assumed that the woman has no GUD. A GUD cofactor estimate of 160 is therefore likely to be an over-estimate. In addition, it is probable that many of the men with GUD acquired GUD during the single exposure to the sex worker, rather than prior to the contact with the sex worker. To some extent, therefore, the GUD cofactor effect estimated by Hayes *et al.* represents the effect of female GUD on HIV *infectiousness* rather than the effect of male GUD on HIV *susceptibility*.

5.1.2 Effect of STIs on HIV infectiousness

HIV-infected individuals are more likely to transmit HIV if they are co-infected with other STIs than they are in the absence of other STIs. This is partly due to the disruption of mucosal barriers caused by ulcerative STIs; genital ulcers can bleed during intercourse, and HIV is often detected in ulcer specimens (Gadkari *et al*, 1998; Schacker *et al*, 1998a; Kreiss *et al*, 1989; Plummer *et al*, 1990). Independently of their effect on mucosal barriers, STIs also appear to increase HIV infectiousness by promoting HIV viral shedding in the reproductive tract. This may be due to the recruitment of HIV-infected leucocytes to the genital tract in response to local infection, or it may be the result of increased production of inflammatory cytokines, which may stimulate HIV replication (Al-Harthi *et al*, 2001; Zara *et al*, 2004; Lawn *et al*, 2000; Cummins *et al*, 2006). Herpes simplex virus type 2 (HSV-2) can co-infect HIV-infected CD4+ cells and cause increased HIV replication (Kucera *et al*, 1990; Moriuchi *et al*, 2000), and bacterial vaginosis-associated flora may stimulate HIV replication through a heat-stable HIV-inducing factor (Cohn *et al*, 2005).

Several studies have examined the effect of STIs on HIV shedding in genital secretions. A meta-analysis of these studies (Rotchford *et al*, 2000) estimated that the odds of detecting HIV in the genital tracts of HIV-infected individuals was increased in the presence of gonorrhoea (OR 2.4, 95% CI: 1.8-3.3) and chlamydial infection (OR 1.5, 95% CI: 0.9-2.5). To update these estimates and obtain pooled estimates for other STIs, a systematic review and meta-analysis was conducted. The PubMed, Embase and AIDSearch databases were searched, and the details of those studies that were found to estimate the effect of STIs on the detection of HIV in genital specimens are summarized in Appendix E. Random effects meta-analyses were conducted for each STI using STATA 9.2 (StataCorp, College Station, Texas, USA). A more detailed description of the analysis has been published elsewhere (Johnson and Lewis 2008). The summary odds ratios are shown in Table 5.1.2, and the associated forest plots are shown in Appendix E.

Table 5.1.2: Combined estimates of effect of STIs on the odds of detectable HIV shedding in the genital tract

STI/symptom	All studies		Studies in women	
	# studies	OR (95% CI)	# studies	OR (95% CI)
Gonorrhoea	7	1.8 (1.2-2.7)	6	1.6 (1.1-2.4)
Chlamydial infection	5	1.8 (1.1-3.1)	5	1.8 (1.1-3.1)
Candidiasis	13	1.8 (1.3-2.4)	13	1.8 (1.3-2.4)
Bacterial vaginosis	11	1.0 (0.7-1.5)	11	1.0 (0.7-1.5)
Trichomoniasis	9	0.9 (0.7-1.3)	9	0.9 (0.7-1.3)
Vaginal discharge	6	1.5 (0.9-2.6)	6	1.5 (0.9-2.6)
Cervical discharge/ cervical mucopus	5	1.8 (1.2-2.7)	5	1.8 (1.2-2.7)
Cervicitis	5	2.7 (1.4-5.2)	5	2.7 (1.4-5.2)
Urethritis	3	3.1 (1.1-8.6)	0	-
Genital ulcer disease	4	1.8 (0.8-3.8)	3	2.4 (1.2-4.9)
HSV shedding	6	1.3 (0.7-2.5)	6	1.3 (0.7-2.5)
Syphilis	4	1.3 (0.9-1.9)	3	1.3 (0.9-1.9)

Table 5.1.2 suggests that there is a strong association between HIV shedding and the concentration of leucocytes in the reproductive tract. This is evident from the high odds ratios calculated for urethritis (3.1, 95% CI: 1.1-8.6) and cervicitis (2.7, 95% CI: 1.4-5.2), both of which are defined in terms of the concentration of white blood cells (WBCs) or polymorphonuclear leucocytes (PMNLs). It is reinforced by several studies that have found PMNL or WBC counts in the reproductive tract to have a 'dose-response effect' on HIV shedding (Cohen *et al*, 1997; Mostad *et al*, 1997; Moss *et al*, 1995; Kreiss *et al*, 1994). Studies have found that trichomoniasis is associated with lower leucocyte counts in genital secretions than gonorrhoea and chlamydial infection (Krieger *et al*, 1993a; Hobbs *et al*, 1999; Levine *et al*, 1998), and bacterial vaginosis has also been shown to have little or no effect on leucocyte counts in cervicovaginal secretions (Levine *et al*, 1998; Cook *et al*, 1992; Eschenbach *et al*, 1988; Wang *et al*, 2001). The absence of any effect of trichomoniasis and bacterial vaginosis on HIV-1 shedding in the genital tract could therefore be explained by the relatively weak inflammatory responses associated with these infections.

Few studies have assessed the relative significance of symptomatic and asymptomatic infections on HIV shedding in the genital tract. As noted in section 5.1.1, however, symptomatic infections tend to be associated with greater leucocyte concentrations than asymptomatic infections, and one might therefore expect symptomatic infections to have a more significant effect on HIV-1 shedding. The fact that the detection of HIV-1 shedding in the genital tract is significantly associated with GUD but not with HSV-2 or serological evidence of syphilis suggests that HSV-2 and syphilis could increase HIV-1 shedding when symptomatic, but have relatively little effect when asymptomatic. The effect of syphilis on HIV shedding is therefore probably only significant during the primary syphilis stage, as symptoms and immune activation in the genital tract are rare after the primary stage. Although trichomoniasis does not significantly affect the detection of HIV-1 in the genital tracts of women, symptomatic trichomoniasis does have a substantial effect on the concentration of HIV-1 RNA in the genital tracts of both men and women (Hobbs *et al*, 1999; Price *et al*, 2003; Wang *et al*, 2001). Wang *et al* (2001) have also shown that the reductions in HIV-1 RNA concentrations after the treatment of candidiasis and bacterial vaginosis are significantly greater in the women with symptoms or signs of infection.

The associations between HSV-2 shedding, candidiasis and HIV-1 shedding may be confounded by CD4+ count and/or blood plasma viral load, since both HSV-2 recurrences and candidiasis are more frequent in the advanced stages of HIV infection. This review did not find any significant evidence to suggest that univariate associations differ consistently from multivariate associations, after controlling for CD4+ count and blood plasma viral load. However, one cannot exclude the possibility of confounding. It is also possible that the association between candidiasis and HIV shedding may be confounded by the stage of the menstrual cycle, as some studies suggest that HIV shedding is most intense during the luteal phase and at the time of menstruation (Reichelderfer *et al*, 2000; Benki *et al*, 2004; Money *et al*, 2003), the same period in which candidiasis is believed to be most frequent (Bradshaw *et al*, 2005; Eckert *et al*, 1998; Hurley 1981; Kalo-Klein and Witkin 1989). The high odds ratio estimated for vulvovaginal candidiasis (1.8, 95% CI: 1.3-2.4) could therefore be an overestimate of the true effect of vulvovaginal candidiasis on HIV shedding.

For most of the infections considered in this meta-analysis, there is little information relating to HIV shedding in males, and it is therefore not possible to establish whether there are gender differences in the effects of these infections on genital HIV shedding. However, since urethritis occurs in almost all male cases of gonorrhoea (Krieger *et al*, 1993a; Hobbs *et al*, 1999; Sturm *et al*, 2004b), and since urethritis is associated with a greater increase in the detection of HIV shedding (OR 3.1, 95% CI: 1.1-8.6) than female gonococcal infection (OR 1.6, 95% CI: 1.1-2.4), it seems likely that gonococcal infection has a more pronounced effect on HIV shedding in males than in females. The evidence also suggests that there may be a gender difference in the effect of GUD on HIV shedding, since the one study conducted in males did not find a significant association (OR 0.8, 95% CI: 0.3-2.2), while the three studies conducted in females suggest a significant effect (combined OR 2.4, 95% CI: 1.2-4.9). However, this is likely to reflect a difference in sampling methods rather than a true gender difference. In patients with GUD, HIV shedding is likely to be greatest in ulcers; this shedding is unlikely to be picked up in male urethral specimens (since male ulcers are external) but would be picked up in cervicovaginal specimens (all three female studies considered only cervicovaginal ulcers). The effect estimated for males is therefore likely to under-state the true effect of GUD on male HIV infectiousness.

Although the pooled odds ratios presented in Table 5.1.2 provide a useful indication of the *relative* effects of different STIs on HIV detection in the genital tract, there has been no attempt to quantify the relationship between HIV detection in the genital tract and HIV transmissibility, and it is therefore unclear how these odds ratios relate to the STI cofactor effect. The model of Chakraborty *et al* (2001) provides an alternative means of estimating the cofactor magnitudes. In this model of male-to-female transmission, it is estimated that if the amount of non-synctium-inducing HIV-1 RNA per ejaculate increases by a factor of ten, the HIV transmission probability would increase by a factor of six ($10^{0.778}$). In the studies of Cohen *et al* (1997) and Sadiq *et al* (2005), urethritis is estimated to be associated with increases of 0.91 and 0.72 log HIV RNA copies per ml of semen respectively. Applying the model of Chakraborty *et al* to these estimates gives STI cofactors of 5.1 and 3.6 respectively. These are slightly higher than the pooled odds ratio for urethritis in Table 5.1.2 (3.1, 95% CI: 1.1-8.6), which suggests that the odds ratios in Table 5.1.2 could slightly under-state the true STI cofactor effect. However, Chakraborty *et al* do not report confidence intervals

around the estimate of 0.778, and it is therefore not possible to determine the range of uncertainty around the estimated cofactor effects. In addition, the model of Chakraborty *et al* applies only to male-to-female transmission, and it is not clear how STI cofactors for female-to-male transmission of HIV would relate to the odds ratios in Table 5.1.2.

5.1.3 Multiplicative, additive and saturation effects

Three different models have been proposed for the increase in the HIV transmission probability when multiple STIs are present (Korenromp *et al*, 2001). To illustrate these models, suppose that p is the HIV transmission probability per act of sex, in the absence of other STIs. Suppose that an individual is exposed to HIV in the presence of two other STIs, A and B. Further suppose that δ_x is the percentage increase in the HIV transmission probability if STI x alone is present. The probability of HIV transmission in the presence of both A and B, p_{AB} , could be modelled in at least three ways:

- Multiplicative model: $p_{AB} = p(1 + \delta_A)(1 + \delta_B)$
- Additive model: $p_{AB} = p(1 + \delta_A + \delta_B)$
- Saturation model: $p_{AB} = p(1 + \max(\delta_A, \delta_B))$

Statistical models, such as the Cox proportional hazards and Poisson regression models, assume multiplicative or additive effects. However, there is very little empirical evidence to indicate which of these models is likely to be most realistic. Korenromp *et al* (2001) argue that if the biological mechanisms responsible for the increase in the transmission probability differ between A and B, a multiplicative model would be biologically plausible. On the other hand, if A and B affect HIV transmission through the same mechanism, their effects are more likely to saturate.

5.2 Model estimates of the contribution of STIs to HIV incidence

In Chapter 4, HIV, STI and sexual behaviour parameters were estimated in the absence of any allowance for the effect of STIs on HIV transmission probabilities.

The purpose of this section is to assess the extent to which different STIs have contributed to the spread of HIV, when allowance is made for the effect of STIs on HIV transmission probabilities. Because the model is relatively slow to run when HIV and all other STIs are being modelled simultaneously, and because there are a large number of sources of uncertainty affecting these results, we do not attempt to conduct a formal Bayesian analysis in this chapter. For the purpose of this analysis, the most important source of uncertainty is the STI cofactor effects (Freeman *et al*, 2007). The approach adopted here is therefore to fix the sexual behaviour parameters at the posterior means estimated in section 4.1 and to fix the STI natural history parameters at the posterior medians estimated in section 4.2. HIV transmission parameters are then estimated for a number of different STI cofactor scenarios. The sections that follow describe these STI cofactor scenarios and present the estimated proportions of HIV cases attributable to each STI, for each STI cofactor scenario.

5.2.1 STI cofactor scenarios

As discussed in section 5.1.1, the multiple by which HIV susceptibility is increased by other STIs could be under-estimated in epidemiological studies, due to lack of precision regarding the timing of STI exposure and lack of precision regarding the timing of HIV infection. However, it is also possible that epidemiological studies could over-estimate the true STI cofactor effects, due to residual confounding with unmeasured sexual behaviour and sexual network variables, confounding with the effect of STIs in the HIV-infected partner, and publication bias. There is also little clarity regarding the relationship between the odds ratios estimated in section 5.1.2 and the true effect of STIs on HIV infectiousness. Given this uncertainty regarding the true STI cofactor effects, it is appropriate to consider a range of possible scenarios when modelling HIV-STI interactions. Three scenarios are considered here:

- Baseline scenario: assumed STI cofactors are similar to those in Tables 5.1.1 and 5.1.2;
- High cofactor scenario: STI cofactors are calculated as the STI cofactors in the baseline scenario, raised to the power of 1.5; and
- Low cofactor scenario: STI cofactors are calculated as the STI cofactors in the baseline scenario, raised to the power of 0.5.

Because the evidence reviewed in section 5.1 suggests that STI cofactors differ according to the severity of the symptoms involved, separate STI cofactors are assumed for symptomatic ulcerative STIs, symptomatic non-ulcerative STIs, and asymptomatic STIs. It is assumed that STI cofactors saturate at the individual level; for example, HIV-positive men who are experiencing both ulcerative and non-ulcerative symptoms are assumed to have the same probability of transmitting HIV as men who have ulcerative symptoms alone. However, when STIs are present in both sexual partners, the male and female cofactors calculated for each partner are multiplied when determining the probability of HIV transmission. Although it is possible to allow for multiplicative effects at the individual level, it was found that it was not possible to obtain a reasonable fit to HIV prevalence trends in South Africa if there was no allowance for saturation of STI cofactors at the individual level.

In the baseline scenario, STI cofactors are set equal to the odds ratios estimated by Røttingen *et al* (2001) and those estimated in Table 5.1.2 as far as possible. The assumed STI cofactors are shown in Table 5.2.1. The assumed multiple by which female HIV infectiousness is increased in the presence of GUD (3.5) is greater than the OR relating HIV shedding in females to the presence of GUD (2.4), because the latter does not reflect the effect of direct contact with genital ulcers on the probability of HIV transmission. In the absence of reliable data for males, the same STI cofactor for male GUD is assumed. The assumed multiple by which HIV infectiousness is increased in the presence of female non-ulcerative symptoms (1.7) is close to the odds ratios estimated for vaginal discharge (1.5) and cervical discharge (1.8), while the corresponding multiple for males has been set equal to the odds ratio for urethritis (3.1), since virtually all men with symptomatic gonorrhoea, trichomoniasis or chlamydial infection have urethritis (Krieger *et al*, 1993a; Hobbs *et al*, 1999). The assumed multiple by which asymptomatic STIs increase HIV infectiousness (1.2) is based on the odds ratios estimated for bacterial vaginosis (1.0), trichomoniasis (0.9), HSV shedding (1.3) and syphilis (1.3), all of which are mostly asymptomatic. In men, most asymptomatic infection is related to HSV-2, and the assumed effect of asymptomatic STIs on male susceptibility to HIV is therefore set at 2.0, slightly lower than the OR relating HSV-2 to male HIV susceptibility (2.7). The assumed multiple by which HIV susceptibility is increased in asymptomatic females (1.5) is similar to

the odds ratios estimated for bacterial vaginosis (1.4), trichomoniasis (1.5) and candidiasis (2.2). In the case of syphilis, no cofactor effect is assumed to apply in the latent stage of disease, as there are no symptoms or immune activation in the genital tract to increase either HIV susceptibility or HIV infectiousness during the latent stage.

Table 5.2.1: Assumed STI cofactors

Scenario	Symptoms	Susceptibility		Infectiousness	
		cofactor		cofactor	
		Male	Female	Male	Female
Baseline scenario	Ulcerative symptoms	4.4	2.8	3.5	3.5
	Discharge/dysuria symptoms	2.6	1.6	3.1	1.7
	Asymptomatic infection	2	1.5	1.2	1.2
High cofactor scenario	Ulcerative symptoms	9.2	4.7	6.5	6.5
	Discharge/dysuria symptoms	4.2	2.0	5.5	2.2
	Asymptomatic infection	2.8	1.8	1.3	1.3
Low cofactor scenario	Ulcerative symptoms	2.1	1.7	1.9	1.9
	Discharge/dysuria symptoms	1.6	1.3	1.8	1.3
	Asymptomatic infection	1.4	1.2	1.1	1.1

For each scenario, HIV transmission probabilities in the absence of STIs and initial HIV prevalence levels in the high risk group are set at levels that produce model results consistent with the HIV prevalence observed in surveys. These assumed HIV transmission probabilities and initial HIV prevalence levels in the high-risk group are shown in Table 5.2.2. For comparison purposes, the posterior means of these parameters, from the analysis in which STI cofactors were not included (section 4.1), are also shown. Although it might be expected that HIV transmission probabilities in the absence of other STIs would be similar for all relationship types, different HIV transmission probabilities are specified for each relationship type because HIV susceptibility would be expected to vary in relation to the cumulative level of HIV exposure, and because it is difficult to obtain reasonable fits to South African HIV prevalence data if the HIV transmission probabilities are assumed to be the same for all relationship types.

Table 5.2.2: Assumed initial HIV prevalence and HIV transmission probabilities in the absence of STIs

Parameter	Baseline scenario	High cofactor scenario	Low cofactor scenario	Posterior mean (no STIs)
Initial HIV prevalence in high risk group	0.17%	0.16%	0.19%	0.1827%
Male-to-female HIV transmission probability if no STIs present				
Client-sex worker contacts	0.0012	0.0005	0.0022	0.003
Short-term relationships	0.0048	0.0034	0.0076	0.006483
Long-term relationships	0.001	0.0007	0.0015	0.002434
Female-to-male HIV transmission probability if no STIs present				
Client-sex worker contacts	0.02	0.01	0.025	0.03
Short-term relationships	0.003	0.0017	0.0045	0.003586
Long-term relationships	0.0006	0.0004	0.001	0.00173

5.2.2 Calibration to HIV prevalence data

Figure 5.2.1 shows the calibration of the model to the antenatal prevalence and sex worker prevalence data, for each of the STI cofactor scenarios described previously. On the whole, the calibration is reasonable, with levels of HIV prevalence similar to those estimated in section 4.1. It was found to be difficult to reproduce the HIV prevalence trends observed in the 15 to 19 age group, particularly when high STI cofactors were assumed. This is probably because the reductions in the prevalence of syphilis, chancroid, gonorrhoea and trichomoniasis in recent years (section 4.2) imply a substantial reduction in HIV incidence if high STI cofactors are assumed, and the HIV prevalence trends in the 15 to 19 age group are not consistent with such a steep decline in HIV incidence. It was also found to be difficult to match the “levelling off” of HIV prevalence levels in the general population in recent years if low STI cofactors were assumed. This is probably because low STI cofactors imply relatively little heterogeneity in HIV transmission probabilities between high and low risk groups,

with the result that the incidence of HIV in the low risk group is higher than in other STI cofactor scenarios, and HIV prevalence therefore stabilizes at a relatively high level, at a relatively late stage in the epidemic. The difficulties experienced in fitting the model in the high and low cofactor scenarios suggest that the STI cofactors assumed in these scenarios probably are upper and lower bounds on the true STI cofactors.

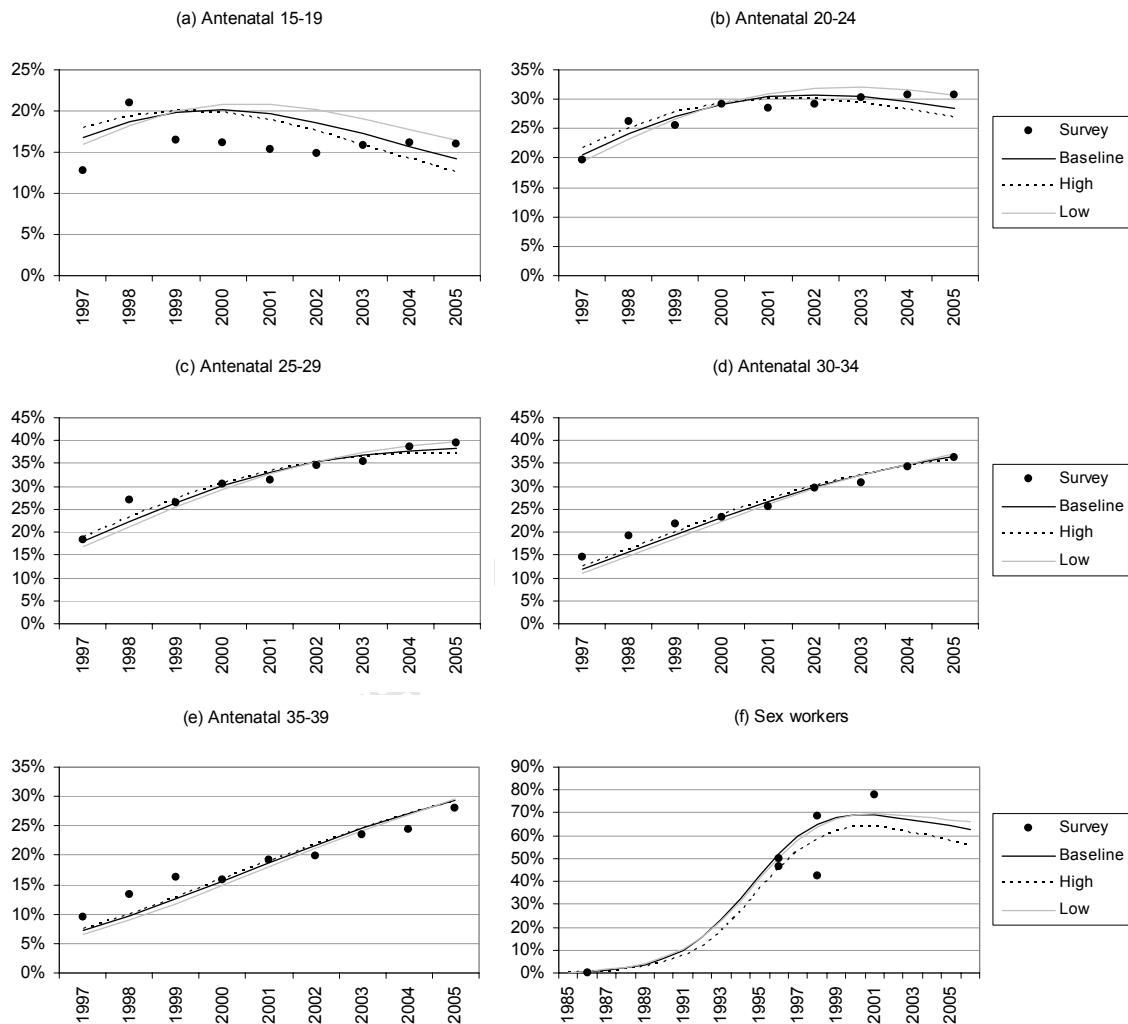


Figure 5.2.1: Calibration of model to HIV prevalence data from national antenatal clinic surveys and studies of sex workers

Figure 5.2.2 shows the calibration of the model to HIV prevalence data from the national household survey that was conducted in 2005 (Shisana *et al*, 2005). The model estimates are again reasonably consistent with the levels of HIV prevalence observed in the survey.

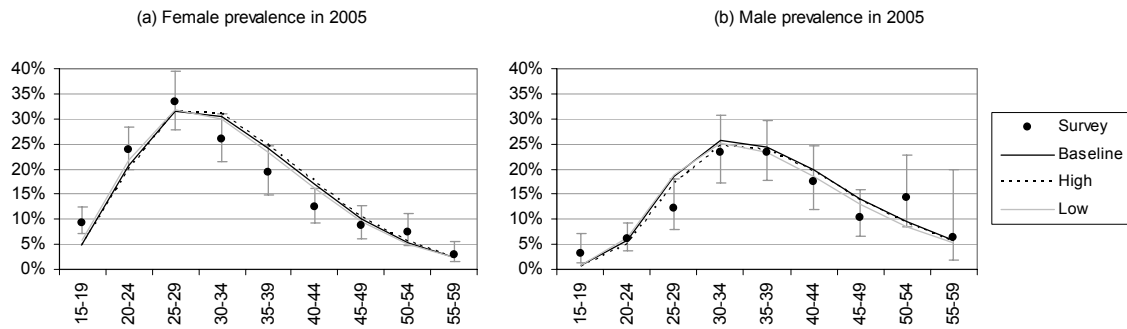


Figure 5.2.2: Calibration of model to HIV prevalence data from the 2005 HSRC household survey

5.2.3 Population attributable fractions

The population attributable fraction (PAF) of a particular STI for HIV transmission is estimated by running the model up to a particular year, calculating the number of new HIV infections in that year, and then recalculating the number of new HIV infections that would be expected in that year if the STI of interest were eliminated at the start of the year. The PAF is then calculated as the percentage reduction in the number of new HIV infections that occurs as a result of the removal of the STI. This calculation was performed for each STI, for each STI cofactor scenario and for four different years (1990, 1995, 2000 and 2005). The results of these calculations are shown in Figure 5.2.3.

Figure 5.2.3 shows that at all stages in the South African HIV/AIDS epidemic, genital herpes is the STI that has contributed most substantially to the transmission of HIV, accounting for roughly 20% of all new HIV cases in the baseline scenario, throughout the 1990-2005 period. Gonorrhoea and chancroid also contributed significantly to the transmission of HIV in the early stages of the HIV/AIDS epidemic (PAFs of 13% and 12% respectively, in the baseline scenario in 1990), probably because they are both highly symptomatic infections and are thus associated with high STI cofactors. However, the contribution of chancroid and gonorrhoea to the transmission of HIV has diminished considerably since the initiation of behaviour changes and improvements in STI treatment in the mid-1990s. Syphilis, trichomoniasis and chlamydial infection each contributed 5 to 10% of new HIV infections in 1990 in the

baseline scenario, but their importance has also diminished as a result of subsequent declines in the prevalence of these infections. Bacterial vaginosis and vulvovaginal candidiasis have the smallest PAFs (less than 5% in all scenarios and in all years), probably because these infections occur only in women and are mostly asymptomatic. Although bacterial vaginosis and vulvovaginal candidiasis are both highly prevalent in women, there is a high prevalence of other asymptomatic infections in women, and hence the removal of one infection has relatively little effect on the overall prevalence of asymptomatic infection in women. This means that the removal of one predominantly asymptomatic infection in women has relatively little effect on HIV transmission probabilities, if it is assumed that STI cofactors saturate at the individual level.

The PAFs of all STIs for HIV transmission were calculated in the same way as before, except that the effect of eliminating all STIs was modelled by setting all STI cofactor multiples to one at the start of the year of interest. Similarly, the PAFs of ulcerative symptoms for HIV transmission were calculated by setting only the ulcerative symptom cofactor to one at the start of the relevant year. The results of these PAF calculations are shown in Figure 5.2.4. It is estimated that in 1990, 69% of all new HIV infections were attributable to other STIs, but that by 2005 this proportion had declined to 48% (baseline scenario). A more substantial reduction is estimated in the case of the proportion of new HIV cases attributable to genital ulcer disease: from 25% in 1990 to 6% in 2005, in the baseline scenario. The substantial reduction in the PAF of ulcerative symptoms for HIV transmission is a reflection of the steep declines in the prevalence of chancroid and syphilis, which were previously the leading causes of genital ulcers.

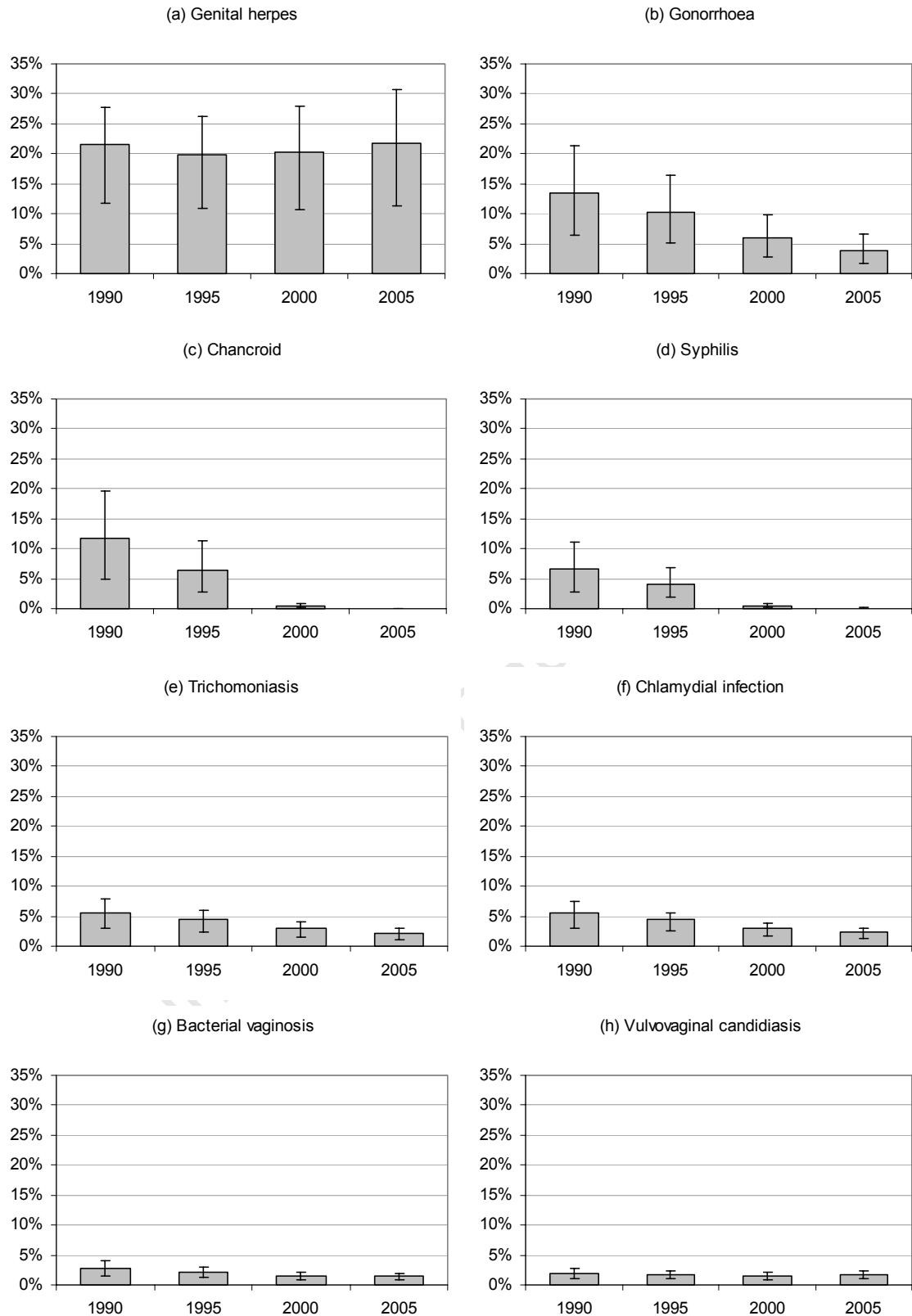


Figure 5.2.3: Population attributable fractions of STIs for HIV transmission

Grey bars represent results from baseline scenario. Upper and lower error bars represent results from 'high STI cofactor' and 'low STI cofactor' scenarios respectively.

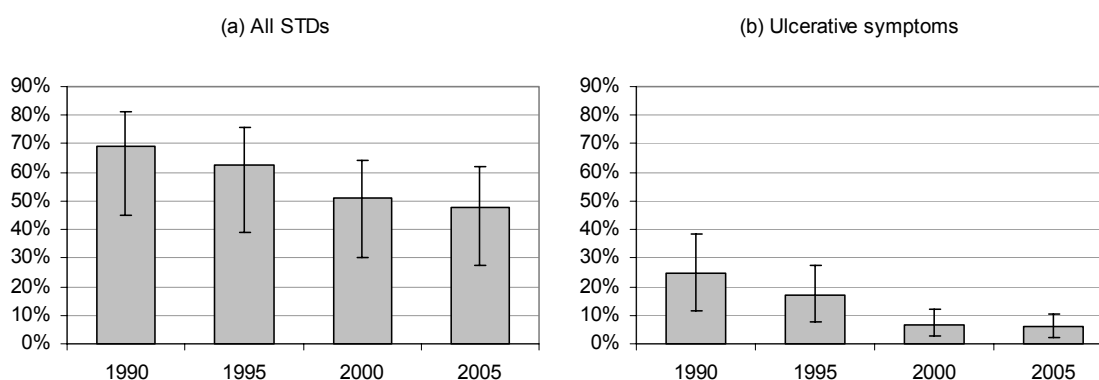


Figure 5.2.4: Population attributable fractions of STIs for HIV transmission

Grey bars represent results from baseline scenario. Upper and lower error bars represent results from ‘high STI cofactor’ and ‘low STI cofactor’ scenarios respectively.

5.3 Comparison with other estimates of population attributable fractions

Since there is much uncertainty regarding STI cofactors, it is useful to compare the population attributable fractions (PAFs) estimated in section 5.2.3 with empirical estimates of PAFs and other model-based estimates of PAFs. PAFs of STIs for HIV transmission can be expected to vary between populations and even between different groups within the same population (Vittinghoff and Padian 1996), and these comparisons should therefore be treated with some caution. Section 5.3.1 compares our model estimates with empirical PAF estimates, and section 5.3.2 compares our estimates with other model-based PAF estimates.

5.3.1 Comparison with empirical estimates of population attributable fractions

The method used to derive empirical estimates of PAFs differs in several respects from the method used in model-based evaluations of PAFs. Empirical estimates of the PAF of a particular STI for HIV transmission are usually calculated using the following formula (Miettinen 1974):

$$PAF = CF \left(\frac{RR - 1}{RR} \right) \quad (5.1)$$

where CF is the ‘case fraction’ (the prevalence of the STI in those who acquire HIV over the study period), and RR is the relative risk of HIV acquisition in individuals with the STI, compared to those without the STI. The PAF thus represents the proportion of incident cases that would not have occurred if the STI of interest was absent. In model-based evaluations, however, the PAF of an STI for HIV transmission is calculated as the reduction in HIV incidence that would be expected over one year if the STI were eliminated at the start of that year (Robinson *et al*, 1997; Orroth *et al*, 2006; Boily *et al*, 2002).

Empirical estimates of PAFs might under-estimate the ‘true’ proportion of HIV cases attributable to other STIs for several reasons:

- The limited sensitivity of STI diagnostics and self-reporting of STI symptoms implies that empirical estimates of PAFs are likely to be based on under-estimates of CF .
- The limited sensitivity of STI diagnostics and self-reporting of STI symptoms also weakens the strength of association, as measured by RR . Empirical estimates of PAFs are therefore also likely to be based on under-estimates of RR .
- Empirically derived PAFs only measure the effect of STIs when present in the HIV-negative partner and not the effects of STIs when present in the HIV-positive partner (Orroth *et al*, 2006).

However, empirical estimates of PAFs could also over-estimate the true fractions. Firstly, the relative risk estimates used in the PAF calculation could exaggerate the true association if sexual behaviour variables and sexual network characteristics have not been adequately controlled for. Secondly, it is common for empirical estimates of PAFs to be based on the odds ratio, as an approximation to the relative risk (Hennekens and Buring 1987). Although the approximation is acceptable when the rate of HIV incidence is low, the odds ratio is likely to overstate the risk ratio when the relative risk exceeds one. The empirically estimated PAF may therefore overstate

the ‘true’ PAF, particularly when the HIV incidence in the cohort being studied is high (as is typically the case in studies of sex workers and their clients).

Empirically derived PAFs are summarized in Table 5.3.1. Several of these estimates have been calculated by Fleming and Wasserheit (1999). Although 95% confidence intervals are generally not calculated due to the difficulties associated with determining these (Miettinen 1974), a crude measure of spread can be obtained by substituting the upper and lower 95% confidence interval limits around the RR/OR into equation (5.1). This understates the true range of uncertainty, as it does not take into account the uncertainty regarding the *CF* variable. The ranges of uncertainty are nevertheless very wide, indicating that it is difficult to determine PAFs precisely in empirical studies.

The studies of Cameron *et al* (1989), Plummer *et al* (1991) and Laga *et al* (1993) were all conducted in high-risk populations in the late 1980s. The PAFs estimated in these studies therefore correspond to the very early stages of the AIDS epidemic, and can be compared with the South African model estimates for 1990 (see Figures 5.2.3 and 5.2.4). The study of Orroth *et al* (2000) was conducted in the early stage of the Tanzanian epidemic, in the general population, and is therefore comparable with the South African model estimates for 1995. The study of Gray *et al* (1999) was conducted in the general population in the later stages of the Ugandan epidemic, after significant behaviour change had already occurred, and is therefore comparable with the South African model estimates for 2000-2005.

Table 5.3.1: Empirically-determined PAFs of STIs for HIV incidence

Study	Population, date	Disease/ symptoms	Diagnosis	PAF (range)	OR/ RR
Cameron <i>et al</i> (1989)	Male clients of Nairobi sex workers, experiencing an STI, 1986-7	GUD	Genital examination	69% (20-82%) ^a	OR ^c
Plummer <i>et al</i> (1991)	Female sex workers in Nairobi, 1985-7	GUD	Genital examination	44% (10-56%) ^a	OR ^c
		Chlamydial infection	Culture	25% (0-34%) ^a	OR ^c
		Syphilis	Serology	10% (0-27%) ^a	OR ^d
Laga <i>et al</i> (1993)	Female sex workers in Kinshasa, 1988	Gonorrhoea	Culture	44% (33-50%) ^a	OR ^c
		Chlamydial infection	EIA	22% (9-28%) ^a	OR ^c
		Trichomoniasis	Microscopy	18% (0-29%) ^a	OR ^c
		GUD	Genital examination	4%	OR ^d
		Syphilis	Serology	6% (0-8%) ^a	OR ^d
		Chancroid	Serology	1%	OR ^d
Gray <i>et al</i> (1999)	Men and women in control arm of Rakai trial, 1994-5	GUD	Self-reported	13% (4-20%) ^b	RR ^c
		Discharge/ dysuria	symptoms	4% (0-12%) ^b	RR ^c
Orroth <i>et al</i> (2000)	Men in control arm of Mwanza trial, 1991-4	GUD	Self-reported	30% (12-45%) ^b	OR ^d
		Discharge	symptoms	25% (2-42%) ^b	OR ^d
		Syphilis	Serology	4% (0-17%) ^b	OR ^d
	Women in control arm of Mwanza trial, 1991-4	GUD	Self-reported	7% (0-15%) ^b	OR ^d
		Discharge	symptoms	4% (0-19%) ^b	OR ^c
		Syphilis	Serology	7% (0-25%) ^b	OR ^c

^a Approximate, based on 95% confidence interval around RR/OR. ^b Published 95% CI. ^c Controlling for sexual behaviour. ^d Not controlling for sexual behaviour.

EIA = enzyme immunoassay. GUD = genital ulcer disease. PAF = population attributable fraction.

Model estimates in the baseline scenario suggest that the PAF of GUD for HIV transmission would be expected to decline from 25% in 1990 to 6% in 2005. These estimates are roughly consistent with the high empirical PAFs estimated in studies of sex workers and their clients (69%, 44% and 4%, with wide ranges of uncertainty), and also consistent with the lower PAF estimates in the general population in more

advanced epidemics (30%, 13% and 7%, also with wide ranges of uncertainty). Empirical PAFs of syphilis are between 4% and 10%, consistent with the model baseline predictions of the proportion of HIV cases attributable to syphilis up to 1995 (4-7%). The model estimates that in 1990, 6% of new HIV infections were attributable to chlamydial infection, which is lower than the empirical estimates of 22% and 25% in sex workers, though the ranges of uncertainty around the empirical estimates are very wide. Plummer *et al* (1991) found that gonorrhoea did not increase the risk of HIV acquisition among sex workers in Nairobi, but gonorrhoea was estimated to have accounted for almost half of new HIV cases among sex workers in Kinshasa (Laga *et al*, 1993). The model estimates that 14% of new HIV infections in 1990 are attributable to gonorrhoea, which is between these two empirical estimates for early-stage epidemics. The incidence of chancroid in the study of Kinshasa sex workers was unusually low, which explains the low PAF calculated for chancroid in this study. Self-reported symptoms of discharge are generally not considered to be reliable indicators of sexually transmitted infection, and empirical PAFs for discharge/dysuria are therefore not considered in this comparison, though the empirical PAFs are shown in Table 5.3.1.

In summary, empirical estimates of the proportion of incident HIV attributable to STIs are likely to be biased for several reasons, and ranges of uncertainty around these empirical estimates are extremely wide. The true proportion of HIV cases attributable to STIs can also be expected to vary substantially between populations, and the empirical estimates of PAFs in other African settings therefore cannot be used to validate the assumed STI cofactors in a South African model of HIV-STI interactions. Nevertheless, our model estimates of the proportions of incident HIV cases attributable to other STIs appear to be roughly consistent with most empirical estimates.

5.3.2 Comparison with other model-based estimates of population attributable fractions

The PAF estimates presented in section 5.2 are compared here with estimates from the SimulAIDS model (Robinson *et al*, 1997), applied to Uganda; estimates from the STDSIM model, applied in six different African settings (Freeman *et al*, 2007; Orroth

et al, 2006); and estimates of a model of HIV-HSV interactions (Abu-Raddad *et al*, 2008), applied to Kenya. The STI cofactor assumptions in these analyses are shown in Table 5.3.2. Due to the uncertainty regarding STI cofactors, Robinson *et al* present estimates for both ‘high’ and ‘low’ STI cofactor scenarios. In both the SimulAIDS and STDSIM models, the multiple by which the HIV transmission probability per sex act is increased is assumed to be the same whether the STI is present in the HIV-infected or HIV-susceptible partner. No gender differences in STI cofactors are assumed in any of the models.

Table 5.3.2: Assumed STI cofactors

Study	STI	Cofactor
Robinson <i>et al</i> (1997)	Ulcerative STIs: High cofactor	100
	Low cofactor	10
	Non-ulcerative STIs: High cofactor	5
	Low cofactor	2
Orroth <i>et al</i> (2006)	Chancroid	25
	Herpes: Primary ulcer	25
	Recurrent ulcer	10
	Asymptomatic	1
	Syphilis: Primary/secondary	7.5
	Latent infection	1
	Chlamydial infection	3
	Gonorrhoea	3
	Trichomoniasis: Symptomatic	2
Asymptomatic	1	
Abu-Raddad <i>et al</i> (2008)	Herpes: HSV-2 shedding in HIV-positive partner	3
	HSV-2 shedding in HIV-negative partner	4
	No HSV-2 shedding	1

All model-based PAF estimates presented here are calculated in the same way, i.e. as the percentage reduction in the incidence of HIV over one year as a result of the removal of the relevant STI(s) at the start of that year. Because PAFs of STIs for HIV transmission can be expected to change substantially over the course of the

HIV/AIDS epidemic, the PAFs estimated in different analyses are arranged according to the number of years from the assumed start of the HIV/AIDS epidemic (Figure 5.3.1).

Our model estimates of the proportion of new HIV infections attributable to all STIs combined are roughly consistent with results from other analyses (Figure 5.3.1(a)). Although our estimates of the proportion of incident HIV attributable to genital herpes is consistent with the STDSIM model in the early stages of the HIV/AIDS epidemic, the STDSIM model suggests a substantial rise in the PAF of HSV-2 for HIV transmission in the later stages of the HIV/AIDS epidemic, which our model does not predict (Fig 5.3.1(b)). This is probably because the STDSIM model assumes a much greater cofactor than our model in the case of symptomatic HSV-2, and symptomatic HSV-2 infection becomes more prevalent as the HIV/AIDS epidemic progresses. The model of Abu-Raddad *et al* (2008), which assumes that the HSV-2 cofactor only applies during periods of HSV-2 shedding, predicts that about 25% of incident HIV can be attributed to HSV-2, with no significant increase in the proportion of incident HIV attributable to HSV-2 as the HIV/AIDS epidemic matures. These results for Kenya are more consistent with our model predictions for South Africa.

STDSIM projections of PAFs for chancroid and chlamydial infection are compared with our model predictions in Figures 5.3.1(c) and (d). The STDSIM model predicts a higher proportion of incident HIV attributable to chancroid than our model in the early stages of the HIV/AIDS epidemic, probably because of the high cofactor assumed for chancroid in the STDSIM model (25). In most of the applications of the STDSIM model, a dramatic decline in the proportion of HIV attributable to chancroid is predicted, which is consistent with our model. The STDSIM model also predicts a slightly higher proportion of HIV attributable to chlamydial infection when compared with our model (Fig 5.3.1(d)).

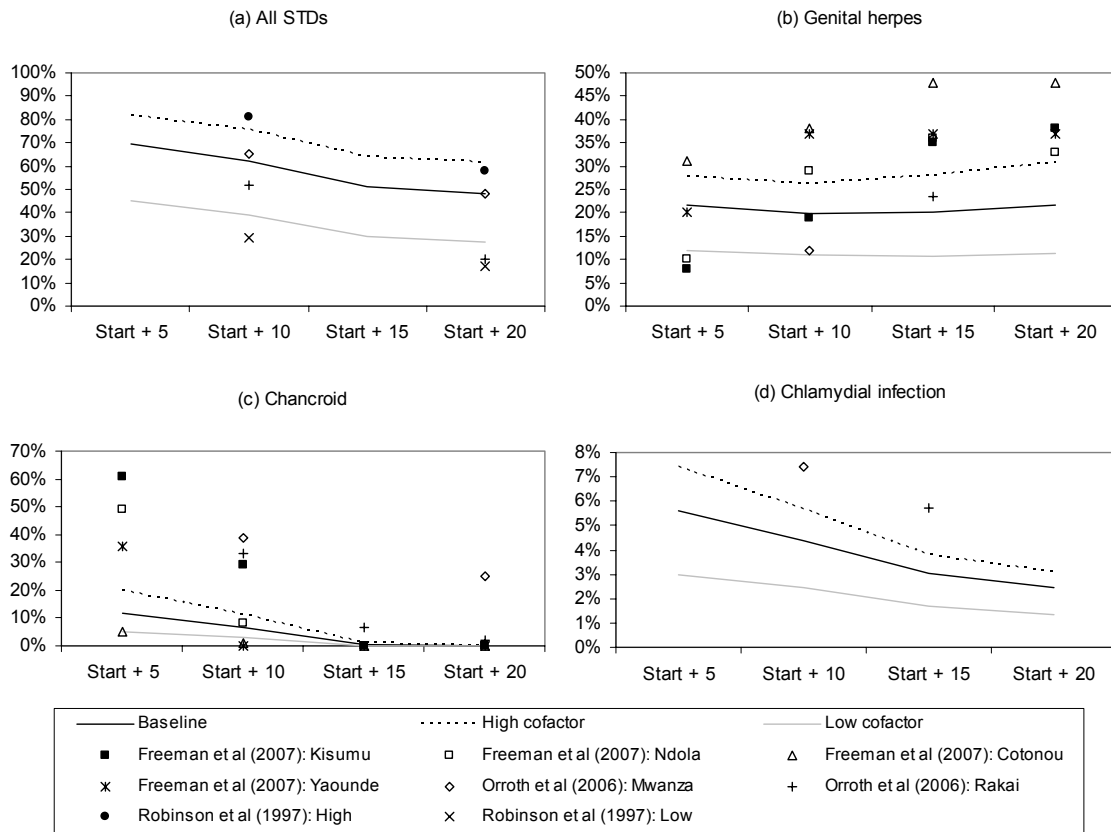


Figure 5.3.1: Comparison of population attributable fractions of STIs for HIV transmission, estimated in different models

PAFs are arranged according to the number of years from the assumed start of the HIV/AIDS epidemic (x axis).

In summary, our model estimates of the overall proportion of new HIV infections attributable to other STIs are roughly consistent with estimates from other models. However, our estimates of the proportions of incident HIV attributable to chancroid and herpes are lower than those estimated by STDSIM in the early and late stages of the HIV/AIDS epidemic respectively. This is likely to be a reflection of the differences in STI cofactor assumptions rather than differences in estimated STI prevalence levels.

5.4 Discussion

The results presented in section 5.2.3 show clearly that a high proportion of new HIV infections are directly attributable to other STIs. Consistent with the results of other models (Orroth *et al*, 2006; Robinson *et al*, 1997), this proportion appears to decline over the course of the HIV/AIDS epidemic. There are two likely explanations for this decline: (a) behavioural change and change in STI treatment, in response to the HIV/AIDS epidemic, can be expected to reduce STI prevalence; and (b) in the early stages of the HIV/AIDS epidemic, it is the individuals with the highest risk of other STIs who are the first to get infected with HIV. The PAFs of genital herpes and vulvovaginal candidiasis increase slightly after 1995, largely as a result of the assumed effect of HIV immunosuppression on the incidence of symptomatic HSV-2 and candidiasis.

Considering that around 20% of new HIV infections are currently attributable to genital herpes, it is particularly important that interventions be introduced to prevent and treat HSV-2. Gonorrhoea and chlamydial infection also account for a significant proportion of new HIV infections, and these should also be the focus of prevention efforts. Possible strategies for limiting the spread of these infections are assessed in chapter 6. Syphilis and chancroid, however, account for a negligible fraction of new HIV cases, and improvements to treatment for these STIs would therefore not affect future HIV incidence to any significant extent.

In assessing the contribution of different STIs to the incidence of HIV, we have considered a simple one-way sensitivity analysis rather than a formal uncertainty analysis. The 'baseline', 'high' and 'low' scenarios therefore do not reflect the full range of uncertainty around the PAFs of STIs for HIV transmission. This is partly because uncertainty surrounding the true STI prevalence is not reflected in these calculations. In addition, uncertainty regarding the relative magnitude of asymptomatic and symptomatic STI cofactors is not reflected, and this could be significant for STIs such as HSV-2, which are largely asymptomatic. For example, Orroth *et al* (2006) estimate that if the cofactor for asymptomatic HSV-2 were to increase from 1 to 5 (half the assumed cofactor for symptomatic infection), the PAF

of HSV-2 for HIV transmission would increase from 12% to 32% in the context of the Mwanza trial, and from 23% to 53% in the context of the Rakai trial.

There is also much uncertainty regarding STI cofactors when multiple STIs are present, and this significantly affects PAF calculations because of the high proportion of the population that has multiple infections. We have assumed that STI cofactors 'saturate' at the individual level, i.e. if the same individual is infected with multiple STIs, only the STI with the greatest cofactor affects the HIV transmission probability. If one were to assume instead that the multiplicative effect of a particular STI remains the same regardless of the other STIs present, the PAFs would be higher, particularly for those infections that are largely asymptomatic, and particularly in females (since females have a much higher prevalence of multiple infections than males). The PAFs for bacterial vaginosis and vulvovaginal candidiasis could therefore be underestimated substantially if STI cofactors were indeed fully multiplicative and did not saturate at the individual level. However, attempts to fit the model using multiplicative STI cofactors did not produce reasonable results when using the cofactor estimates presented in Tables 5.1.1 and 5.1.2. Under the fully multiplicative model, the substantial reductions in the prevalence of chancroid, syphilis, gonorrhoea and trichomoniasis since 1995 would imply substantial reductions in the incidence of HIV in recent years, in excess of the reductions suggested by the available HIV prevalence data. Under the 'saturation' model, however, the effect of the decline in curable STIs is weaker because of the relatively stable prevalence of HSV-2, bacterial vaginosis and vulvovaginal candidiasis. In addition to the saturation model producing HIV incidence trends more consistent with the available data, it is arguably a more biologically plausible model than the fully multiplicative model (Korenromp *et al*, 2001).

It is possible that different STIs may have different STI cofactors, even after controlling for whether they are symptomatic. This is another source of uncertainty not reflected in the PAF calculations. For example, if asymptomatic candidiasis has a higher STI cofactor than asymptomatic bacterial vaginosis and asymptomatic trichomoniasis (as Tables 5.1.1 and 5.1.2 suggest), the PAF of candidiasis for HIV transmission could be underestimated substantially. However, given the wide confidence intervals around the odds ratios estimated in the various meta-analyses,

and the sources of bias inherent in STI cofactor estimation, it is difficult to argue that there is indeed heterogeneity between STIs in terms of their effects on HIV transmission, after controlling for symptoms. We have adopted the parsimonious approach of setting STI cofactor assumptions for each STI syndrome, as it would be difficult to set STI cofactor assumptions separately for each STI (both symptomatic and asymptomatic) on the basis of the limited data available.

Most models of HIV-STI interactions assume that the probability of HIV transmission per act of sex is constant with respect to the relationship type and the cumulative number of exposures to the infected partner. Our model is unusual in that it assumes that the probability of HIV transmission, in the absence of other STIs, is dependent on the nature of the relationship. Although initial attempts were made to fit the model with HIV transmission probabilities that were constant with respect to the relationship type, this was found to give poor fits to the age- and sex-specific HIV prevalence data. This suggests that variation in HIV transmission probabilities cannot be explained only by variation in viral load over the course of HIV disease or variation in HIV transmission probabilities due to other STIs, since both factors are already allowed for in the model. As discussed in section 3.3.2, there is much evidence showing that the probability of HIV transmission per sex act reduces as the cumulative number of sexual exposures to the HIV-infected partner increases (Downs and De Vincenzi 1996; Padian *et al*, 1990). Consistent with these empirical observations, we have estimated substantially lower HIV transmission probabilities, per act of sex, in long-term spousal relationships than in short-term non-spousal relationships. We have also estimated that the risk of female-to-male transmission in a single act of sex is higher in once-off encounters between sex workers and clients than in short-term relationships. However, the estimated probability of male-to-female transmission per sex act is substantially lower in contacts between sex workers and clients than in short-term relationships. Sex workers do not generally have many contacts with the same partner, and might therefore be expected to have a greater risk of transmission per act of sex with an infected partner than women in short-term relationships. The fact that they do not supports the hypothesis that individuals who are highly exposed to HIV may develop immune responses that protect against HIV infection (Rowland-Jones *et al*, 1998; Lo Caputo *et al*, 2003; Mazzoli *et al*, 1999).

These sources of variation in HIV transmission probabilities should be further explored in future HIV modelling work.

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Chapter 6: Prospects for HIV and STI prevention

This chapter assesses the impact of past HIV and STI prevention programmes (section 6.1), and then examines the potential effect of future changes to STI treatment and sexual behaviour (sections 6.2 and 6.3 respectively). Results are compared with empirical estimates and results from other models, and policy implications are discussed in section 6.4.

6.1 The effect of past changes in sexual behaviour and STI treatment on STI prevalence and HIV incidence

The Bayesian analysis presented in section 4.2 suggests that there have been significant declines in the prevalence of most STIs in South Africa, over the last two decades. There are three possible explanations for these declines. Firstly, the declines may be due to the effects of improvements in the quality of STI treatment, especially the introduction of syndromic management protocols. Secondly, declines in STI prevalence could be due to increases in condom use, which have been the result of information and education campaigns (IEC) and condom promotion programmes. Lastly, declines in the prevalence of STIs may be the result of rising levels of AIDS mortality, which would be expected to deplete the ‘high risk’ groups to a greater extent than the ‘low risk’ groups, and thus change the overall STI prevalence. The purpose of this section is to evaluate the relative significance of each of these three explanations, for each of the STIs, through the consideration of a number of different counterfactual scenarios.

6.1.1 Method

In order to quantify the relative significance of each of the three factors affecting the trends in STI prevalence, four scenarios are considered:

- ‘Baseline’ scenario: This is the same as the scenario presented in Chapter 4 and described in Chapter 3, i.e. it represents our most realistic assessment of what has occurred in South Africa to date.

- ‘No syndromic management’ scenario: This is the same as the ‘baseline’ scenario, except that there is assumed to be no introduction of syndromic management protocols in South Africa and no reduction in the extent of STI drug shortages.
- ‘No IEC’ scenario: This is the same as the ‘no syndromic management’ scenario, except that levels of condom use are assumed to remain unchanged from their levels in 1985, i.e. it represents what might have been expected if there had been no information and education campaigns, no change in sexual behaviour in response to HIV/AIDS, and no change in STI treatment practices.
- ‘No AIDS’ scenario: This is the same as the ‘No IEC’ scenario, except that HIV is assumed never to have entered the population.

The means of the posterior predictions are compared graphically for each scenario. In addition, the percentage reduction in STI prevalence attributable to each of the three factors is calculated in 2005, by comparing the first and second scenarios (to assess the role of improvements in STI treatment), the second and third scenarios (to assess the role of increased condom use) and the third and fourth scenarios (to assess the role of HIV/AIDS). The effects of the three factors could be calculated in different ways, and the percentage reductions in STI prevalence would change slightly if one were to alter the order in which the different model parameters are changed.

The first three scenarios are also considered when examining the effects of past changes in sexual behaviour and STI treatment on HIV incidence. Trends in annual numbers of new HIV infections are calculated for each of these three scenarios, for each of the three cofactor settings described in section 5.2.1. Percentage reductions in annual numbers of new HIV infections are then calculated for each cofactor setting.

6.1.2 Factors accounting for past changes in STI prevalence

Figure 6.1.1 shows the posterior mean STI prevalence trends, for each of the four scenarios defined previously. Results are shown for women aged 15 to 49 (prevalence levels in men follow similar trends). The percentage reductions in STI prevalence in 2005, attributable to each of the three factors, are shown in Figure 6.1.2.

Syndromic management has substantially reduced the prevalence of chancroid, syphilis and gonorrhoea, probably because all of these infections become symptomatic in a high proportion of cases, and are thus particularly amenable to improvements in the quality of treatment for symptomatic STIs. However, current syndromic management protocols do not represent any improvement over past STI treatment practices in the cases of genital herpes and vaginal candidiasis, and hence the prevalence of these infections is virtually unchanged with the introduction of syndromic management. Although there have been marked improvements in the quality of treatment for trichomoniasis and chlamydial infection under the new syndromic management protocols, the trends in the prevalence of these two infections are virtually indistinguishable under the 'baseline' and 'no syndromic management' scenarios. This is because in both cases the estimated duration of untreated symptomatic infection is substantially shorter than the duration of untreated asymptomatic infection, and most infections do not become symptomatic. As a result, reductions in the duration of symptomatic infection have relatively little effect, especially when counterbalanced by reductions in the prevalence of immunity (in both cases it is assumed that immunity is less likely to develop after treatment than after spontaneous resolution of infection).

Increases in condom usage also appear to have brought about substantial reductions in STI prevalence, and in many cases, this reduction is greater than that achieved through improvements in STI treatment alone. The prevalence of bacterial vaginosis and vaginal candidiasis is not significantly affected by changes in condom use, since neither infection is assumed to be sexually transmissible, and the 'No IEC' scenario is therefore not shown in Figures 6.1.1(g) and (h).

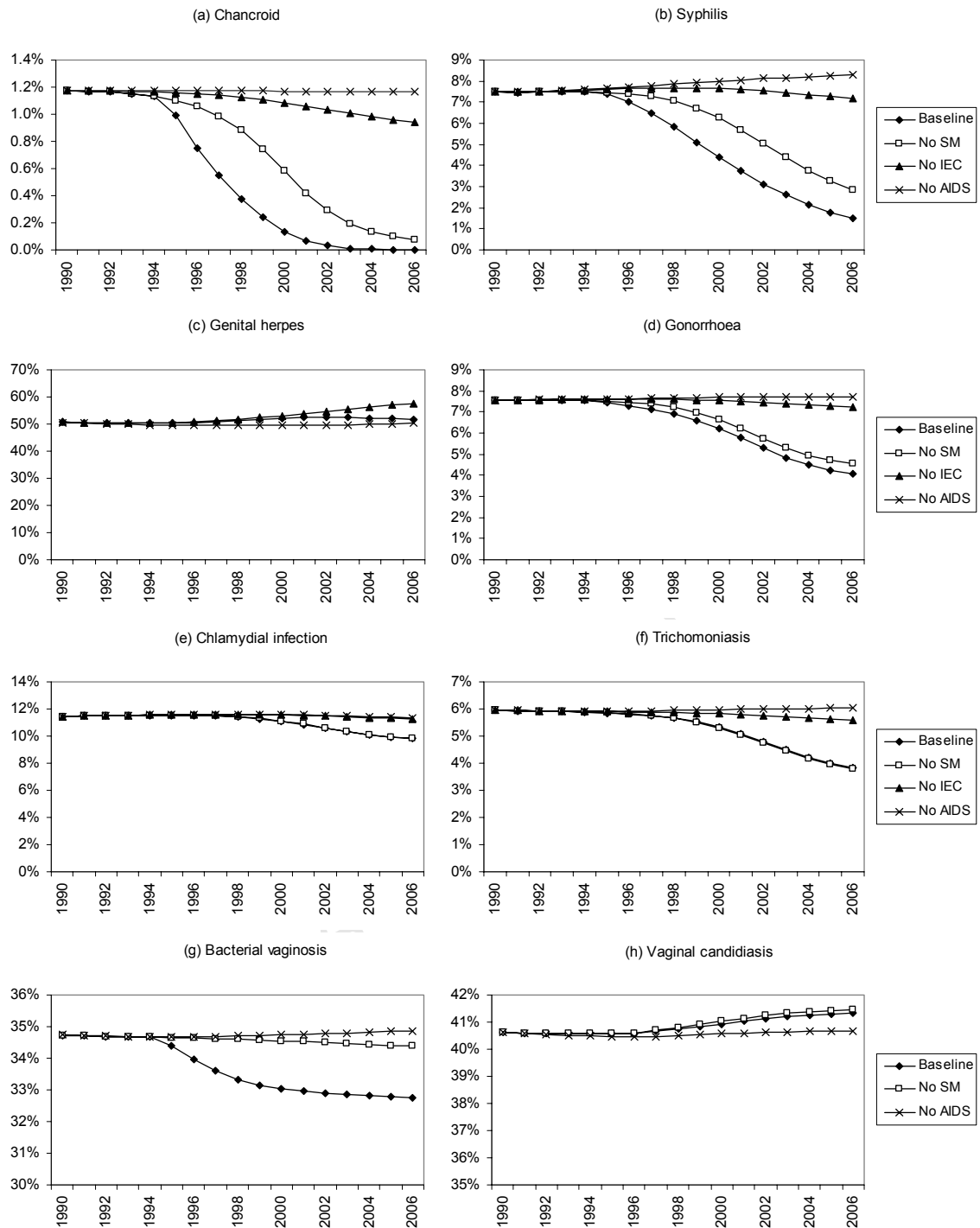


Figure 6.1.1: Trends in STI prevalence among women aged 15-49, over the 1990-2006 period, under different scenarios

‘Baseline’ is the actual past trend in STI prevalence, ‘no SM’ is the trend that would have been expected in the absence of change in STI treatment practices, ‘no IEC’ is the trend that would have been expected if no changes in STI treatment or sexual behaviour occurred, and ‘no AIDS’ is the trend that would have been expected in the absence of any HIV and HIV prevention strategies.

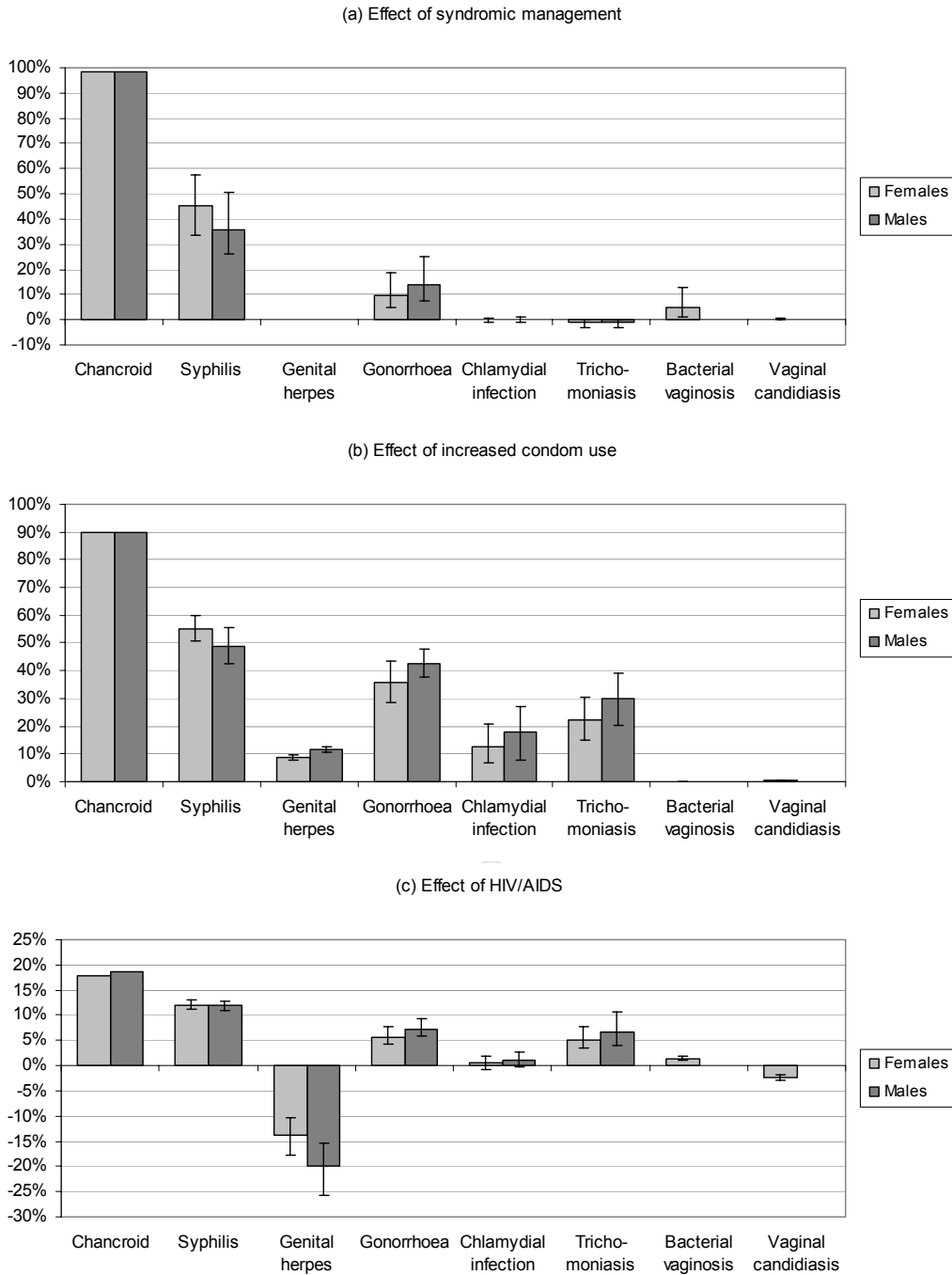


Figure 6.1.2: Percentage reductions in STI prevalence in 2005, among individuals aged 15-49, attributable to different factors

Error bars represent 95% prediction intervals. The percentage reduction in prevalence due to syndromic management is the difference between the ‘no SM’ and ‘baseline’ scenarios, expressed as a percentage of the prevalence in the ‘no SM’ scenario. Similarly, the percentage reduction in prevalence due to increased condom use is the difference between the ‘no IEC’ and ‘no SM’ scenarios, expressed as a percentage of the prevalence in the ‘no IEC’ scenario, and the percentage reduction due to AIDS mortality is the difference between the ‘no AIDS’ and ‘no IEC’ scenarios, expressed as a percentage of the prevalence in the ‘no AIDS’ scenario.

Lastly, HIV/AIDS has brought about modest reductions in the prevalence of most STIs. Two exceptions are HSV-2 and vaginal candidiasis. The prevalence of HSV-2 is expected to rise as a result of HIV/AIDS because HSV-2-infected individuals who are co-infected with HIV are assumed to experience greater frequency of HSV-2 shedding and HSV-2 symptoms, and are thus more likely to transmit HSV-2 than they would be in the absence of HIV infection. The prevalence of vaginal candidiasis is also expected to rise slightly, due to the assumed increase in the frequency of vaginal candidiasis in the later stages of HIV infection. Figure 6.1.1 shows that for most STIs, the prevalence in the 'no AIDS' scenario is stable over time. However, the prevalence of syphilis increases slightly over time, probably because of declining levels of fertility and associated declines in the rate at which women receive antenatal screening for syphilis.

6.1.3 The effect of past interventions on HIV incidence

Figure 6.1.3 shows the annual percentage reduction in HIV incidence attributable to (a) improvements in STI treatment and (b) increases in condom use, for each of the STI cofactor scenarios. The improvements in STI treatment that have occurred to date are estimated to have achieved a modest 6.0% reduction in the total number of new HIV infections over the period from mid-1994 to mid-2004 (i.e. the ten years following the introduction of syndromic management protocols in South Africa). Corresponding reductions in the low and high cofactor scenarios are 3.0% and 10.0% respectively. The reduction in HIV incidence is greatest around 1998, when the rollout of syndromic management protocols in the public health sector is close to its maximum, but thereafter the effect on HIV incidence starts to diminish. A possible interpretation of this result is that syndromic management delays new HIV infections without bringing about a substantial reduction in individuals' long-term risk of HIV acquisition. The reduction after 1998 could also be due to the decline in the proportion of new HIV infections attributable to curable STIs.

Much greater reductions in HIV incidence have been achieved as a result of increases in condom use, and these reductions are relatively insensitive to the assumed magnitudes of the STI cofactors. The decline in the total number of new HIV

infections over the period from mid-1994 to mid-2004 is 27.3% in the baseline cofactor scenario, 26.3% in the low cofactor scenario and 28.8% in the high cofactor scenario. These reductions in HIV incidence have increased steadily over time, in line with the assumed trends in condom use. By 2005, the annual number of new HIV infections is between 46% and 51% lower in the ‘no syndromic management’ scenario than in the ‘no IEC’ scenario.

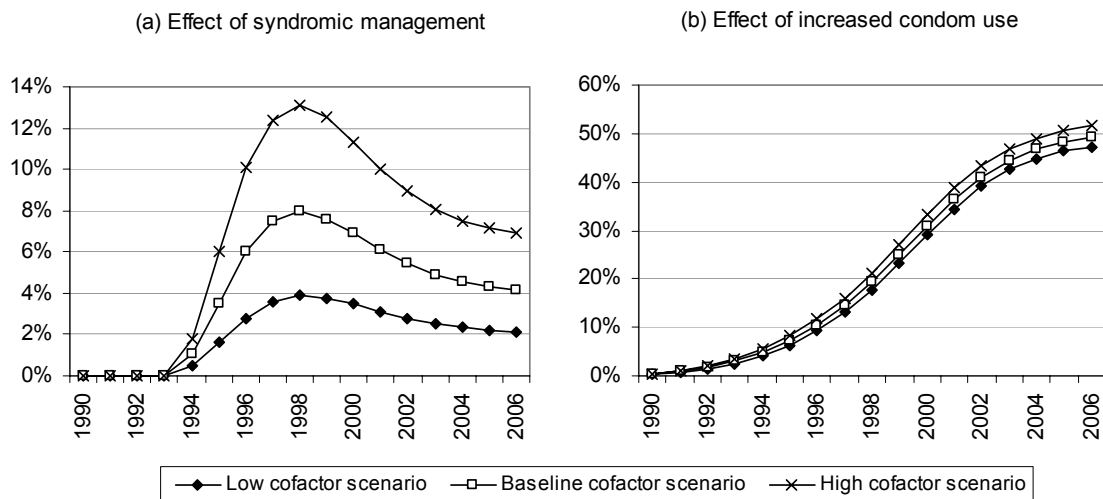


Figure 6.1.3: Percentage reductions in annual HIV incidence due to past interventions, over the 1990-2006 period

Percentage reductions are calculated by comparing the ‘baseline’ and ‘no syndromic management’ scenarios in panel (a) and the ‘no syndromic management’ and ‘no IEC’ scenarios in panel (b).

6.2 The potential effects of future improvements in STI treatment

The analysis thus far has examined the effects of past improvements in STI treatment practices in South Africa. As discussed in section 3.3.4, however, many significant obstacles still prevent the prompt and effective treatment of STIs in South Africa. Section 6.2.1 reviews some of the strategies that have been proposed for improving treatment of STIs and expanding current programmes, and explains how the model has been extended to allow for the effect of these interventions. In section 6.2.2, the effects of these interventions on STI prevalence are assessed, and in section 6.2.3 the effects on HIV incidence are presented.

6.2.1 Assumed future changes to STI treatment

Several changes to STI treatment in South Africa have been proposed by various experts in STI epidemiology. These potential changes can be divided into five categories:

- Increases in adoption of syndromic management protocols
- Modifications to existing syndromic management protocols
- Patient-initiated treatment for genital herpes
- Changes in health-seeking behaviour
- Improvements in screening and/or presumptive STI treatment

Each of these potential changes is discussed in the sections that follow, together with an explanation of the assumptions made in modelling these changes. In each case, it is assumed that the intervention is phased in uniformly over the period from mid-2010 to mid-2014, thus allowing for a realistic delay in the formulation and implementation of new health interventions. The levels of rollout that can ultimately be achieved are open to debate, and these rollout assumptions should therefore be seen as illustrative.

6.2.1.1 Increases in adoption of syndromic management protocols

As shown in Table 3.3.13, it is assumed in the baseline scenario that the proportion of public practitioners following syndromic management protocols levels off at 80%, and that the proportion of public STI clinics with STI drug shortages levels off at 4%, based on data from recent surveys (Ramkisson *et al*, 2004; Reagon *et al*, 2004; Colvin *et al*, 2006). The proportion of private practitioners following syndromic management protocols is assumed to rise to 33% by 2005 and to increase by 2% per annum (absolute) thereafter, as the proportion of private practitioners trained in syndromic management increases (Schneider *et al*, 2005b).

In order to increase adoption of syndromic management protocols, a range of interventions will be required. Heavy patient loads in the public health sector may compromise the quality of treatment provided (Sonko *et al*, 2003), and interventions to reduce under-staffing may therefore be important. STI syndrome packets have also

been proposed as a means of improving overall STI case management; studies conducted in South Africa and Uganda have shown that the use of packaged treatment for STI syndromes can increase the proportion of STI cases that are correctly treated (Harrison *et al*, 2000; Jacobs *et al*, 2003), though another South African study found that syndrome packets only improved the counselling component of the STI case management, not the STI treatment (Colvin *et al*, 2006). In the private health sector, the high costs of treating STI patients with multiple drugs, and the lack of training provided to private practitioners regarding recent STI treatment methods are major obstacles to the adoption of syndromic management guidelines. An education programme for private practitioners in South Africa did not appear to improve the quality of STI treatment significantly (Schneider *et al*, 2005a), though a similar programme in Jamaica achieved significant improvements in knowledge of correct STI treatment (Green *et al*, 1998).

Although it is not clear how effective the above interventions would be if implemented in South Africa on a national scale, we consider a hypothetical scenario in which the proportion of cases treated according to syndromic management protocols increases to 80% in the private health sector and to 100% in the public health sector, over the 2010-2014 period. Drug shortages in public health facilities are also assumed to be eliminated over the same period.

6.2.1.2 Modifications to existing syndromic management protocols

Three different revisions to current South African treatment protocols have been proposed, and are considered here. Firstly, recent WHO guidelines recommend the inclusion of antiviral treatment in the treatment of patients with GUD, in countries with an HSV-2 prevalence of over 30% (World Health Organization 2003). This is in recognition of the increasingly high proportion of GUD cases that are due to genital herpes. Studies have shown that the incorporation of acyclovir (the cheapest antiviral effective against herpes) into syndromic management guidelines can significantly reduce ulcer duration and HIV shedding in HIV-coinfected subjects (Paz-Bailey *et al*, 2007b). Recent South African protocols, however, do not make provision for antiviral treatment of GUD patients (Department of Health 2003), and it does not appear that this has been incorporated in recent treatment practice. In the analysis that follows, it

is assumed that 90% of practitioners treating according to syndromic management protocols include the provision of acyclovir to patients presenting with GUD. This is assumed to be phased in uniformly over the 2010-2014 period. As with other STI drugs, acyclovir is assumed to be 90% effective.

The second proposed change is to replace ciprofloxacin with ceftriaxone in the treatment of male patients with urethral discharge and female patients with vaginal discharge or lower abdominal pain. This is recommended due to the rising prevalence of ciprofloxacin resistance in South African gonococcal isolates (Lewis *et al*, 2007; Black *et al*, 2008; Moodley and Sturm 2005). In order to model the effect of this intervention, it is necessary to specify the assumed proportions of gonorrhoea cases that are ciprofloxacin-resistant and the proportion of cases treated with ciprofloxacin, in each year. The treatment effectiveness parameter is then reduced in proportion to the product of the ciprofloxacin-resistant fraction and the ciprofloxacin-treated fraction. Based on the available surveillance data (Lewis *et al*, 2007; Black *et al*, 2008; Moodley and Sturm 2005), resistance is assumed to have been absent prior to 2003, then increased to 4% of cases in 2003, 10% in 2004, 16% in 2005, 25% in 2006 and 38% in 2007. Future trends in ciprofloxacin resistance are unclear, but in the absence of significant changes to treatment practices, selection pressures would be expected to lead to a continued upward rise. It is assumed that the proportion of cases resistant to ciprofloxacin would rise to 55% in 2008, 70% in 2009, 82% in 2010, 90% in 2011, 96% in 2012 and 100% in all subsequent years. In the absence of interventions, it is assumed that 50% of treated gonorrhoea cases receive drugs other than ciprofloxacin, since private practitioners often use ceftriaxone and spectinomycin in the treatment of gonorrhoea (Chabikuli *et al*, 2002) and alternatives to ciprofloxacin are often used in second-line drug regimens (Moodley and Sturm 2005). This proportion is assumed to rise to 90% over the 2010-2014 period if interventions to promote alternatives to ciprofloxacin are introduced in the private and public health sectors.

The last proposed change is to add metronidazole to the treatment of male patients presenting with urethral discharge, as a first-line treatment. This has been advocated on the grounds that the existing drug combination is not effective against trichomoniasis, which may be a significant cause of male urethral discharge in some

populations (Price *et al*, 2004). However, in a randomized controlled trial to test the effect of including treatment for trichomoniasis in the syndromic management protocol for male urethral discharge, it was found that the inclusion of trichomoniasis treatment had no positive effect on the rate at which discharge resolved (Price *et al*, 2003). The effect of extending the syndromic management protocols to include metronidazole in the first-line treatment of male urethral discharge is simulated by assuming that the proportion of male trichomoniasis cases treated correctly rises from 50% to 90%, over the 2010-2014 period.

6.2.1.3 Patient-initiated treatment for genital herpes

Although the incorporation of antiviral treatment into syndromic management protocols for GUD may be an effective strategy for treating herpetic lesions, it may not be the optimal approach to dealing with genital herpes, as it relies on individuals with recurrent HSV-2 symptoms attending health services and it avoids counselling HSV-2-infected individuals on the nature of their infection. An alternative approach may be to test GUD patients for HSV-2, counsel those infected with the virus on the nature of their infection, and provide them with a supply of antivirals so that they can self-initiate treatment when they experience future recurrences, rather than return to the health facility for treatment (O'Farrell *et al*, 2007a; Apoola and Radcliffe 2004; Hudson 1999). In addition to reducing case loads, this would avoid unnecessarily providing antibiotics to patients with herpetic lesions. Studies have shown that patient-initiated treatment of HSV-2 recurrences can reduce the proportion of recurrences that develop into ulcers, shorten the duration of ulcers and improve quality-of-life outcomes (Aoki *et al*, 2006; Fife *et al*, 2007; Whatley and Thin 1991; Wald *et al*, 2002). In addition, counselling of patients on the importance of reducing their risk of HSV-2 transmission to their sexual partners could significantly reduce HSV-2 incidence (Wald *et al*, 2006).

To model the effect of such an intervention, it is assumed that the rate of HSV-2 recurrence reduces by 80% over the 2010-2014 period. Although in reality it is the duration of recurrences rather than the incidence of recurrences that would reduce, patients would be counselled to abstain from unprotected sex while experiencing HSV-2 recurrences. Reducing the incidence of recurrences by 80% would hence be

equivalent to reducing the duration of 80% of ulcers, from the point of view of HIV and HSV-2 transmission, assuming that counselled individuals do indeed abstain from unprotected sex while experiencing recurrences of genital herpes.

6.2.1.4 Changes in health-seeking behaviour

Delays in seeking treatment for STIs are a significant problem, particularly since symptomatic STIs play a greater role in HIV transmission than asymptomatic STIs. In developed countries such as the US and the UK, the average time to seeking STI treatment is typically around 4 days for men and around 12 days for women (Garnett *et al*, 1999; Schofield 1982), while in African countries, the average delay is around 14 days for men and 30 days for women (Wilkinson *et al*, 1998; Voeten *et al*, 2004; O'Farrell *et al*, 1991a; O'Farrell *et al*, 1991b). This problem could be partly addressed through the extension of health services, particularly in rural areas. However, it would also be important to increase the promotion of prompt health-seeking for STI symptoms through social marketing programmes. In the Mwanza trial, for example, campaigns to improve health-seeking behaviour were introduced in intervention communities. It was observed that numbers of public STI clinic attendances were roughly 25% higher in intervention communities than in control communities (Grosskurth *et al*, 2000) and the proportion of individuals with genital ulcer or discharge syndromes who sought treatment was 31% higher in the intervention communities (Buvé *et al*, 2001a).

Since it is not clear what would be a realistic target for the reduction in the treatment delay, we consider a scenario in which the average treatment delay is reduced by 50%. (This does not apply to sex workers, as they already have a high rate of health-seeking behaviour in the baseline scenario.) Such a reduction would bring the average treatment delays assumed in the model close to those observed in the developed world.

6.2.1.5 Improvements in screening and/or presumptive STI treatment

Several studies have examined the potential effects of monthly screening or presumptive treatment of STIs in sex workers. Reviews of these studies have noted

that behavioural interventions are often combined with the periodic treatment/screening, which makes it difficult to isolate the independent effect of the STI treatment component of the intervention (Shahmanesh *et al*, 2008; Steen and Dallabetta 2003). In the few studies in which the effect of STI treatment could be isolated, it was generally found to reduce STI prevalence, although often not significantly so. Two randomized controlled trials have examined the effect of monthly presumptive treatment on HIV incidence in sex workers (Kaul *et al*, 2004; Ghys *et al*, 2001), but neither detected any significant decrease in HIV incidence as a result of the intervention.

In order to model the effect of periodic presumptive treatment (PPT) in sex workers, it is assumed that the rate at which enrolled sex workers get treated for asymptomatic STIs rises to 0.25 per week over the 2010-2014 period (0.25 per week corresponds roughly to the monthly frequency of screening in most studies). It is also assumed that the treatment provided to sex workers is as effective as the STI treatment provided to women treated according to syndromic management protocols. Since sex work is illegal and sex workers are a difficult group to reach with health interventions, it is assumed that the PPT programme would enrol only 50% of active sex workers by mid-2014, and thereafter the proportion participating in the programme would remain constant at 50%.

The evidence reviewed in section 3.3.4.4 suggests that there is a need for improvements in the antenatal screening for syphilis. Although the antenatal prevalence of syphilis has declined substantially in recent years, the proportion of pregnant women who receive syphilis testing needs to increase, and the proportion of women testing positive who receive treatment also needs to increase. It is assumed that both proportions would increase to 100% over the 2010-2014 period (from the default levels of 75% and 80% respectively), if adequate management systems were introduced.

6.2.2 Effect of future changes in STI treatment on STI prevalence

The effects of different improvements in STI treatment are compared by examining the percentage reductions in STI prevalence by 2020. Table 6.2.1 shows the mean

percentage reductions (together with 95% prediction intervals), for each STI and for each intervention, in the case of females aged between 15 and 49. Similar reductions are shown for males aged between 15 and 49 in Table 6.2.2. Results are not shown for chancroid, as this STI has been virtually eliminated (the predicted prevalence in 2005 is around 0.001%), and improvements in STI treatment would therefore have no noticeable impact on the prevalence of this STI in absolute terms.

Overall, the intervention that is likely to have the greatest impact on STI prevalence is the campaign to halve the time to seeking treatment for STI symptoms. This would substantially reduce the prevalence of syphilis (by an average of 35% in men and 52% in women) and the prevalence of gonorrhoea (by an average of 29% in men and 21% in women), but would have relatively little effect on the prevalence of other STIs, which are mostly asymptomatic. Most interventions have no effect on the prevalence of genital herpes, as it is not affected by the antibiotics currently used in syndromic management. The inclusion of acyclovir treatment in syndromic management protocols for genital ulcer disease could reduce HSV-2 prevalence slightly (by about 1% in both men and women), but a much more effective strategy would be to encourage patient-initiated treatment of genital herpes. It is predicted that this would reduce the prevalence of genital herpes by an average of 6.6% in women and 7.5% in men; greater reductions would be expected over the longer term.

Increased adoption of syndromic management protocols and elimination of drug shortages would be expected to have a substantial effect on the prevalence of syphilis, but other STIs would be relatively unaffected. The effects of changes in the public health sector are greater than the effects of changes in the private health sector, probably because the proportion of STI patients using the public health sector is higher than the proportion using the formal private health sector. Extending syndromic management protocols for male urethral discharge to include metronidazole would have no significant effect on the prevalence of trichomoniasis, and could possibly even increase the prevalence of trichomoniasis as a result of delayed development of immunity to the infection. Monthly presumptive treatment of sex workers would have little effect on STI prevalence at a population level, but could have a significant effect on STI prevalence among sex workers. Improvements in

antenatal screening for syphilis would reduce the prevalence of syphilis in females by 12% on average, but would have little effect on the prevalence of syphilis in men.

To assess the effect of combining interventions, a combined intervention scenario is considered. This scenario includes all interventions except presumptive treatment for sex workers, metronidazole treatment for male urethral discharge, and incorporation of acyclovir into syndromic management guidelines (the latter intervention is excluded because it would be obviated if the more effective patient-initiated acyclovir strategy were introduced). The combined intervention strategy would have a significant impact on the prevalence of gonorrhoea, syphilis and genital herpes, but reductions in the prevalence of other STIs would probably be less than 5%.

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Table 6.2.1: Percentage reductions in STI prevalence in 2020, among females aged 15 to 49

Intervention	Syphilis	HSV-2	Gonorrhoea	Chlamydia	Trichomoniasis	BV	Candidiasis
Increased adoption of SM in private health sector	11.1% (1.4, 20.7)	-	0.7% (0.3, 1.4)	0.0% (-0.1, 0.0)	-0.1% (-0.2, 0.0)	0.2% (0.1, 0.6)	0.0% (0.0, 0.0)
Increased adoption of SM in public health sector + no drug shortages	20.7% (2.0, 34.9)	-	1.8% (1.0, 3.1)	0.0% (-0.1, 0.1)	-0.1% (-0.4, 0.0)	0.6% (0.1, 1.6)	0.1% (0.0, 0.2)
Incorporation of acyclovir into SM protocols for GUD	-	0.9% (0.5, 1.3)	-	-	-	-	-
Replacement of ciprofloxacin with ceftriaxone in treatment of gonorrhoea	-	-	17.6% (11.0, 27.3)	-	-	-	-
Incorporation of metronidazole into SM protocols for MUD	-	-	-	-	-0.4% (-0.9, 0.3)	-	-
Patient-initiated treatment of genital herpes	-	6.6% (3.3, 10.1)	-	-	-	-	-
Halving of time to seeking treatment	51.9% (4.3, 82.2)	-	20.5% (12.8, 32.0)	0.0% (-1.4, 1.1)	-1.3% (-2.9, 0.3)	3.1% (0.7, 6.9)	2.0% (0.8, 3.8)
Monthly presumptive treatment for sex workers	0.0% (0.0, 0.0)	-	0.0% (0.0, 0.0)	0.0% (0.0, 0.1)	0.1% (0.0, 0.3)	0.0% (0.0, 0.0)	0.0% (0.0, 0.0)
Improved antenatal screening for syphilis	12.0% (10.3, 13.3)	-	-	-	-	-	-
Combined strategy	58.6% (15.6, 85.5)	6.6% (3.3, 10.1)	37.0% (22.5, 57.5)	0.0% (-1.6, 1.2)	-1.5% (-3.5, 0.4)	3.6% (0.9, 8.5)	2.1% (0.8, 3.9)

95% prediction intervals are shown in brackets. GUD = genital ulcer disease. MUD = male urethral discharge. SM = syndromic management.

Table 6.2.2: Percentage reductions in STI prevalence in 2020, among males aged 15 to 49

Intervention	Syphilis	HSV-2	Gonorrhoea	Chlamydia	Trichomoniasis
Increased adoption of SM in private health sector	7.3% (0.5, 16.9)	-	1.3% (0.5, 2.4)	0.0% (-0.2, 0.0)	-0.1% (-0.3, 0.1)
Increased adoption of SM in public health sector + no drug shortages	13.6% (0.7, 28.3)	-	2.7% (1.6, 4.4)	0.0% (-0.2, 0.2)	-0.1% (-0.4, 0.1)
Incorporation of acyclovir into SM protocols for GUD	-	0.8% (0.4, 1.2)	-	-	-
Replacement of ciprofloxacin with ceftriaxone in treatment of gonorrhoea	-	-	25.3% (17.5, 35.9)	-	-
Incorporation of metronidazole into SM protocols for MUD	-	-	-	-	-1.0% (-2.3, 0.4)
Patient-initiated treatment of genital herpes	-	7.5% (3.7, 11.6)	-	-	-
Halving of time to seeking treatment	35.0% (1.5, 71.5)	-	29.2% (20.1, 41.3)	0.1% (-1.9, 1.4)	-2.0% (-4.0, 0.4)
Monthly presumptive treatment for sex workers	0.0% (0.0, 0.0)	-	0.0% (0.0, 0.1)	0.0% (0.0, 0.1)	0.2% (0.1, 0.4)
Improved antenatal screening for syphilis	0.4% (-0.2, 1.0)	-	-	-	-
Combined strategy	35.1% (1.5, 71.6)	7.5% (3.7, 11.6)	48.6% (33.5, 68.2)	0.1% (-2.1, 1.5)	-2.2% (-4.6, 0.4)

95% prediction intervals are shown in brackets. GUD = genital ulcer disease. MUD = male urethral discharge. SM = syndromic management.

6.2.3 Effect of future changes in STI treatment on HIV incidence

Table 6.2.3 shows the percentage reductions in the total number of new HIV infections over the period from mid-2010 to mid-2020, as a result of improvements in STI treatment, for each of the STI cofactor scenarios described in section 5.2.1. The projected absolute number of new HIV infections over the 2010-2020 period, in the absence of further changes to STI treatment, is 4.1 million in the baseline cofactor scenario, 3.8 million in the high cofactor scenario and 4.6 million in the low cofactor scenario. The greatest reductions in HIV incidence, in all three cofactor scenarios, would be achieved through patient-initiated acyclovir, followed by the halving of treatment delays, followed by the substitution of ciprofloxacin in the treatment of gonorrhoea. Increases in the adoption of syndromic management in the private and public health sectors and incorporation of acyclovir into syndromic management guidelines for GUD would have a modest effect on HIV incidence (less than a 1% reduction). Other interventions (metronidazole for male urethral discharge, presumptive treatment for sex workers and improved antenatal screening for syphilis) would have no appreciable effect on HIV incidence. The combined strategy described in section 6.2.2 would achieve an overall reduction in HIV incidence equal to 7.9% of new HIV infections in the baseline cofactor scenario (330 000 HIV infections averted over the 2010-2020 period), 3.6% of new infections in the low cofactor scenario (170 000 HIV infections averted), and 13.5% of new infections in the high cofactor scenario (510 000 HIV infections averted).

Table 6.2.3: Percentage reduction in new HIV infections, 2010-2020, as a result of improvements in STI treatment

Intervention	Baseline cofactor scenario	Low cofactor scenario	High cofactor scenario
Increased adoption of SM in private health sector	0.2%	0.1%	0.3%
Increased adoption of SM in public health sector + no drug shortages	0.3%	0.1%	0.5%
Inclusion of acyclovir in SM protocols for GUD	0.5%	0.2%	0.8%
Replacement of ciprofloxacin with ceftriaxone in treatment of NG	1.9%	0.8%	3.2%
Incorporation of metronidazole into SM protocols for MUD	0.0%	0.0%	0.0%
Patient-initiated treatment of genital herpes	3.7%	1.6%	6.5%
Halving of time to seeking treatment	2.8%	1.3%	4.7%
Monthly presumptive treatment for sex workers	0.0%	0.0%	0.0%
Improved antenatal screening for syphilis	0.0%	0.0%	0.0%
Combined strategy	7.9%	3.6%	13.5%

GUD = genital ulcer disease. MUD = male urethral discharge. NG = Neisseria gonorrhoeae. SM = syndromic management.

The projected reductions in HIV incidence are not uniform over the 2010-2020 period, as Figure 6.2.1 shows. For all three of the most effective interventions, as well as the combined intervention, the annual percentage reduction in the number of new HIV infections increases monotonically over the 2010-2020 period.

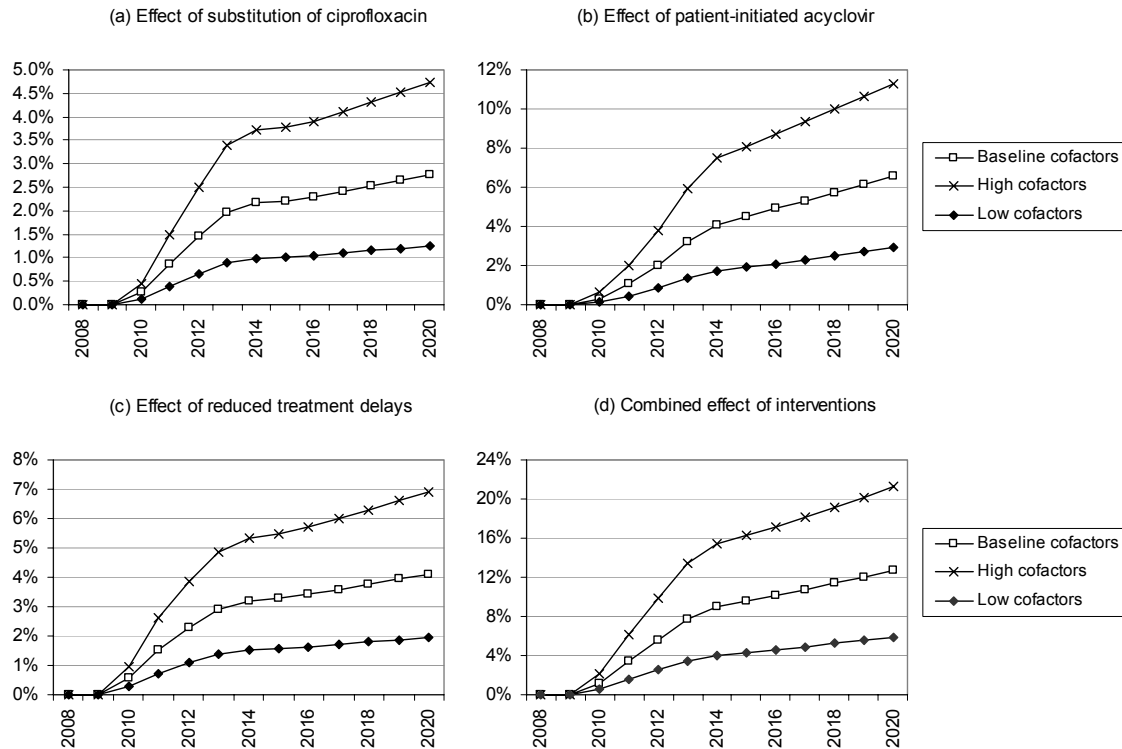


Figure 6.2.1: Annual percentage reductions in new HIV infections, as a result of improvements in STI treatment

6.3 The potential effects of behaviour change

As shown in section 6.1, increases in condom usage have already contributed significantly to reducing HIV incidence and STI prevalence in South Africa. The objective of this section is to evaluate how further changes in behaviour could potentially influence the incidence of HIV and the prevalence of STIs. The intention of this analysis is not to identify specific programmes to reduce the incidence of HIV, but rather to identify the forms of behaviour that are contributing most significantly to the transmission of HIV and other STIs, and that should be addressed through social marketing programmes. The behaviour change scenarios presented in this section are therefore purely illustrative, and should not be considered realistic. The section begins with a brief review of the forms of sexual behaviour that have been most often linked to the spread of HIV infection in the Sub-Saharan African context, then describes the method used to assess the roles of these behavioural factors, and finally shows the

results of different forms of behaviour change in terms of both HIV incidence and STI prevalence.

6.3.1 Review of behaviours linked to the spread of HIV in Sub-Saharan Africa

Uganda is frequently cited as an example of an African country in which reductions in HIV risk behaviour have brought about significant declines in HIV prevalence. However, different studies produce conflicting explanations for these declines. Asiimwe-Okiror *et al* (1997) found that in urban Uganda there had been significant increases in condom usage, increases in age at sexual debut and marriage, and reductions in proportions of men reporting sex involving exchange for money. It was also found that there was no significant change in the reporting of non-regular partners or extramarital sex. Similar findings in rural Uganda were reported by Kamali *et al* (2000); this study also found increased condom use and delayed sexual debut and marriage, but no reduction in numbers of partners. In contrast, Stoneburner and Low-Beer (2004) attribute the significant declines in HIV prevalence in Uganda to the reductions in the proportions of individuals reporting sex with non-regular partners in national behavioural surveys, and attach relatively little importance to the increases in levels of condom use.

More recently, there has been evidence of reductions in HIV prevalence in Zimbabwe, which have been attributed mainly to reductions in the rate at which individuals acquire new partners – particularly casual partners – and delays in sexual debut (Gregson *et al*, 2006). There has also been evidence of declines in HIV prevalence in urban Kenya, which has been attributed to the same factors (Hallett *et al*, 2006). In Zambia, nationally representative household surveys suggest that there has been an overall increase in the age at sexual debut and a reduction in unprotected sex with non-cohabiting partners, as well as a reduction in numbers of partners (Slaymaker and Buckner 2004). However, another Zambian study found that this behaviour change was limited to urban areas (Fylkesnes *et al*, 2001). The existence of urban-rural differences in the extent of behaviour change is also suggested by data from Tanzania. In a study of male factory workers in urban Tanzania, Ng'weshemi *et al* (1996) found significant reductions in numbers of partners and contacts with casual partners, as well as increases in condom use with casual partners. In another study in rural

Tanzania, however, no significant changes were observed over time, either in age at sexual debut, numbers of partners per annum, or condom use with casual partners (Mwaluko *et al*, 2003).

Studies have generally not considered the role of concurrent partnerships in the spread of HIV, as information on concurrency is often not captured in sexual behaviour surveys. Although a comparison of data from five African cities showed that differences in the prevalence of concurrency did not account for differences in HIV prevalence between the cities (Lagarde *et al*, 2001), it has been argued that the prevalence of concurrency in Sub-Saharan Africa is higher than that in other global regions and that concurrent partnerships may therefore be one of the most important factors explaining the high prevalence of HIV in Sub-Saharan Africa (Halperin and Epstein 2004). Mathematical models support the view that partner concurrency is a major factor promoting the spread of HIV (Morris and Kretzschmar 1997), but there is relatively little empirical evidence to support the hypothesis.

It has also been hypothesized that late age at first marriage – and more specifically, a long average interval between sexual debut and first marriage – is a key factor driving the spread of HIV, particularly in the countries of Southern Africa, where marriage tends to occur relatively late (Bongaarts 2007). The assumption underlying this argument is that marriage is protective against HIV. However, African studies that have examined the relationship between HIV and marital status have yielded conflicting findings, some suggesting that marriage is associated with an increased risk of HIV (Auvert *et al*, 2001b; Clark 2004; Zuma *et al*, 2003) and some suggesting the opposite (Shisana *et al*, 2004; Bongaarts 2007). The significance of the relatively late age at first marriage in South Africa is therefore not clear.

Attempts to explain observed HIV prevalence trends in terms of changes in reported behaviours are problematic for a number of reasons. Most importantly, social desirability bias may differentially affect the reporting of risk behaviours in different periods and different locations, depending on the extent of social marketing programmes (Gregson *et al*, 2002b; Curtis and Sutherland 2004; Cleland *et al*, 2004). Secondly, differences in HIV prevalence trends may reflect differences in epidemic maturity rather than differences in behavioural responses to HIV/AIDS. In addition,

observed reductions in risk behaviours could be a direct consequence of AIDS mortality and morbidity (since HIV/AIDS mortality effectively removes those individuals who have the highest levels of sexual risk behaviour), rather than a result of spontaneous changes in sexual behaviour (Gregson *et al*, 2006; Hallett *et al*, 2006). In light of these limitations, mathematical models have an important role to play in evaluating whether reported changes in sexual behaviour are consistent with observed trends in HIV prevalence (Hallett *et al*, 2006).

6.3.2 Method

To assess the potential effect of behaviour changes, the following scenarios are considered:

- ‘Halve concurrency’: It is assumed that the rate at which new partners are acquired is halved among those individuals who are already in partnerships. (Men in relationships still visit sex workers at the same rate, however.)
- ‘Halve partner acquisition’: The rate at which new non-spousal partners are acquired is halved, but the rate at which marriage occurs is unchanged (this has the effect of reducing the number of non-spousal partnerships). The rate at which men visit sex workers is also unchanged.
- ‘Halve rate of sexual debut’: The rate at which virgins enter their first sexual relationship is halved (this is equivalent to a roughly two-year increase in the median age at first sex).
- ‘Halve sex worker contacts’: The rate at which men visit commercial sex workers is assumed to be halved.
- ‘Double incidence of marriage’: The age-specific rates of marriage are doubled (this is equivalent to a roughly three-year decrease in the median age at first marriage).
- ‘Halve unprotected non-spousal sex’: The proportion of sex acts that are unprotected in non-spousal relationships (excluding sex worker-client contacts) is assumed to be halved.
- ‘Halve unprotected spousal sex’: The proportion of sex acts that are unprotected in spousal relationships is assumed to be halved.

All changes in behaviour are introduced in the middle of 2010, and the impact of the behaviour change is evaluated by examining the percentage reduction in the number of new HIV infections over the period from mid-2010 to mid-2020. To assess whether the effects of these behaviours change over the course of the HIV/AIDS epidemic, we also consider hypothetical scenarios in which the changes occur in the middle of 1990 and effects are measured over the period from mid-1990 to mid-2000. The last two scenarios are not included among these hypothetical scenarios, since the baseline scenario already allows for significant increases in condom use after 1990.

The reductions in HIV incidence are calculated for the initial analysis presented in section 4.1 (which does not allow for STI cofactor effects) and for the three STI cofactor scenarios presented in section 5.2 (for which there is no formal uncertainty analysis). However, the reductions in STI prevalence are calculated only for the baseline cofactor scenario, since the formal uncertainty analysis in section 4.2 does not reflect the uncertainty with respect to the sexual behaviour parameters, and is therefore of little value when assessing the uncertainty regarding the effect of behaviour change on STI prevalence.

6.3.3 The effect of behaviour change on HIV incidence

Figure 6.3.1 shows the percentage reduction in HIV incidence over the 2010-20 period, for each of the behaviour change scenarios described previously. The percentage reductions predicted by the STI cofactor model (i.e. the baseline cofactor, high cofactor and low cofactor scenarios) are generally similar to or greater than those predicted by the model that does not allow for STI cofactors, except in the case of delayed sexual debut. Model results suggest that a high level of HIV transmission is occurring within non-spousal relationships, with the greatest reductions in HIV incidence being achieved through reductions in unprotected sex in non-spousal partnerships and through reductions in the rate at which new non-spousal partnerships are formed. Halving the incidence of concurrent partnerships would reduce the total number of new HIV infections by an average of 11.4% (95% prediction interval: 9.8-13.1%). Halving the rate of sexual debut and doubling the incidence of marriage would have relatively little effect on the incidence of HIV. The latter could possibly even be associated with increases in HIV incidence, as condoms are used less

frequently in marriage and the frequency of sex in the early years of marriage is higher than that in non-spousal relationships. Male contact with sex workers also does not significantly influence the transmission of HIV in the advanced stages of the epidemic.

The combined effect of halving the rate of non-spousal partner acquisition by 50%, reducing the rate of secondary partner acquisition by an additional 50% (i.e. a net reduction of 75% in the rate at which concurrent partnerships are formed) and halving the proportion of sex acts in non-spousal partnerships that are unprotected, would be to reduce the total number of new HIV cases over 2010-2020 by 49% (95% prediction interval: 43-54%). Allowing for STI cofactors, the same set of changes would reduce HIV incidence by 55%, 56% and 54% in the baseline cofactor, high cofactor and low cofactor scenarios respectively.

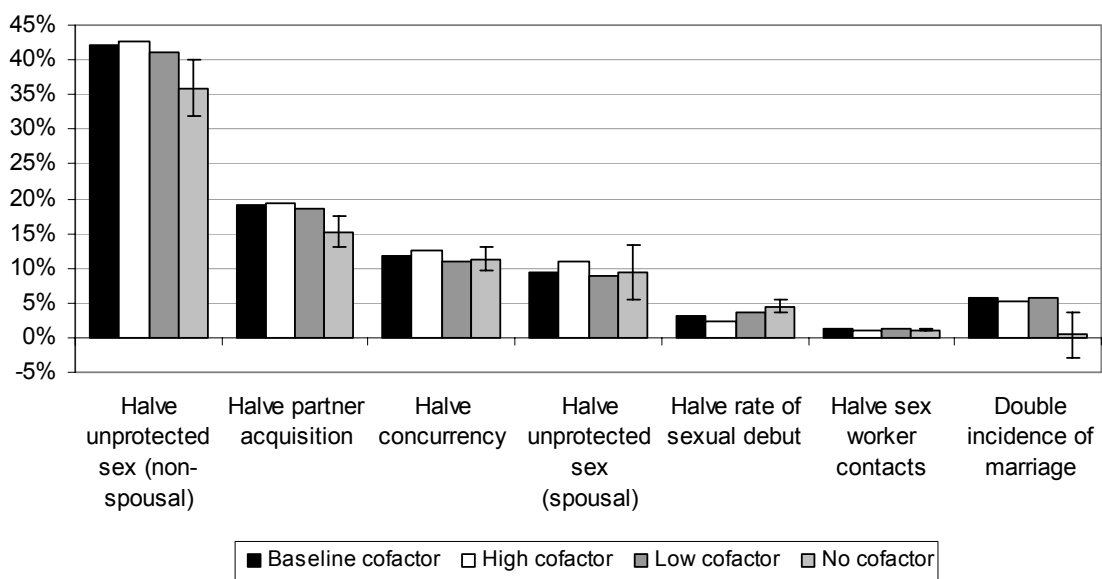


Figure 6.3.1: Percentage reductions in new HIV infections over the 2010-2020 period, as a result of changes in sexual behaviour

The relationship between the model parameters controlling behaviour change and the percentage reduction in HIV incidence is seldom linear. Figure 6.3.2 shows the effect of varying the percentage reduction in the risk parameter in two cases: the reduction in the rate at which secondary (concurrent) partners are acquired and the reduction in

the proportion of sex acts in non-spousal partnerships that are unprotected. There are increasing marginal returns to reducing the rate at which concurrent partnerships are formed; the effect of reducing the rate of secondary partner acquisition by 100% (39%, 95% interval: 32-45%) is more than double the effect of reducing the rate by 50% (11%, 95% interval: 10-13%). In contrast, there are diminishing marginal returns to reducing the proportion of non-spousal sex acts that are unprotected; the effect of reducing the proportion by 100% (65%, 95% interval: 57-72%) is less than double the effect of halving the proportion by 50% (36%, 95% interval: 32-40%).

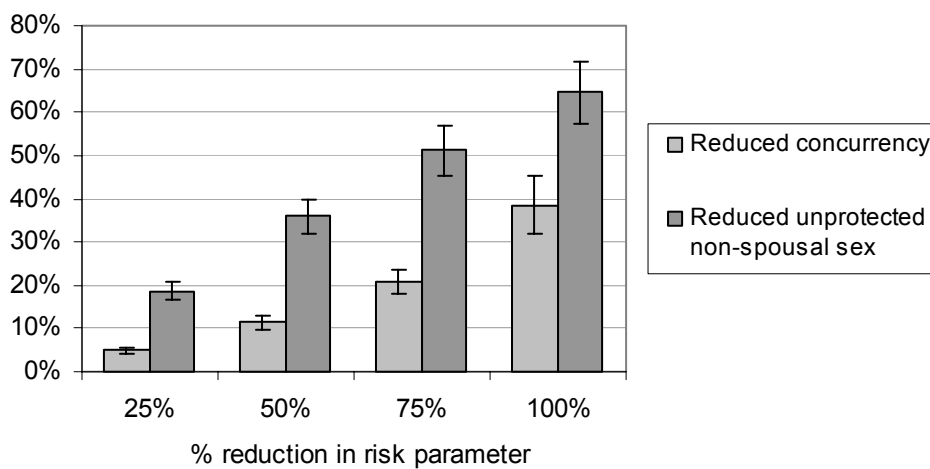


Figure 6.3.2: Percentage reductions in new HIV infections over the 2010-2020 period, for different levels of behaviour change

Results are generated using the model that does not allow for STI cofactors (see section 4.1).

The effect of high risk sexual behaviours on the spread of HIV is more significant in the early stages of the HIV/AIDS epidemic than in the more advanced stages of the epidemic. This is shown in Figure 6.3.3, which compares the reductions in HIV incidence that would have been achieved if the behaviour changes had occurred in 1990, with the reductions that would be achieved if the behaviour changes occurred in 2010. The difference is particularly stark in the case of the effect of reductions in commercial sex worker contacts, which suggests that client-sex worker contact is important in driving the spread of HIV in the early stages of the HIV/AIDS epidemic, but is a relatively unimportant determinant of HIV spread in the later stages of the epidemic. Halving the rate at which secondary partners are acquired, in 1990, has

almost the same effect as halving the rate at which all non-spousal partners are acquired.

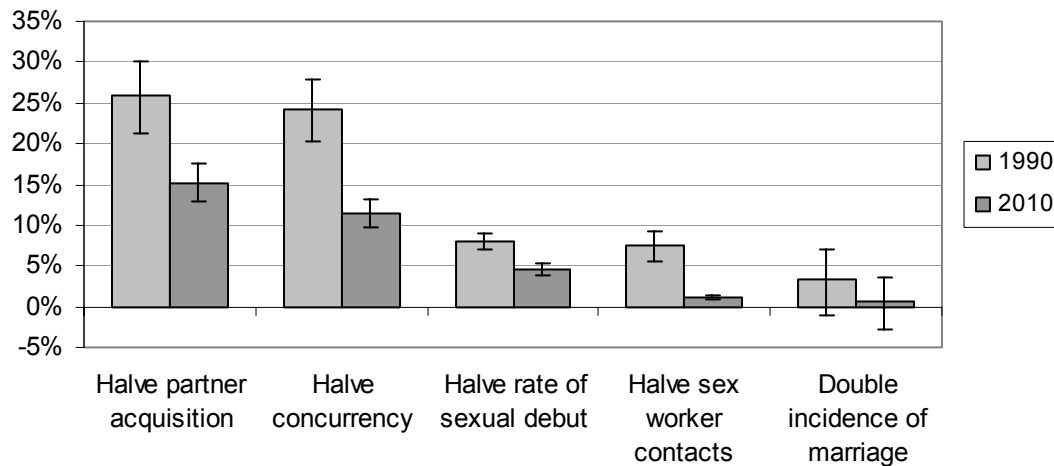


Figure 6.3.3: Percentage reductions in new HIV infections that would occur if behaviour changes occurred in 1990 and 2010

Results are generated using the model that does not allow for STI cofactors (see section 4.1).

6.3.4 The effect of behaviour change on STI prevalence

Table 6.3.1 shows the predicted percentage reductions in STI prevalence in the population aged 15-49, by 2020, when compared with the scenario in which there is no behaviour change after 2010, for each of the behaviour change scenarios described in section 6.3.2. Chancroid is not included, as its prevalence has already been reduced to negligibly low levels, and bacterial vaginosis and vulvovaginal candidiasis are also not included, as neither is assumed to be sexually transmitted.

The results shown in Table 6.3.1 suggest that the effects of different forms of behaviour change differ significantly between STIs. In the case of syphilis, halving unprotected sex in spousal relationships would achieve the greatest reduction in prevalence, while doubling the incidence of marriage would significantly increase the prevalence of syphilis. This suggests that syphilis transmission is occurring mainly in spousal relationships, probably because past increases in condom use have already reduced the basic reproductive number of syphilis below one in the unmarried population. The transmission of gonorrhoea also appears to be relatively more

frequent in spousal relationships, with increases in the incidence of marriage predicted to increase the overall prevalence of gonorrhoea. For the other three STIs, transmission in non-spousal relationships appears to be relatively more important, with the effect of reduced unprotected sex being substantially greater in the case of non-spousal partnerships than in the case of spousal partnerships. Consistent with the results shown for HIV, changes in commercial sex activity appear to have little effect on the overall prevalence of any of the STIs. In the case of chlamydial infection, delays in sexual debut, increases in the rate of marriage and reductions in unprotected non-spousal sex would be particularly important in reducing the prevalence of infection, probably because of the high susceptibility to chlamydial infection in young females and the relatively high concentration of chlamydial infection in non-spousal relationships.

Table 6.3.1: Percentage reduction in STI prevalence by 2020, when comparing the scenarios with behaviour change in 2010 to the scenario without behaviour change

Behaviour change	STI				
	Syphilis	Genital herpes	Gonorrhoea	Chlamydial infection	Trichomoniasis
Halve unprotected non-spousal sex	15.9%	14.2%	40.1%	19.5%	36.2%
Halve partner acquisition	8.0%	6.9%	12.5%	6.3%	12.1%
Halve concurrency	8.7%	3.5%	9.7%	0.8%	6.2%
Halve unprotected spousal sex	50.8%	1.5%	29.0%	2.4%	12.4%
Halve rate of sexual debut	0.3%	3.6%	6.9%	11.4%	8.0%
Halve sex worker contacts	0.1%	0.2%	0.2%	0.0%	0.1%
Double incidence of marriage	-33.6%	5.0%	-8.2%	6.3%	0.8%

Results are generated using the baseline cofactor scenario (see section 5.2).

6.3.5 The effect of AIDS mortality and morbidity on levels of sexual risk behaviour

In the context of generalized HIV/AIDS epidemics, it is often assumed that reductions in levels of sexual risk behaviour – as reflected in comparisons of cross-sectional behavioural surveys – are the result of deliberate changes in behaviour following

information and education programmes and other interventions. However, some of the reduction in levels of sexual risk behaviour may be a direct result of the selective effect of AIDS morbidity and mortality (i.e. high-risk individuals are more likely to acquire HIV, and their removal from the sexually active population reduces the average levels of sexual risk behaviour). In our model of the South Africa population, it is assumed that the only form of deliberate behaviour change up to the current time is increased condom usage, and there is thus no allowance for reductions in concurrent partnerships or increases in abstinence. This section quantifies the extent of the reduction in reported risk behaviour that might be expected as a result of the high levels of AIDS morbidity and mortality in South Africa.

Figure 6.3.4 compares the levels of sexual risk behaviour in 1995, before significant AIDS mortality and morbidity occurred, and in 2005, after significant increases in morbidity and mortality. AIDS appears to have reduced significantly the proportion of men and women with multiple partners, with the reduction in men being greatest between the ages of 40 and 44 (15%) and the reduction in women being greatest between the ages of 35 and 39 (23%). AIDS has also increased significantly the proportion of men and women who report that they have no current partner, with the increase in men being greatest between the ages of 50 and 54 (21%) and the increase in women being greatest between the ages of 35 and 39 (16%). AIDS has also reduced slightly the proportion of the population that is married, though this effect is relatively small (the reduction is less than 5% at all ages, in both men and women).

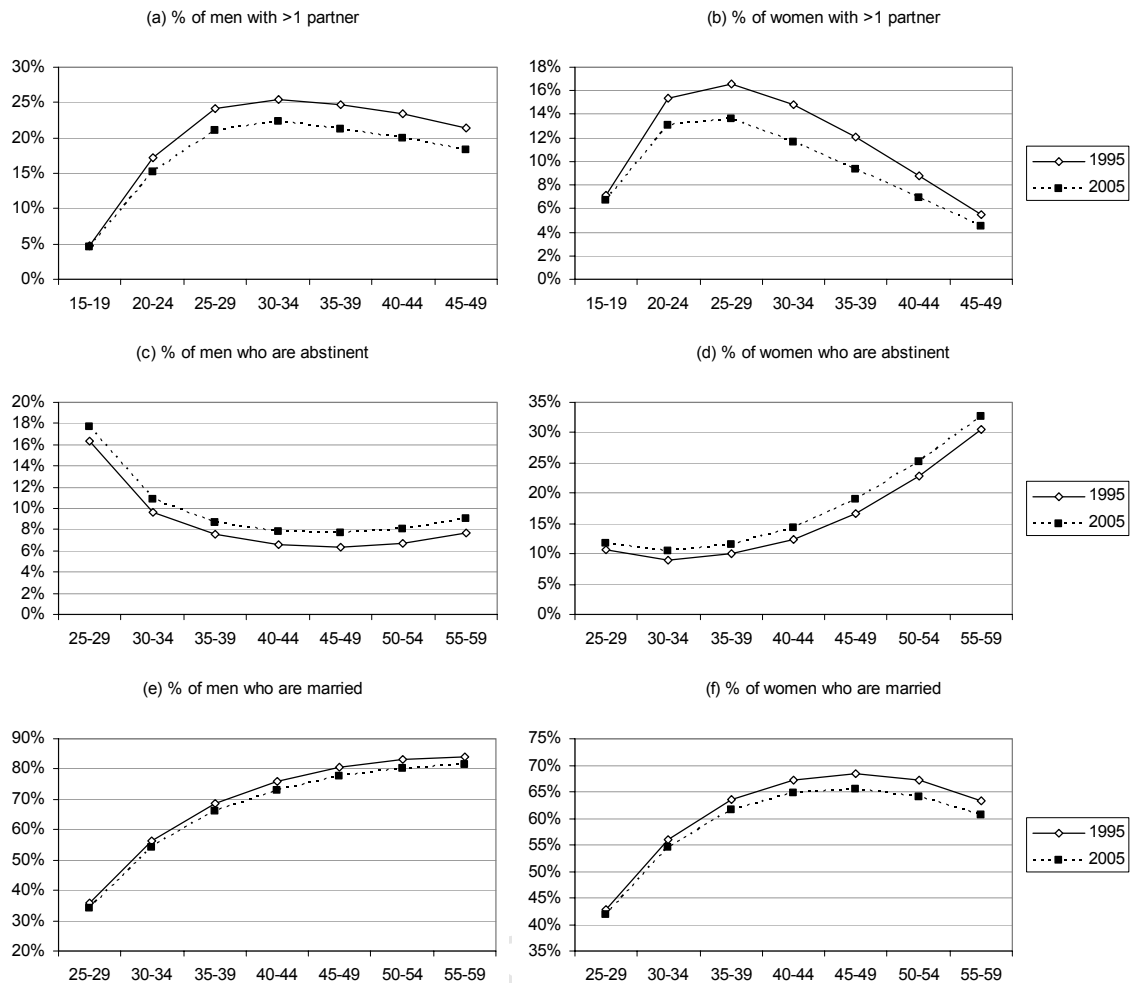


Figure 6.3.4: Changes in sexual behaviour between 1995 and 2005, by age and sex. Proportions are posterior means generated using the model that does not allow for STI cofactors (see section 4.1).

6.4 Discussion

6.4.1 Comparison with changes in STI prevalence in other African countries

Our model suggests that there have been significant declines in the prevalence of syphilis, chancroid, gonorrhoea, chlamydial infection and trichomoniasis in South Africa since the early 1990s, as result of improvements in STI treatment, increases in condom use and the selective effect of AIDS mortality and morbidity. However, the prevalence of HSV-2, bacterial vaginosis and vulvovaginal candidiasis has remained relatively unchanged. To the extent that the same factors determine STI prevalence

trends in other African countries, similar trends in STI prevalence might be expected in other African settings. Table 6.4.1 summarizes the evidence from studies that have tracked STI prevalence trends over time in different Sub-Saharan African populations.

Consistent with the model estimates and the South African national antenatal survey results (Department of Health 2007), most African surveys show significant declines in the prevalence of syphilis over time. Several African studies have also found significant declines in the prevalence of gonorrhoea and trichomoniasis, coinciding with significant changes in sexual behaviour. These are consistent with the predictions of the model, which estimates that most of the reduction in the prevalence of gonorrhoea and trichomoniasis is likely to be the result of behaviour change rather than syndromic management. Although a number of the observational studies show no significant reduction in the prevalence of chlamydial infection (Sturm *et al*, 2003; Ndhlovu *et al*, 2005; Alary *et al*, 2002; Nagot *et al*, 2004), significant reductions have been observed in Botswana (Creek *et al*, 2005), Kenya (Moses *et al*, 2000) and Senegal (Meda *et al*, 1999b). Chlamydial prevalence trends therefore appear to be fairly heterogeneous. Lastly, no African study has identified statistically significant changes in the prevalence of bacterial vaginosis over time, which is consistent with the relatively stable prevalence of bacterial vaginosis predicted by the model.

No African studies have examined recent trends in the seroprevalence of HSV-2 (Smith and Robinson 2002). However, there is evidence from other African countries of significant changes in the aetiology of genital ulcer disease over the last two decades. The model predictions of rising GUD attributable to HSV-2 and reductions in GUD attributable to chancroid are consistent with observed changes in GUD aetiologies in South Africa (Ye *et al*, 2007; Kharsany *et al*, 2000), Botswana (Paz-Bailey *et al*, 2005), Rwanda and Kenya (Mayaud and Mabey 2004), as well as an 86% drop in chancroid cases in Harare between 1990 and 1998 (O'Farrell 1999). The model prediction that chancroid is close to being eradicated in South Africa therefore appears to be in agreement with the limited empirical data.

Table 6.4.1: Trends in STI prevalence in other Sub-Saharan African populations

Study	Location	Sample	STI	Initial prevalence	Ultimate prevalence	Test for trend	Factors potentially explaining change in prevalence
Sturm <i>et al</i> (2003)	Hlabisa, South Africa	Antenatal clinics	Gonorrhoea	7% (1999)	4% (2002)	>0.05	
			Chlamydia	11%	11%	>0.05	
			Trichomoniasis	32%	27%	-	
			Bacterial vaginosis	38% (1995)	31% (2002)	>0.05	
Ndhlovu <i>et al</i> (2005)	Khutsong, South Africa	Men aged 13-59	Syphilis	6% (1998)	5% (2001)	0.29	Increases in casual partners
			Gonorrhoea	3%	4%	0.32	
			Chlamydia	5%	7%	0.17	
		Women aged 13-59	Syphilis	10%	13%	0.05	
			Gonorrhoea	7%	11%	0.01	
			Chlamydia	8%	12%	0.01	
Creek <i>et al</i> (2005)	Francistown, Botswana	Antenatal clinics	Syphilis	12.4% (1992)	4.3% (2003)	≤0.001	Syndromic mngt (since 1992), delayed sexual debut, increased condom use
Paz-Bailey <i>et al</i> (2005)	3 cities in Botswana	Family planning clinics ^a	Syphilis	18.0% (1993)	1.5% (2002)	<0.0001	Syndromic mngt (since 1992), delayed sexual debut, increased condom use
			Gonorrhoea	9.1% ^b	2.9% ^b	0.04	
			Chlamydia	30.9% ^b	13.9% ^b	0.001	
			Trichomoniasis	26.2% ^b	9.2% ^b	<0.0001	
Taha <i>et al</i> (1998)	Blantyre, Malawi	Antenatal clinic	Syphilis	13.4% (1990)	11.1% (1996)	0.027	Possibly improved STI treatment, but no increase in condom usage
			Gonorrhoea	4.9% (1990)	2.5% (1995)	<0.001	
			Trichomoniasis	32.5%	23.8%	<0.001	

Table 6.4.1 (continued)

Study	Location	Sample	STI	Initial prevalence	Ultimate prevalence	Test for trend	Factors potentially explaining change in prevalence
Alary <i>et al</i> (2002)	Cotonou, Benin	Sex workers	Syphilis	8.9% (1993)	1.5% (1998-9)	0.0002 ^c	Improved STI treatment for sex workers, fewer clients per week, greater condom use with clients
			Gonorrhoea	43.2%	20.5%	0.0001 ^c	
			Chlamydia	9.4%	5.1%	0.13 ^c	
Swai <i>et al</i> (2006)	Tanzania	Antenatal clinics	Syphilis	7.3% (2001-2)	7.2% (2003-4)	-	
Moses <i>et al</i> (2000)	Nairobi, Kenya	Antenatal & family planning clinics	Syphilis	5.4% (1992)	2.5% (1999)	<0.001	Improvements in STI treatment, reduced numbers of sexual partners, increases in condom use
			Gonorrhoea	5.3%	1.7%	<0.001	
			Chlamydia	30.1% (1992)	20.6% (1994)	0.001	
Nagot <i>et al</i> (2004)	Bobo Dioulasso, Burkina Faso	Sex workers and bar girls	Syphilis	12.5% (1989-91)	0.8% (1998-00)	<0.001	Syndromic mngt (since 1996), increases in condom distribution, increases in antibiotic self-treatment
			Chlamydia	10.0%	6.6%	0.16	
			Trichomoniasis	32.0%	9.7%	<0.001	
			Gonorrhoea	13% (1994)	1% (1998-00)	<0.001	
			Bacterial vaginosis	37% ^d	27% ^d	-	
Meda <i>et al</i> (1999b)	Dakar, Senegal	Antenatal clinics	Syphilis	7.5% (1991)	4.4% (1996)	0.04	Increased condom distribution, improved STI treatment services
			Gonorrhoea	2.0%	0.9%	0.21	
			Chlamydia	11.9%	6.7%	<0.01	
			Trichomoniasis	30.1%	18.1%	<0.001	

Where dates are not given for prevalence estimates, the date should be assumed to be the same as that for the preceding estimate.

^a 2003 sample included cities and clinic types that were not in the 1993 sampling frame. ^b Adjusted for changes in sensitivity and specificity of STI diagnostics. ^c After adjustment for changes in age and nationality of sex workers. ^d Approximate values, read from graph.

Empirical estimates of the impact of syndromic management on STI prevalence are also available from randomized controlled trials. In the intervention arm of the Mwanza trial, in which syndromic management was introduced in the absence of any major change in sexual behaviour, the prevalence of gonorrhoea, chlamydial infection and trichomoniasis did not change significantly over the course of the trial, either among men or among pregnant women in a separate sub-study (Mayaud *et al*, 1997). This supports our model results, which suggest that syndromic management has not reduced the prevalence of any of these three infections to any significant extent. The trial results in respect of syphilis are difficult to interpret, since syphilis treatment was provided at baseline to all individuals who were infected with syphilis, both in the intervention and control arms. However, the prevalence of active syphilis (RPR titre \geq 1:8) at follow-up was significantly lower in the intervention arm than in the control arm. This suggests that syndromic management significantly reduces the prevalence of syphilis, which is consistent with the model predictions.

The effect of syndromic management was also evaluated in the Masaka trial (Kamali *et al*, 2003), though the syndromic management intervention was combined with an information and education campaign (IEC), making it difficult to isolate the independent effect of syndromic management on STI prevalence. The IEC was found to increase condom use with casual partners significantly, and the net effect of this behaviour change, together with syndromic management, was a significant reduction in the incidence of active syphilis (RPR titre \geq 1:8), a significant reduction in the prevalence of gonorrhoea, and no change in the prevalence of chlamydial infection. These findings are consistent with the results of our model, which predicts that the combined effect of IEC and syndromic management is substantial in the case of syphilis and gonorrhoea but relatively modest in the case of chlamydial infection.

6.4.2 Comparison with other model estimates of the effects of behaviour change on HIV in Sub-Saharan Africa

Although several HIV/AIDS models have evaluated the potential effects of behaviour change in Sub-Saharan Africa, published results are difficult to compare. Evaluations have differed in terms of the assumed timing of the change in behaviour, the assumed time period over which the impact of the change is assessed, and whether the impact

of the change is measured in terms of incidence or prevalence. Consistent with our model simulations, other models show that changes in behaviour that are initiated in the early stages of the HIV/AIDS epidemic tend to reduce the incidence of HIV to a greater extent than those initiated in the later stages of the epidemic (Boily *et al*, 2002). Reductions in HIV incidence tend to be more significant than reductions in prevalence in the short term, though over the long term, one would expect the two to converge. These issues need to be considered when comparing the effects of behaviour change simulated by different HIV/AIDS models.

One of the most commonly modelled forms of behaviour change is reduced male contact with sex workers. A 50% reduction in the frequency of unprotected sex with commercial sex workers is predicted to reduce HIV prevalence by roughly 25% in the STDSIM model, if introduced 15 years into an urban African HIV/AIDS epidemic (Korenromp *et al*, 2000a). The same change is predicted to reduce HIV incidence by 23-68% in the SimulAIDS model, if introduced 10 years after the start of the Ugandan HIV/AIDS epidemic (Robinson *et al*, 1995), and by 38% in the model of Boily *et al* (2002), if introduced 13 years after the start of a 'high prevalence' HIV/AIDS epidemic. In the model of Bracher *et al* (2004), a 50% reduction in male contact with sex workers is predicted to reduce Malawian women's lifetime risk of HIV infection by 19% – a greater reduction would be expected in men, but this is not reported.

Our model predicts a smaller reduction in HIV incidence following reductions in sex worker contact. The percentage reductions in HIV incidence, following a 50% reduction in male contacts with sex workers five years into the epidemic, are between 11 and 15%, if calculated using the three cofactor scenarios described in section 5.2. The reductions in incidence are lower when the behaviour change occurs at later epidemic durations, or when the reductions are calculated using the model that does not allow for STI cofactors. The relatively low impact predicted in our model can be attributed to the relatively low assumed frequency of male contact with sex workers: 0.13 contacts per annum among men aged 15-49, compared with 1.4 per annum in the STDSIM model, 3-12 per annum in the SimulAIDS model, approximately 4 per annum in the model of Boily *et al* (2002) and 0.6-3.8 per annum in the model of Bracher *et al* (2004). The average proportion of men reporting contact with a sex worker in the last 12 months, in Southern African surveys of the general population, is

0.063 (Caraël *et al*, 2006). This appears to support the relatively low frequency of sex worker contact assumed in our model, though there remains much uncertainty regarding the frequency of sex worker contact among those men who do report such contacts, and there is also much uncertainty regarding the likely extent of social desirability bias in male reporting of sex worker contacts.

A few models have also evaluated the effects of reducing the frequency of unprotected sex in spousal and non-spousal relationships. Van Vliet *et al* (2001) predict that halving the level of unprotected sex in long-term marital relationships would reduce HIV incidence by approximately 20%, and halving the level of unprotected sex in short-term relationships (excluding commercial sex encounters) would reduce HIV incidence by approximately 45%, if introduced 15 years into an urban African HIV/AIDS epidemic. Bracher *et al* (2004) predict that halving unprotected sex in extramarital relationships (again excluding commercial sex) would reduce women's lifetime risk of HIV infection by 31%. These simulations are roughly consistent with our model, which suggests that halving unprotected sex in short-term relationships would reduce HIV incidence by 74% (95% interval: 70-78%) if introduced 5 years into the South African HIV/AIDS epidemic, and by 36% (95% interval: 32-40%) if introduced 25 years into the South African HIV/AIDS epidemic. Corresponding estimates for long-term relationships are 9% (95% interval: 4-16%) and 9% (95% interval: 5-13%) respectively.

Our model suggests that the *actual* increases in condom use that have occurred in South Africa have had a significant impact, reducing HIV incidence in 2005 by 46-51%. This is in spite of the assumed levels of condom use being lower than those reported; as noted in section 3.2.8, setting the assumed levels of condom usage at those reported would result in HIV prevalence trends in youth that are inconsistent with observed HIV prevalence trends. It is likely that responses to survey questions about condom use at last sex exaggerate the true proportion of sex acts that are protected, principally because condom use tends to be more common in those relationships in which sex is less frequent (Pettifor *et al*, 2004a; Hargreaves *et al*, 2007). However, it is also possible that condoms may be less effective than is commonly assumed. Garnett and Anderson (1995) show that if the marginal risk of HIV infection reduces as the cumulative number of sex acts with an HIV-positive

partner increases (as evidence suggests), then a very high level of condom use would be required in order to achieve a modest reduction in the average HIV transmission probability, i.e. the relationship between proportion of sex acts that are protected and the HIV transmission probability per partnership is highly non-linear. If this is indeed the case, then the goal of condom promotion should be to increase the proportion of individuals who use condoms consistently, rather than simply to increase the proportion of sex acts in which condoms are used.

A number of models have also evaluated the effects of reductions in the rate at which new partners are acquired. Both Korenromp *et al* (2000a) and Garnett and Anderson (1995) show that halving the rate at which new sexual partners are acquired would roughly halve the long-term prevalence of HIV, if the change occurs around 15 years into an African HIV/AIDS epidemic. Our model, in contrast, predicts that even if the change were to occur 5 years into the epidemic, the reduction in HIV incidence would be only 21-30% if not allowing for STI cofactors and 34-42% if allowing for STI cofactors. A likely explanation for the relatively small impact predicted by our model is the constraint that individuals in the 'low risk' group never have more than one current sexual partner and individuals in the 'high risk' group never have more than two current sexual partners – no such constraint exists in the other two models. Since our model predicts that a high proportion of people already have their maximum number of partners, our model is not as sensitive as other models to changes in the assumed rate at which new partners are acquired.

Relatively few models have examined the effects of delays in sexual debut on the incidence of HIV. Hallett *et al* (2007) predict that in the context of the HIV/AIDS epidemic in rural Zimbabwe, a two-year delay in the average age at sexual debut would reduce the lifetime risk of HIV infection by 6-8%, assuming men do not seek to maintain the same number of sexual partners when women delay sexual debut. This is consistent with the estimates of our model, which shows that a roughly two-year delay in median age at first sex would reduce HIV incidence by 7-9% if introduced 5 years after the start of the South African HIV/AIDS epidemic, and by 2-5% if introduced in 2010. However, the STDSIM model suggests that a two-year delay in sexual debut would have a much more significant impact in the urban African setting; if this were to occur 15 years after the start of the epidemic, prevalence is predicted to

drop by approximately 40% over the next 15 years (Korenromp *et al*, 2000a). The relatively large predicted impact can probably be explained by the assumed high level of risk behaviour among youth; the rate of partnership formation among youth below the age of 25 is assumed in STDSIM to be four times that in adults aged 25 and older.

Although previous modelling work has established that the level of concurrency in a population is a significant determinant of the extent of HIV spread (Watts and May 1992; Kretzschmar and Morris 1996), previous models have not examined the potential effect of reducing the level of concurrency after the epidemic has already started. Our simulations suggest that encouraging individuals to remain faithful to one partner could have a significant impact, with HIV incidence estimated to be reduced by 32-45% if the formation of concurrent partnerships were to cease completely in 2010. Concurrency plays an even more important role in the transmission of HIV in the early stages of the HIV/AIDS epidemic; the reduction in HIV incidence that would have occurred if concurrent partnerships had ceased 5 years after the start of the South African HIV/AIDS epidemic is 74% (95% CI: 69-78%) in the model that does not allow for STI cofactors and 76-87% in the model that does allow for STI cofactors. Concurrent partnerships therefore appear to be a major factor explaining the high levels of HIV prevalence in South Africa.

The model results show that there are increasing marginal returns to reducing the rate of concurrent partnership formation. This may be because the length of time to acquiring a secondary partner is hyperbolically related (not linearly related) to the rate of concurrent partnership formation. Another possible explanation is that there are two distinct factors explaining the effect of reduced concurrency: the reduced rate of partner acquisition in the high risk group and the reduced contact between high and low risk groups, as a result of high risk individuals having fewer partners. If these two factors have a multiplicative effect, then the net effect of reduced concurrency would be non-linearly related to the reduction in the rate of secondary partner acquisition. The results presented in Figure 6.3.2 show that the effect of halving the rate of secondary partner acquisition is only slightly smaller than the effect of halving the rates at which all partnerships are formed. The latter does not imply any change in sexual mixing patterns, while the former implies a reduction in contact between the high risk and low risk groups. This is likely to explain why reductions in concurrent

partnerships have such a significant impact, despite concurrent partnerships accounting for a relatively small proportion of total non-spousal partnerships.

6.4.3 The effect of syndromic management on the incidence of HIV

Our model suggests that the syndromic management programme in South Africa has had a modest but significant impact on HIV incidence, reducing the total number of new HIV infections over the 1994-2004 period by 6% in the baseline cofactor scenario (and by 3% and 10% in the low and high cofactor scenarios respectively). This may be considered disappointing when compared with the substantial reduction in HIV incidence estimated in the randomized controlled trial of syndromic management in Mwanza (38%, 95% CI: 15% to 55%) (Hayes *et al*, 1995a). However, our model results are much more similar to the results of the randomized controlled trial in Masaka (0% reduction, 95% CI: -58% to 37%) (Kamali *et al*, 2003). White *et al* (2004) have used a mathematical model of the HIV/AIDS epidemics in Mwanza and Masaka to show that the substantial difference in the effectiveness of the Mwanza and Masaka trials can be explained by differences in the timing of the intervention, and by the behaviour changes that had already reduced STI prevalence to low levels before the start of the trial in Masaka.

To assess whether these factors explain the differences between our model results and the results of the Mwanza and Masaka trials, we consider two scenarios that might be considered representative of the Mwanza and Masaka interventions. It is assumed that all private and public practitioners use syndromic management protocols after the date of introduction – 1994 in the first scenario and 2002 in the second scenario – and that all drug shortages in public clinics are eliminated after the date of introduction. The 1994 and 2002 start dates correspond to the assumptions made by White *et al*, which were that the Mwanza intervention was introduced 9 years after the start of the HIV/AIDS epidemic and that the Masaka intervention was introduced 17 years after the start of the epidemic. In our baseline model, significant increases in condom usage occur prior to 2002, but there is relatively little increase in condom usage prior to 1994; the 2002 scenario therefore allows for a significant degree of behaviour change similar to that preceding the Masaka trial. For both scenarios, reductions in new HIV infections over the two-year period following the introduction date are calculated,

again in the interests of consistency with the simulations of White *et al.* Results are compared in Table 6.4.2.

Our model confirms the conclusion of White *et al.* (2004) that syndromic management is less effective when introduced in advanced HIV/AIDS epidemics, in which changes in sexual behaviour have already occurred. However, our model estimates of the impact of syndromic management in the early stages of an epidemic are lower than those simulated by White *et al.*, and are towards the lower end of the 95% confidence interval around the Mwanza trial results. The most likely explanation for the difference between our model estimates and those of White *et al.* are the relatively high STI cofactor multiples assumed in the latter analysis, particularly in the case of genital ulcers. However, when applying the same model in four other African settings, White *et al.* (2008) estimate that HIV incidence would have been reduced by between 2 and 20% if the Mwanza intervention had been introduced 9 years into the epidemic. This range is much more consistent with our model estimates for a syndromic management programme introduced 9 years into the South African HIV/AIDS epidemic.

Table 6.4.2: Comparison of observed and simulated reductions in HIV incidence in Mwanza and Masaka conditions, as a result of syndromic management

	Mwanza	Masaka
Observed reduction in HIV incidence	38%	0%
(95% CI)	(15%; 55%)	(-58%; 37%)
Assumed number of years since start of HIV/AIDS epidemic	9	17
Effect of syndromic management simulated by White <i>et al.</i> (2004)	28%	2%
South African model simulations		
Baseline cofactor scenario	15%	3%
Low cofactor scenario	7%	2%
High cofactor scenario	24%	5%

The difference between our model and the observed reductions in HIV incidence in the Mwanza trial could merely be due to chance, since the 95% confidence interval around the observed reduction is very wide. There have been some doubts expressed about whether the reduction in HIV incidence in the Mwanza study was really due to improved STI treatment, especially since the effect of the intervention on the prevalence of most STIs was small relative to the observed effect on HIV incidence (Rygnestad *et al*, 1995; Whitaker and Renton 1995). Indeed, a number of STIs *increased* in prevalence over the course of the trial, but because the increase was greater in the control arm than in the intervention arm, the reported relative risk estimate was less than one (Mayaud *et al*, 1997). It is therefore possible that the Mwanza study may have exaggerated the independent effect of syndromic management on HIV incidence.

Our model may slightly understate the benefit of the syndromic management programme, as syndromic management guidelines often recommend that health workers examining and treating STI-infected patients should also promote condom usage and risk reduction to patients, and provide them with partner notification slips to encourage potentially infected partners to seek treatment (Pettifor *et al*, 2000). Our model does not assess the potential effect of these components of the STI treatment service. However, it would appear that South African health workers often avoid condom promotion in order to deal more swiftly with heavy patient loads. In a national survey of public health facilities, Ramkissoo *et al* (2004) observed that although 80% of STI patients were provided with condoms, only 31% of service providers discussed condom usage with STI patients. It was also found that partner notification slips were only issued to 18% of clients. Even when notification slips are issued, relatively few partners are informed and seek treatment. In a study of STI treatment services in Cape Town, for example, it was found that only 20% of partner notification slips were returned (Mathews *et al*, 2002). These are clearly major problems that need to be addressed, but they are beyond the scope of our modelling. In deterministic frequency-dependent models, it is not possible to link the STI status of the individual to that of their partner, and the effect of partner notification is therefore difficult to quantify accurately using this modelling approach.

Another important benefit of syndromic management, which has not been assessed in this model, is its potential effect on asymptomatic STIs. Although syndromic management is usually thought of as being relevant only to the treatment of symptomatic STIs, individuals who seek treatment for symptomatic STIs are often co-infected with other STIs that are not causing symptoms; treatment with multiple antibiotics is therefore often effective in eliminating these asymptomatic STIs. However, there are also dangers associated with high levels of antibiotic use, which we have not included in our modelling. Antibiotic use is known to increase significantly the risk of vaginal candidiasis (Reed *et al*, 2000; Ohmit *et al*, 2003; Schwebke 2000; Stein *et al*, 1993; Hillier *et al*, 1993), and the introduction of syndromic management protocols could therefore increase the prevalence of vaginal candidiasis. The effect of syndromic management on asymptomatic STIs and vaginal candidiasis has not been considered in previous mathematical modelling work, but may be worth investigating.

6.4.4 The effect of other STI interventions

We have identified a number of forms of STI treatment that could achieve significant reductions in HIV incidence over the next decade. These changes in STI treatment practices have been advocated previously by various experts, but their potential impact has not previously been assessed using mathematical modelling. Future studies will need to examine the costs and the logistical implications of these proposed changes to STI treatment policy, and to assess how the cost-effectiveness of these interventions compares with that of other STI treatment strategies (Gilson *et al*, 1997; White *et al*, 2008) and other HIV prevention strategies (Creese *et al*, 2002). Interventions such as periodic presumptive STI treatment for sex workers and enhanced antenatal syphilis screening, which we predict to have little impact at a population level, may nevertheless be cost-effective and therefore worthy of consideration (Terris-Prestholt *et al*, 2003).

One of the most promising strategies identified is the establishment of a patient-initiated acyclovir treatment programme for individuals who are infected with HSV-2. This is projected to have a significant impact on HIV incidence because a high proportion of new HIV infections are attributable to genital herpes (22% in 2005, in

the baseline cofactor scenario). Since increases in HIV susceptibility and infectiousness appear to be greater during symptomatic genital herpes than during asymptomatic HSV-2 infection, it is particularly important that symptomatic infection be treated, and that this treatment be initiated as soon as possible after the symptoms appear. This is best achieved if treatment is self-initiated, rather than delayed until the patient is able to attend health services. In addition to the short-term benefits of reduced symptomatic HSV-2 (which is important in reducing HIV transmission), there would also be reductions in the transmission of HSV-2, which would reduce HSV-2 prevalence over the long term (by an average of 7% in 2020). One would therefore expect the benefit from the programme to grow over the longer term, as the transmission of HSV-2 is further reduced. We have not modelled the potential additional effect of individuals knowing their HSV-2 status and changing their sexual risk behaviour in order to reduce their risk of transmitting the virus to their sexual partners (Wald *et al*, 2006), and the effect of the counselling and testing component of the programme is therefore not reflected in our estimates.

An obvious concern regarding the proposed patient-initiated acyclovir programme is that it might not be feasible, considering the high proportion of the population that is infected with HSV-2. However, it is important to note that less than 30% of individuals who acquire HSV-2 ever experience symptoms, and in most cases, symptoms reduce in frequency over time. Our model suggests that at any point in time, only about 0.5% of women aged 15 to 49 are experiencing symptoms of genital herpes. It is therefore unlikely that the number of people enrolled on the programme or the total drug requirements would become unmanageable. Blower *et al* (2004) have also shown that by targeting antiviral treatment at a relatively small “core group” of HSV-2 transmitters, significant reductions in HSV-2 transmission can be achieved at the population level.

A logical extension of patient-initiated episodic antiviral treatment is suppressive (continuous) antiviral treatment of individuals with HSV-2. This has been shown to halve the risk of HSV-2 transmission to sexual partners and reduce the rate of symptomatic recurrence by 70% (Corey *et al*, 2004), with potentially significant effects on HSV-2 incidence at a population level (Williams *et al*, 2007). In addition, randomized controlled trials in individuals co-infected with HIV and HSV-2 show

that suppressive HSV-2 treatment can significantly reduce the detection and concentration of HIV in the genital tract, thereby reducing HIV infectiousness (Delany *et al*, 2007; Nagot *et al*, 2007b; Baeten *et al*, 2008). The effect of long-term suppressive antiviral treatment has not been modelled in this analysis, because it is likely to be a much more costly and logistically challenging strategy than episodic antiviral treatment. However, if initial experience with the rollout of an episodic patient-initiated acyclovir treatment programme were favourable, a suppressive antiviral treatment programme might be considered. Since suppressive acyclovir is effective in reducing mortality in HIV-infected individuals (Ioannidis *et al*, 1998), in addition to reducing their HIV infectiousness, it might be cost-effective to limit suppressive acyclovir to HSV-2 and HIV-co-infected individuals, while providing episodic acyclovir to HSV-2-infected patients who are HIV-negative.

Another change in STI treatment that we have found to be highly effective is the replacement of ciprofloxacin in syndromic management protocols. In view of the rapidly emerging resistance to ciprofloxacin in gonococcal isolates, this change should be introduced as a matter of urgency. Ceftriaxone has been proposed as an alternative to replace ciprofloxacin, and indeed, current syndromic management protocols recommend that it be used to treat patients with discharges or dysuria who fail to respond to their first-line treatment. However, resistance to cephalosporins such as ceftriaxone is already emerging in gonococcal isolates in the West Pacific region (Workowski *et al*, 2008), and it is likely that resistance to ceftriaxone would eventually become an issue if this drug were to become the standard therapy for gonorrhoea in South Africa. Treatment options for gonorrhoea are becoming increasingly limited as a result of a steady accumulation of drug resistance worldwide (Workowski *et al*, 2008), and our simulations of the potential effects of switching to ceftriaxone, up to 2020, should therefore be interpreted with caution. If resistance to ceftriaxone were to develop before 2020, our model simulations would overstate the impact of this particular intervention.

Although our model suggests that there would be significant benefits to replacing ciprofloxacin with ceftriaxone, it should be noted that our approach to modelling resistance is slightly simplistic. Based on surveillance data from a few urban centres, an assumed prevalence of ciprofloxacin resistance is specified for each year, and

average gonorrhoea treatment efficacy is reduced by the proportion of cases that are ciprofloxacin-resistant but treated with ciprofloxacin. Although this approach may be appropriate when the prevalence of ciprofloxacin resistance is known, its future prevalence is clearly not known. The more standard approach to modelling drug resistance is to model dynamically the development and transmission of drug-resistant strains, using separate 'states' to represent individuals infected with drug-resistant and wild-type strains (Gershengorn and Blower 2000; Turner and Garnett 2002; Blower *et al.*, 2001). Calibrating such a model to past levels of ciprofloxacin resistance would permit a more reasonable prediction of the future prevalence of ciprofloxacin resistance and the potential effect of switching to other drugs, and this should be considered in future work.

Our model suggests that there would also be significant benefits to reducing treatment delays. The Khomanani social marketing campaign that was introduced in South Africa in 2002 has aimed to improve knowledge of STI symptoms and the importance of prompt STI treatment through dramas performed at soccer stadia and other venues, through TV and radio slots, and through the print media (Health and Development Africa 2004). In a national evaluation of the Khomanani campaign, it was found that roughly a third of respondents had been exposed to STI messages through one of these media, and that knowledge of STI symptoms was better in men who had been exposed to the campaign than in men who had not been exposed to the campaign (Health and Development Africa 2004). Life skills programmes in schools have also been introduced since 1998, and have been shown to have a significant positive effect on knowledge of STI symptoms among youth (Magnani *et al.*, 2005). Whether these interventions have had any impact on rates of health seeking for STI symptoms is not yet clear, but such programmes should clearly continue. It is also necessary to make STI treatment services more accessible, particularly for adolescents, who are often afraid of seeking STI treatment because of health workers' attitudes towards teenage sexuality. The loveLife social marketing programme has aimed to improve youth access to health services through the establishment of adolescent-friendly clinics, and it is estimated that in 2003 roughly 33 000 visits were made to these clinics per month (Collinge 2005). Improved access to health services in rural areas will also be important, and mobile STI clinics may be an effective strategy for improving access to STI services in remote areas.

This analysis is limited to STI interventions that have been advocated by experts in STI treatment and prevention. Important forms of STI treatment that we have not modelled are mass STI treatment and regular STI screening. Mass STI treatment has not been found to be effective in reducing HIV incidence in a randomized controlled trial in Uganda (Wawer *et al*, 1999), and given the substantial resources required to repeat mass treatment at regular intervals, it is unlikely that this would be feasible in South Africa. However, STI screening may be feasible in groups such as women attending antenatal and family planning clinics. The benefit in the former group would be particularly significant, since there would be an associated reduction in the risk of adverse pregnancy outcomes and infections such as neonatal herpes and gonococcal ophthalmia neonatorum in their newborn. However, such antenatal screening does not appear to have been advocated in developing countries, except in the case of syphilis, and this STI prevention strategy has therefore not been evaluated.

Another potential strategy for STI prevention that we have not considered is male circumcision. Although three African randomized controlled trials have shown this to be a highly effective strategy for reducing the incidence of HIV (Auvert *et al*, 2005; Bailey *et al*, 2007; Gray *et al*, 2007), there has been relatively little attention paid to the potential for this strategy to reduce the incidence of other STIs. In two of the trials, the incidence of genital ulcer disease was found to be reduced significantly in the intervention arm (Bailey *et al*, 2007; Gray *et al*, 2007), though the incidence of urethral discharges and individual STIs was not significantly affected. This finding is supported by a meta-analytic review, which has shown that men who are circumcised are at a reduced risk of syphilis, HSV-2 and chancroid (Weiss *et al*, 2006), although the reduction in risk is relatively small in the case of HSV-2 (RR 0.88, 95% CI: 0.77-1.01). It therefore seems likely that most of the reduction in the incidence of genital ulcers in the male circumcision trials was due to syphilis and chancroid. Since syphilis and chancroid have already been reduced to very low levels in South Africa, and now account for a negligible fraction of incident HIV cases, it seems unlikely that any current effect of male circumcision on HIV incidence in South Africa is attributable to the effect of male circumcision on syphilis and chancroid. However, it is possible that male circumcision may protect against herpes, gonorrhoea and trichomoniasis (Moses *et al*, 1998; Krieger *et al*, 1993a; Price *et al*, 2004). If stronger evidence emerges, it

may be appropriate to extend our model to allow for the effect of male circumcision on these STIs.

Vaccines against STIs are another potential STI prevention strategy that we have not modelled, as there are as yet no effective vaccines against any of the STIs considered in this analysis. An HSV-2 vaccine has been developed, but its efficacy is limited to women who are uninfected with HSV-1 (Stanberry *et al*, 2002). Since HSV-1 infection is virtually universal in Africa, such a vaccine would have little impact in the South African setting, though mathematical modelling suggests that it could reduce HSV-2 incidence by as much as 30% in the United States (Garnett *et al*, 2004). Various attempts have been made to develop vaccines against the bacterial STIs, but thus far none have proven effective. Mathematical models suggest that vaccines may be particularly important in controlling STIs such as chlamydial infection, which are difficult to control through treatment programmes (Brunham *et al*, 2005). There is thus an urgent need for effective vaccines against STIs, and models can play an important role in assessing the likely impact of such vaccines.

Chapter 7: Conclusions

Although much previous research has been conducted to estimate the prevalence of HIV in South Africa (Dorrington *et al*, 2006; UNAIDS 2006; Rehle and Shisana 2003), this thesis presents the first attempt to estimate the prevalence of other STIs in South Africa, at a national level. We have developed a novel approach to estimate STI prevalence from sentinel surveillance data, integrating a mathematical model of STI transmission dynamics with a statistical model that takes into account both variation between sentinel sites and variation in diagnostic accuracy. The results suggest that STI prevalence in South Africa is unusually high, even when compared with WHO estimates for the Sub-Saharan African region (Gerbase *et al*, 1998; Rowley and Berkley 1998). This is likely to be a reflection of the high levels of migration in South Africa, the high frequency of concurrent partnerships, the low prevalence of male circumcision and also the relatively late start to the HIV/AIDS epidemic in South Africa. The same technique for estimating national STI prevalence from sentinel surveillance data could be applied in other developing countries, though it is likely that in most other countries, there would be insufficient STI prevalence data to allow reasonable estimation of national STI prevalence.

Our model is the first to evaluate all eight genital tract infections that are known to influence the risk of HIV transmission (Røttingen *et al*, 2001). Results suggest that STIs have contributed significantly to the spread of HIV in South Africa, with an estimated 69% of new HIV infections in 1990 being attributable to other STIs, in the baseline cofactor scenario. Consistent with other models of HIV-STI interactions (Robinson *et al*, 1997; Orroth *et al*, 2006), the contribution of STIs to HIV transmission is predicted to diminish over the course of the HIV/AIDS epidemic, as the prevalence of other STIs declines and as more HIV transmission occurs in 'low risk' groups. However, genital herpes consistently accounts for roughly 20% of new HIV infections at all stages of the epidemic, making it the most significant STI driving the transmission of HIV. It is therefore particularly important that strategies be developed to prevent and treat HSV-2.

Results show significant declines in the prevalence of certain STIs since the mid-1990s. In the case of syphilis and chancroid, these declines appear to have been brought about by the introduction of syndromic management protocols in the public health sector and by increases in condom use, and to a lesser extent, by AIDS morbidity and mortality in 'high risk' groups. In the case of gonorrhoea, syndromic management has brought about a slight decline in prevalence, but most of the decline appears to be due to increases in condom use. The prevalence of trichomoniasis and chlamydial infection, however, appears to have been unaffected by syndromic management programmes, and only behaviour change accounts for the slight reductions in prevalence. The prevalence of HSV-2, bacterial vaginosis and vaginal candidiasis is estimated to have remained relatively stable over the last two decades. Syndromic management has therefore had a significant impact on the prevalence of those STIs that become symptomatic in a high proportion of cases, but has virtually no impact on those STIs that are mostly asymptomatic, and clearly has no impact on genital herpes and vaginal candidiasis, which are assumed to be managed in the same way under syndromic management as they are in the absence of syndromic management.

The model results suggest that there may be significant resistance to reinfection following recovery from gonorrhoea, trichomoniasis and chlamydial infection. The evidence is strongest in the case of resistance following spontaneous resolution, but evidence of resistance following successful treatment is relatively weak. This supports the "arrested immunity" hypothesis of Brunham and colleagues (Brunham and Rekart 2008; Rekart and Brunham 2008), although there remains much uncertainty regarding the exact nature of the immune protection. The long-term persistence of gonorrhoea, trichomoniasis and chlamydial infection at high prevalence levels – in spite of significant improvements in STI treatment and significant reductions in sexual risk behaviour – appears to be easier to explain when using a model that allows for immunity, as the reductions in risk that are associated with the behavioural and treatment changes are partially offset by reduced prevalence of immunity. Models that allow for immunity also produce predictions of STI prevalence in sex workers that are much more consistent with survey data.

Syndromic management appears to have had a modest but significant impact on HIV incidence in South Africa, reducing the total number of new HIV infections over the first ten years of the programme by approximately 6% in the baseline cofactor scenario. The reduction would have been closer to 14% if syndromic management had been scaled up rapidly in 1994, in both the private and public health sectors. Consistent with the results of the STDSIM model (White *et al*, 2004), our model shows that the impact of improved STI treatment on HIV incidence is substantially greater when introduced in the early stages of the HIV/AIDS epidemic, prior to behaviour change, than when introduced in an advanced epidemic in which significant behaviour change has already occurred. This partially explains the significant differences between the effects of syndromic management measured in the randomized controlled trials conducted in Mwanza and Masaka (Grosskurth *et al*, 1995; Kamali *et al*, 2003).

Our model of STI treatment handles several of the factors known to contribute to the low rate of effective treatment in South Africa: delays in health seeking, treatment by untrained or unqualified providers, limitations of syndromic management protocols, poor drug supply, antibiotic failure and drug resistance. This makes the model a particularly useful tool in deciding on STI treatment policy. Results suggest that there is significant potential for further reductions in HIV incidence through changes to existing STI treatment practices. It is especially important that strategies to manage genital herpes be established, as HSV-2 is the most significant STI promoting the transmission of HIV and there is currently no HSV-2 strategy in place in South Africa. One possible strategy may be to include acyclovir in the combination of drugs that is routinely provided to patients presenting with genital ulcers, but a more effective strategy is likely to be the establishment of a programme to screen GUD patients for HSV-2 and encourage self-initiated acyclovir treatment in those who test positive (O'Farrell *et al*, 2007a). Syndromic management protocols also need to be revised so that ciprofloxacin is no longer used in the treatment of patients presenting with urethral or vaginal discharges. There is also a need for greater adoption and implementation of syndromic management protocols in the private and public health sectors; this could be achieved through better training and through CPD schemes, through packaged syndromic management, and through elimination of drug shortages and under-staffing in public clinics. Lastly, it is particularly important that prompt

health-seeking be encouraged, through the strengthening of existing social marketing and school education programmes, and through the expansion of health services in previously under-serviced areas.

By the standards of existing deterministic models, our model of sexual behaviour is relatively detailed, distinguishing between spousal and non-spousal relationships, allowing for concurrent partnerships, and allowing for movements between different behavioural states over the life course. The model is also calibrated to data on sexual behaviour from a variety of South African data sources, allowing for likely biases in the reporting of sexual behaviour in face-to-face interviews. This is an advance on earlier models of HIV transmission in South Africa, which were forced to rely on fairly arbitrary assumptions about sexual behaviour, due to a lack of reliable sexual behaviour data (Doyle and Millar 1990; Schall 1990; Groeneveld and Padayachee 1992; Dorrington 2000; Johnson and Dorrington 2006). Results suggest the role of ‘core groups’ (i.e. sex workers and their clients) in HIV and STI transmission at a population level is smaller than previously thought. Interventions to reduce male contact with sex workers and treat sex workers for STIs regularly are predicted to have relatively little effect, in terms of both HIV incidence and STI prevalence, at a population level. This differs from the results of previously published AIDS models, which suggest that commercial sex is a major driver of HIV/AIDS epidemics in Sub-Saharan Africa (Korenromp *et al*, 2000a; Robinson *et al*, 1995; Boily *et al*, 2002; Bracher *et al*, 2004).

We do find, however, that when a broader definition of ‘core group’ is used (individuals who have a propensity for concurrent partnerships), the role of the core group becomes much more significant. Concurrent partnerships are major drivers of HIV and STI transmission in South Africa, accounting for 74-86% of new HIV infections over the 1990-2000 period, in the STI cofactor model. Eliminating concurrency would reduce HIV incidence in South Africa between 2010 and 2020 by 30-45%, by reducing the total number of non-spousal partnerships and – less obviously – by reducing the extent to which core and non-core groups interact. Changes to the age at sexual debut and the age at marriage appear to have relatively small effects on the incidence of HIV, and earlier marriage could even have a negative effect, due to the relatively high frequency of unprotected sex in the early

years of marriage. However, STIs differ significantly in terms of the particular behaviours that favour their transmission. For example, reducing unprotected sex in spousal relationships would be particularly important in reducing the prevalence of syphilis, while delaying sexual debut would be particularly important in reducing the prevalence of chlamydial infection.

Increases in condom use appear to have had a significant impact on HIV incidence in South Africa, reducing the incidence of HIV in 2005 by almost half in the STI cofactor model. However, the modelled increase in condom use is smaller than that reported in recent surveys (Shisana *et al*, 2005; Pettifor *et al*, 2005b). Setting the levels of condom use at those reported would have resulted in a modelled decline in HIV prevalence in youth much greater than has actually been observed in South Africa. This implies that either (a) the fraction of people who report using a condom at last sex is a relatively poor indicator of the actual proportion of sex acts that are protected, or (b) condoms are less effective than has been assumed. We hypothesize that explanation (a) is likely, though modelling work by Garnett and Anderson (1995) suggests that the cumulative efficacy of condoms may be low if they are not used consistently, and explanation (b) may therefore also have some validity. Apart from the increases in reported condom use, there is little empirical evidence to suggest that sexual behaviour in South Africa has changed substantially over the last two decades. However, our model suggests that modest declines in the reporting of multiple partnerships and modest increases in the reporting of sexual abstinence might be expected to result from the high levels of AIDS mortality and AIDS morbidity in 'high risk' groups, in the absence of any spontaneous change in these behaviours. This has implications for second-generation HIV/AIDS surveillance, as it suggests that changes in reported sexual behaviours may, in part, be a reflection of the impact of AIDS rather than a reflection of the success of interventions.

This thesis advances the use of Bayesian techniques in quantifying uncertainty in HIV and STI simulation models, by proposing a framework for incorporating STI prevalence data and sexual behaviour data, in addition to the HIV prevalence data incorporated in previous Bayesian analyses (Alkema *et al*, 2007). The Bayesian approach has been used to quantify uncertainty in respect of the HIV transmission parameters, sexual behaviour parameters, and STI natural history and transmission

parameters. Considering that these parameters are difficult to measure accurately, it is particularly important that evaluation of different policy options be based on the consideration of a range of plausible parameter values, and the Bayesian approach is therefore important in identifying these plausible parameter values. However, there remain many sources of uncertainty that have not been formally evaluated. Uncertainty regarding the chancroid parameters has not been considered due to the difficulty experienced in defining an appropriate likelihood function. The uncertainty with respect to the effect of STIs on HIV transmission probabilities has also not been evaluated, except through a simple comparison of three scenarios representing high, medium and low STI cofactors. It has also not been possible to consider all sources of uncertainty simultaneously, due to the long time taken to run the model when HIV and all other STIs are simulated together. Perhaps most significantly, uncertainty regarding the choice of model structure has received hardly any attention; the only cases in which it is assessed are in the comparison of different models of immunity and (less formally) the comparison of multiplicative and saturation models of STI cofactor effects. Further exploration of alternative model structures is necessary. For example, it would be useful to examine whether allowing for casual sex (“one night stands”) and greater heterogeneity in sexual behaviour significantly alters the model results. It would also be useful to assess the potential effect of switches between symptomatic and asymptomatic states in the cases of STIs such as gonorrhoea and chlamydial infection.

Our model estimates of HIV and syphilis prevalence appear to be reasonably well validated when compared with HIV and syphilis prevalence data that were not used in defining the likelihood function. However, a limitation of this analysis is that we lack STI prevalence data with which to validate the model predictions of the prevalence of other STIs. Efforts should be made to obtain such data in future. Alternatively, it may be possible to repeat the Bayesian analysis using only half of the available data, and compare the resulting predictions with the omitted observations. A further limitation of our model fitting procedure is that there is no allowance for the behavioural and biological differences between women in the general population and women attending antenatal and family planning clinics (although there is allowance for differences in their age profiles). These differences might be expected to result in differences in STI risk that are not accounted for by the model. The differences have been investigated

extensively in the case of HIV (Gregson *et al*, 2002a; Glynn *et al*, 2001; Fylkesnes *et al*, 1998), but little is known about the magnitude of these differences in the case of other STIs, and this is an area in which further research is required.

The model developed here could be extended to include other STIs. Most important among these is human papillomavirus (HPV), the cause of cervical cancer. Considering that cervical cancer causes more female deaths than any other cancer in South Africa (Norman *et al*, 2006), and considering that a highly effective HPV vaccine has recently been developed (Villa *et al*, 2005), there is a need for investigation into the feasibility of introducing this vaccine in South Africa. Indeed, a number of mathematical models of HPV have already been developed to address this question in other settings (Dasbach *et al*, 2006). It is also possible that HPV infection may increase HIV transmissibility (Spinillo *et al*, 2001a), and some evidence has been found of increased HIV transmission risk in the presence of other STIs that we have not modelled: hepatitis B (Twu *et al*, 1993), *Mycoplasma genitalium* (Manhart *et al*, 2008) and cytomegalovirus (Speck *et al*, 1999; Mostad *et al*, 1999). The current evidence is too weak to justify the modelling of these interactions, but if future evidence suggests that these other STIs do indeed play an important role in HIV transmission, the model could be extended to allow for these other STIs. There is also some evidence to suggest that the probability of mother-to-child transmission of HIV may be increased in the presence of HSV-2 (Bollen *et al*, 2008) and genital ulcers (John *et al*, 2001). Our model does not currently allow for any effect of STIs on the probability of mother-to-child transmission of HIV, but this interaction could be modelled in future.

Our model could also be extended to assess the impact of STIs on infertility and pregnancy outcomes, and the potential effects of maternally-transmitted infections in infants. This would be particularly important in estimating the burden of disease due to STIs other than HIV, as these sequelae account for a significant proportion of the STI disease burden (Rowley and Berkley 1998). In previously published burden of disease estimates for South Africa, the years of life lost due to STIs other than HIV were estimated from 1996 cause of death data, and years lived with disability due to STIs other than HIV were estimated from WHO estimates of the relationship between STI mortality and STI morbidity in other African countries (Norman *et al*, 2006).

More accurate estimates of the STI disease burden might be obtained by entering our model-based estimates of STI incidence into the standard WHO models for burden of disease estimation (Rowley and Berkley 1998; Berkley 1998; Ebrahim *et al*, 2005).

As new STI prevention and treatment strategies are developed, it may be appropriate to adapt the model to assess the likely impact of these interventions in South Africa. Microbicides that are currently being developed to prevent HIV transmission may well be effective in preventing the transmission of other STIs (Weber *et al*, 2005), and vaccines against gonorrhoea and chlamydial infection are currently being explored (Rupp *et al*, 2005). Although suppressive HSV-2 treatment has been found to have little effect on susceptibility to HIV infection (Watson-Jones *et al*, 2008; Celum *et al*, 2008), it remains to be seen whether suppressive HSV-2 treatment reduces HIV infectiousness in individuals who are co-infected with HIV and HSV-2 (Paz-Bailey *et al*, 2007a). Male circumcision is another STI prevention strategy that could be incorporated into the model in future, particularly if strong evidence emerges of a protective effect against genital herpes and other STIs that are currently promoting the transmission of HIV in South Africa.

South Africa remains one of the countries most severely affected by HIV/AIDS, with more HIV infections than any other country in the world (UNAIDS 2008). This thesis advances our understanding of both the behavioural and the biological factors promoting the transmission of HIV in South Africa, integrating South African data from a wide variety of sources in order to present a quantitative perspective on sex and sexually transmitted infection in South Africa. Although it is encouraging to see that past condom promotion and syndromic management interventions have had a significant impact on HIV incidence in South Africa, there is much more that needs to be done to reduce the incidence of HIV, and this thesis offers a number of practical suggestions. It is hoped that government, activists and scientists will work together in taking these proposals forward.

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Appendix A: Mathematical approach to modelling sexual behaviour

The purpose of this appendix is to explain, in mathematical terms, the modelling of sexual behaviour. Table A.1 summarizes the index variables that are used throughout this appendix.

Table A.1: Index variables

Symbol	Definition	State space
i	Individual risk group	01 = virgin with propensity for CS/concurrency 02 = virgin with no propensity for CS/concurrency 1 = Non-virgin, with propensity for CS/concurrency 2 = Non-virgin, with no propensity for CS/concurrency 3 = CS worker (relevant to females only)
j	Risk group(s) of partner(s)	0 = no partner; 1 = 1 high risk partner; 2 = 1 low risk partner; 11 = 2 high risk partners; 12 = primary high risk & secondary low risk; 21 = primary low risk & secondary high risk; 22 = 2 low risk partners*
l	Relationship type	1 = short-term (non-marital) 2 = long-term (marital) [†]
x	Individual age group	10, 15, 20, ..., 85
y	Partner age	10, 15, 20, ..., 85
g	Sex	1 = male; 2 = female
s	HIV disease state	0 = uninfected; 1 = acute HIV; 2 = asymptomatic HIV; 3 = WHO clinical stage 3; 4 = AIDS; 5 = on HAART
t	Time	0 to 40 (in years from mid-1985)

CS = commercial sex. HAART = highly active antiretroviral treatment.

* Where the individual is in a marital relationship with one partner and a non-marital relationship with another, the first index refers to the risk group of the spouse and the second refers to the risk group of the other partner. † Where the individual has two partners, this index refers to the nature of the primary partnership (the secondary relationship is always short-term). Where the individual has no partners, the index is omitted.

Symbols are defined as follows:

K = number of cycles per year, i.e. the frequency at which sexual behaviour variables are updated (the default value is 12, but K can be any integer greater than one)

π = gender equality factor

$N_{g,i,j,l}^s(x,t)$ = number of individuals of sex g , risk group i , aged x , who are in HIV disease state s , in relationship type l with partner(s) in group(s) j , at time t

A.1 Rates at which short-term partnerships are formed

To determine the rates at which short-term partnerships are formed, it is necessary to define the following symbols:

$c_{g,i,j,l}^s(x)$ = desired rate at which new short-term partnerships are formed, for an individual of sex g , risk group i , aged x , who is in HIV disease state s , in relationship type l with a partner in group j ($j = 0, 1$ or 2 only)

$\rho_{g,i,j}(t)$ = desired proportion of new short-term partners who are in risk group j , if individual is of sex s and in risk group i ($j = 1$ or 2 only)

$\rho_{g,i,j}(t)$ is calculated according to the following formula:

$$\rho_{g,i,j}(t) = (1 - \varepsilon_g) \delta_{ij} + \varepsilon_g \frac{\sum_{u=0}^2 \sum_l \sum_y \sum_{s=0}^5 N_{g^*,j,u,l}^s(y,t) c_{g^*,j,u,l}^s(y)}{\sum_{v=1}^2 \sum_{u=0}^2 \sum_l \sum_y \sum_{s=0}^5 N_{g^*,v,u,l}^s(y,t) c_{g^*,v,u,l}^s(y)}, \quad (\text{A1})$$

where $\delta_{ij} = 1$ if $i = j$ and 0 otherwise, g^* is the sex opposite to g , and ε_g is the degree of assortative mixing for sex g . As explained in section 3.2.6, the degree of assortative mixing can assume any value on the interval $[0, 1]$, with lower values of the parameter indicating greater tendency to form partnerships with individuals in the same sexual activity class.

In order to balance the male and female rates of short-term partnership formation, it is necessary to define the following parameter:

$B_{g,i,j}^1(t)$ = adjustment factor applied to the rate at which individuals of sex g , in risk group i , form short-term partnerships with individuals in risk group j ($j = 1$ or 2 only).

For women ($g = 2$):

$$B_{2,i,j}^1(t) = \frac{\left[\pi \sum_{s=0}^5 \sum_u \sum_v \sum_y N_{2,i,u,v}^s(y,t) c_{2,i,u,v}^s(y) \rho_{2,i,j}(t) + (1-\pi) \sum_{s=0}^5 \sum_u \sum_v \sum_y N_{1,j,u,v}^s(y,t) c_{1,j,u,v}^s(y) \rho_{1,j,i}(t) \right]}{\sum_{s=0}^5 \sum_u \sum_v \sum_y N_{2,i,u,v}^s(y,t) c_{2,i,u,v}^s(y) \rho_{2,i,j}(t)} \quad (A2)$$

The gender equality factor (π) can assume any value on the interval $[0, 1]$. The closer π is to 1, the closer the adjustment factor $B_{2,i,j}^1(t)$ is to 1. A similar formula is used to define the adjustment factor for males ($B_{1,i,j}^1(t)$), which approaches 1 as π approaches 0. The gender equality factor thus determines the extent to which rates of partnership formation are driven by male and female desires. An equality factor of 0.5 would imply that men and women have equal control over the formation of partnerships, while an equality factor of 0 would effectively imply that women are coerced into sexual relationships and have no control over the rate at which they enter partnerships. Similar approaches to balancing rates of partnership formation in males and females have been proposed by Garnett and Bowden (2000) and Turner *et al* (2004).

The independent probability of forming a new short-term partnership with a partner in risk group u , over the time period $[t, t + 1/K)$, is calculated as

$$1 - \exp\left(-c_{g,i,j,l}^s(x) B_{g,i,u}^1(t) \rho_{g,i,u}(t) / K\right) \quad (A3)$$

for $j = 0, 1$ or 2 , and is set to 0 for all other values of j (since it is assumed that an individual who already has two partners cannot form further partnerships).

A.2 Rates at which long-term (marital) partnerships are formed

Analogous to the previous section, the following variables are defined:

$m_{g,i,j}^s(x)$ = desired rate at which marriage occurs, for an individual of sex g , risk group i , aged x , who is in HIV disease state s , in a short-term relationship with a partner in group j ($j = 1$ or 2 only)

$B_{g,i,j}^2(t)$ = adjustment factor applied to the rate at which individuals of sex g , in risk group i , marry individuals in risk group j if they are currently in a short-term partnership with them ($j = 1$ or 2 only)

Similarly to the previous section, $B_{g,i,j}^2(t)$ is calculated for women as:

$$B_{2,i,j}^2(t) = \frac{\left[\pi \sum_{s=0}^5 \sum_u \sum_y N_{2,i,u,1}^s(y,t) m_{2,i,j}^s(y) I_{u,1}(j,1) + (1-\pi) \sum_{s=0}^5 \sum_u \sum_y N_{1,j,u,1}^s(y,t) m_{1,j,i}^s(y) I_{u,1}(j,1) \right]}{\sum_{s=0}^5 \sum_u \sum_y N_{2,i,u,1}^s(y,t) m_{2,i,j}^s(y) I_{u,1}(j,1)}, \quad (\text{A4})$$

where $I_{u,v}(j,l)$ is the number of partners of type l in risk group j , if the individual has partner(s) in group(s) u , with the primary partnership being of type v . It is thus assumed that the probability of marriage to a particular partner is independent of any other short-term partnerships the individual is in.

The independent probability that an individual in a short-term relationship with a partner in group j , at time t , becomes married to that partner over the time period $[t, t + 1/K)$, is then

$$1 - \exp\left(-m_{g,i,j}^s(x) B_{g,i,j}^2(t)/K\right), \quad (\text{A5})$$

provided the individual is not already married to another partner.

A.3 Rates at which partnerships are terminated

Partnerships can be terminated through death of the partner, through divorce (in the case of marital relationships) or through ‘break up’ (in the case of short-term relationships). In order to calculate rates of termination, it is necessary to define the following variables:

$D_{g,l}(x)$ = annual rate at which partnerships of type l dissolve, among individuals aged x , of gender g (ignoring mortality)

$f_g(y|x)$ = proportion of partners in age band y , if individual is of gender g and in age band x

$\mu_g^s(x,t)$ = force of mortality at time t , in individuals aged x , of gender g , who are in HIV disease state s

For a man who is of age x , in group i , in relationship type l with a partner in group j at time t , the independent probability of the relationship being terminated over the time period $[t, t + 1/K)$ is

$$1 - \exp\left(-\frac{1}{K}\left(D_{1,l}(x) + \sum_y f_1(y|x) \sum_{s=0}^5 \mu_2^s(y,t)\right)\right). \quad (\text{A6})$$

A similar formula is used to determine the probability that a woman’s partnership is terminated.

A.4 Rates at which women become sex workers

In order to calculate the rate at which women become sex workers, it is necessary to specify the following variables:

C = average annual number of sex acts a sex worker has with clients

$w_{i,j,l}(x)$ = rate at which men in group i , aged x , visit sex workers when in relationship type l with partner(s) in group(s) j ($w_{i,j,l}(x) = 0$ if $i \neq 1$)

$W^s(x)$ = factor by which the rate of recruitment into the ‘sex worker’ group is multiplied when the woman is of age x and in HIV disease state s

$\Delta_c(t, t+1/K)$ = the number of new sex workers required over the period $[t, t+1/K)$ in order to satisfy male demand

The variable $\Delta_c(t, t+1/K)$ is calculated as

$$\frac{1}{C} \sum_{s=0}^5 \sum_j \sum_l \sum_x N_{1,1,j,l}^s(x,t) w_{1,j,l}(x) - \sum_{s=0}^5 \sum_x N_{2,3,0}^s(x,t). \quad (\text{A7})$$

The independent probability that a woman in the ‘high risk’ group, who has no partners and is aged x and in HIV disease state s at time t , becomes a sex worker over the period $[t, t+1/K)$ is calculated as

$$\frac{\Delta_c(t, t+1/K) W^s(x)}{\sum_{s=0}^5 \sum_u N_{2,1,0}^s(u,t) W^s(u)}. \quad (\text{A8})$$

A.5 Rates at which youth become sexually experienced

The independent probability that a male virgin aged x at time t , with a propensity for commercial sex and concurrent relationships, has his first sexual encounter over the time interval $[t, t+1/K)$ is

$$1 - \exp(-c_{1,01,0}^s(x)/K). \quad (\text{A9})$$

This expression is a function of s , the HIV disease state of the male, though the only HIV-infected virgins would be those infected through mother-to-child transmission. Note that the equation is independent of $w_{01,0}(x)$, i.e. men are assumed not to have their first sexual encounter with sex workers (this assumption is made in order to simplify the modelling of STI and HIV transmission). Similar equations are used to determine the rates at which females and males in the ‘low risk’ group become sexually experienced.

A.6 Calculating the transition probability matrix

In order to calculate the elements of the transition probability matrix over the $[t, t+1/K)$ time interval, it is necessary to convert the independent probabilities described previously into dependent probabilities, i.e. probabilities net of competing decrements. Suppose that there are m possible movements out of state S_v (excluding death and ignoring changes in x and s for now), and the potential states to which an individual can move are denoted $S_1, S_2, S_3, \dots, S_m$. Suppose that the independent probability of moving from state S_v to state S_u is q_u over the $[t, t+1/K)$ time period. If it is assumed that in the absence of other decrements, the times of transition from state S_v to state S_u would be uniformly distributed over the interval $[t, t+1/K)$, then it can be shown that the dependent probability of movement from state S_v to state S_u is

$$(aq)_u = q_u \left(1 - \frac{1}{2} \sum_{i=1}^m q_i + \frac{1}{3} \sum_{i=1}^m \sum_{j \neq i} q_i q_j - \frac{1}{4} \sum_{i=1}^m \sum_{j \neq i} \sum_{\substack{k \neq i, \\ k \neq j}} q_i q_j q_k + \dots \right) \times \exp(-\mu_g^s(x, t)/K) \quad (\text{A10})$$

Since the mortality rate is assumed to be independent of changes between states over the $[t, t+1/K)$ time interval (ignoring changes in x and s), the dependent rate of mortality is effectively the same as the independent rate of mortality. The dependent probability of remaining in state S_v over the interval $[t, t+1/K)$ is

$$(ap)_v = \exp(-\mu_g^s(x, t)/K) \prod_{u=1}^m (1 - q_u) = \exp(-\mu_g^s(x, t)/K) - \sum_{u=1}^m (aq)_u \quad (\text{A11})$$

The elements of the transition probability matrix are the $(ap)_v$ and $(aq)_u$ values.

Appendix B: Mathematical approach to modelling STI transmission and cure

This appendix builds on the mathematical developments of Appendix A, to derive expressions for an individual's probability of acquiring a particular STI over a particular time period, and the individual's probability of being cured of a particular STI if they seek treatment. Three additional index variables are defined in Table B.1. Although bacterial vaginosis and vaginal candidiasis are included in the state space for d , none of the transmission variables in section B.1 are defined for the case in which $d = BV$ and $d = VC$, since these infections are assumed not to be sexually transmitted.

Table B.1: Index variables

Symbol	Definition	State space
d	STI	BV = bacterial vaginosis CT = chlamydia (<i>Chlamydia trachomatis</i>) HD = chancroid (<i>Haemophilus ducreyi</i>) HIV = human immunodeficiency virus HSV = herpes simplex virus type 2 NG = gonorrhoea (<i>Neisseria gonorrhoeae</i>) TP = syphilis (<i>Treponema pallidum</i>) TV = trichomoniasis (<i>Trichomonas vaginalis</i>) VC = vaginal candidiasis
h	Health sector	0 = public health sector 1 = private health sector 2 = traditional healers
z	STI state	0 (susceptible), 1, 2, ... (as defined in section 3.3.1)

The variable k is defined as the number of STI cycles per year, i.e. the frequency at which movements between STI states are updated. The default value is 48, but it can be any integer multiple of K , the number of sexual behaviour cycles per year.

B.1 Rates of STI transmission

Symbols are defined as follows:

$\beta_{g,i,l}^{d,z,s}$ = probability of transmitting STI d when in state z , in a single act of unprotected sex in relationship type l , if the infected individual is of sex g and is in risk group i and HIV stage s (if subscript l is omitted, the probability relates to commercial sex relationships)

$\alpha_{g,i,j,l}^s(x,t)$ = multiple by which the probability of transmitting HIV is increased as a result of other STIs in the HIV-positive partner, given that the HIV-positive partner is of sex g , in risk group i , in HIV disease stage s , in relationship type l with partner(s) in group(s) j , at time t

$\alpha_{g,i,j,l}^-(x,t)$ = multiple by which the probability of acquiring HIV is increased as a result of other STIs in the HIV-negative partner, given that the HIV-susceptible partner is of sex g , in risk group i , in relationship type l with partner(s) in group(s) j , at time t

$\gamma_{g,l}(x,t)$ = probability that a condom is used in relationship type l at time t , if the susceptible partner is of sex g and age x

E^d = probability that a condom prevents the transmission of STI d

$a_g^d(x)$ = factor by which susceptibility to STI d is increased at age x among individuals of sex g

$X_{g,i,j,l}^{d,z,s}(x,t)$ = proportion of individuals in state z of disease d , out of people of sex g , in risk group i , in HIV disease stage s , in relationship type l with partner(s) in group(s) j , at time t (in the case of $d = \text{HIV}$, the proportion is 0 for $z \neq s$ and 1 for $z = s$)

$T_{g,i,j,l}^d(x,t)$ = the probability that an individual of sex g , in risk group i , aged x , transmits STI d to a susceptible partner of type l (short-term or long-term partnerships only) in risk group j , in a single act of unprotected sex, over the period $[t, t + 1/k)$

The latter variable is defined as follows in the case of $d = \text{HIV}$:

$$T_{g,i,j,l}^d(x,t) = \frac{\sum_{s=0}^5 \sum_u \sum_v N_{g,i,u,v}^s(x,t) I_{u,v}(j,l) \sum_z X_{g,i,u,v}^{d,z,s}(x,t) \beta_{g,i,v}^{d,z,s} \alpha_{g,i,u,v}^s(x,t)}{\sum_{s=0}^5 \sum_u \sum_v N_{g,i,u,v}^s(x,t) I_{u,v}(j,l)},$$

where $I_{u,v}(j,l)$ is the number of partnerships of type l with partners in risk group j , if the individual has partner(s) in group(s) u , with their primary partnership being of type v (as in Appendix A). The above equation is the weighted average probability of transmitting HIV, where the weights are the numbers of individuals in relationships of type l . The same formula is used to calculate $T_{g,i,j,l}^d(x,t)$ for other STIs, except that the $\alpha_{g,i,u,v}^s(x,t)$ factor is omitted.

The next step is to define $P_{g,i,j,l}^d(x,t)$ as the probability that a susceptible individual of sex g and age x , in risk group i , becomes infected with STI d through a single act of sex with a partner in group j in the context of relationship type l , over the period $[t, t+1/k)$. In the case of HIV, this represents the probability of becoming infected with HIV, *before* allowing for the effect of other STIs in the HIV-negative individual on their susceptibility to HIV. In the context of short-term and long-term relationships, $P_{g,i,j,l}^d(x,t)$ is calculated as

$$P_{g,i,j,l}^d(x,t) = a_g^d(x) (1 - \gamma_{g,l}(x,t) E^d) \sum_y f_g(y|x) T_{g^*,j,i,l}^d(y,t).$$

Weighting $T_{g^*,j,i,l}^d(y,t)$ by $f_g(y|x)$, the proportion of partners aged y , takes into account the individual's partner age preferences. In the context of interactions between sex workers and their clients, a different approach is taken. Since the variable $T_{g,i,j,l}^d(x,t)$ is not defined for sexual relations between sex workers and their clients, it is necessary to define the probability of infection in susceptible male clients as

$$P_{1,1,3}^d(x,t) = a_1^d(x) \left(1 - \gamma^*(t) E^d\right) \frac{\sum_{s=0}^5 \sum_y N_{2,3,0}^s(y,t) \sum_z X_{2,3,0}^{d,z,s}(y,t) \beta_{2,3}^{d,z,s}}{\sum_{s=0}^5 \sum_y N_{2,3,0}^s(y,t)},$$

and the probability of infection in susceptible female sex workers as

$$P_{2,3,1}^d(x,t) = a_2^d(x) \left(1 - \gamma^*(t) E^d\right) \times \frac{\sum_{s=0}^5 \sum_y \sum_j \sum_l N_{1,1,j,l}^s(y,t) w_{1,j,l}(y) \sum_d X_{1,1,j,l}^{d,z,s}(y,t) \beta_{1,1}^{d,z,s}}{\sum_{s=0}^5 \sum_y \sum_j \sum_l N_{1,1,j,l}^s(y,t) w_{1,j,l}(y)},$$

where $\gamma^*(t)$ is the rate of condom use in acts of sex between sex workers and their clients at time t . As noted in Appendix A, it is assumed that there are no age preferences in interactions between sex workers and their clients, and hence the $f_g(y|x)$ factor does not appear in either of the previous two equations.

The last step is to define $\lambda_{g,i,j,l}^d(x,t)$ as the probability that a susceptible individual of sex g and age x , in risk group i , in relationship type l with partner(s) in group(s) j , becomes infected with STI d over the period $[t, t+1/k)$. For STIs other than HIV, this probability is calculated in males as

$$\lambda_{g,i,j,l}^d(x,t) = 1 - \left[\prod_{u=1}^2 \left(1 - P_{g,i,u,1}^d(x,t)\right)^{I_{j,l}(u,1) n_{g,1}(x) K/k} \right] \times \left[\prod_{u=1}^2 \left(1 - P_{g,i,u,2}^d(x,t)\right)^{I_{j,l}(u,2) n_{g,2}(x) K/k} \right] \times \left[\left(1 - P_{g,i,3}^d(x,t)\right)^{w_{i,j,l}(x)/k} \right]$$

The average number of sex acts per K^{th} of a year, $n_{g,l}(x)$, is a function of only the individual's sex (g), age (x) and the relationship type (l), and is independent of the number or type of other relationships the individual is in. The terms in the three sets of square brackets represent the probabilities of not being infected in each of the three relationship types (short-term, long-term and sex worker-client respectively). In the

case of women, the same formula applies, except that the last factor representing the risk of infection through sex worker contact is omitted. The probability that a sex worker becomes infected is

$$\lambda_{2,3,0}^d(x,t) = 1 - \left(1 - P_{2,3,1}^d(x,t)\right)^{C/k},$$

where C , as mentioned before, is the average annual number of clients a sex worker has. For HIV, the same formulas apply, except that the $P_{g,i,j,t}^d(x,t)$ terms are multiplied by $\alpha_{g,i,j,t}^-$ in order to determine the effect of other STIs on susceptibility to HIV.

B.2 Rates of STI cure

Symbols are defined as follows:

$\psi_g^d(t)$ = probability that an individual of sex g , experiencing symptoms of disease d , is cured if they seek treatment at time t

$r_{g,h}$ = % of individuals of sex g who seek STI treatment in health sector h

$\Omega_h(t)$ = % of health workers in sector h who correctly follow syndromic management protocols at time t ($h = 0$ or 1 only)

A_g^{d-} = % of individuals of sex g , with symptoms of STI d , who receive appropriate treatment if the health worker is not following syndromic management protocols (ignoring the potential effect of drug shortages)

A_g^{d+} = % of individuals of sex g , with symptoms of STI d , who receive appropriate treatment if the health worker is following syndromic management protocols (ignoring the potential effect of drug shortages)

$V(t)$ = % reduction in the probability of cure in public STI clinics as a result of drug shortages, at time t

ζ_A^d = probability that STI d is cured if treated with appropriate drugs

ζ_T^d = probability that STI d is cured if treated by a traditional healer

The probability of cure is then calculated as:

$$\psi_g^d(t) = \left[r_{g,0} \left((1 - \Omega_0(t)) A_g^{d-} + \Omega_0(t) A_g^{d+} \right) (1 - V(t)) \right. \\ \left. + r_{g,1} \left((1 - \Omega_1(t)) A_g^{d-} + \Omega_1(t) A_g^{d+} \right) \right] \zeta_A^d + r_{g,2} \zeta_T^d$$

This is the weighted average probability of cure in the different health sectors, where the weights are the proportions of individuals seeking treatment in each sector, $r_{g,h}$. In the case of bacterial vaginosis and vulvovaginal candidiasis, the $\psi_g^d(t)$, ζ_A^d and ζ_T^d symbols are modified slightly by adding a subscript after the first to indicate whether cure is complete (1) or only partial (2), as explained in section 3.3.4.3.

B.3 Initial STI profile

The method used to determine the initial proportion of the population infected with HIV at the start of the projection has already been described in section 4.1.1. For each simulation of STIs other than HIV, it is necessary to approximate the proportion of each age, sex and sexual activity cohort in the different STI states at the start of the HIV/AIDS projection period (1985). This is done by first running the model for five years, prior to any changes in condom use, STI treatment and HIV prevalence, in order to estimate the endemic STI prevalence that would be expected at the start of the HIV/AIDS epidemic. This endemic STI profile is calculated for each of the age, sex and sexual activity cohorts. The projection is then restarted in 1985, in the same way as before, but this time using the previously calculated endemic STI prevalence profiles in each cohort as the starting point. Although a five-year projection is sufficient to approximate the endemic prevalence of most STIs, it might not be adequate for chronic STIs such as genital herpes, which could take decades to reach endemic prevalence due to the long-term nature of the infection.

Appendix C: Estimates of STI prevalence from sentinel surveillance

The following tables summarize the data used in the Bayesian analysis described in section 4.2. Although data from patients with genital ulcer disease (GUD) were not used in the Bayesian analysis, they have been used in validating the model, and are therefore included here too. For readers interested in identifying the distribution of sampled populations between provinces and between urban and rural areas, Table C.1 provides information on the geographical classification of the various sites. In subsequent tables, prevalence estimates are arranged according to sample type and then according to the year in which the study was conducted.

Table C.1: Sentinel surveillance sites

Location	Urban/rural	Province
Bloemfontein	Urban	Free State
Bushbuckridge	Rural	Limpopo
Cape Town	Urban	Western Cape
Durban	Urban	KwaZulu-Natal
Empangeni	Rural	KwaZulu-Natal
Hewu district	Rural	Eastern Cape
Hlabisa (/Umkanyakude)	Rural	KwaZulu-Natal
Johannesburg	Urban	Gauteng
Khutsong (/Carletonville)	Urban	Gauteng ¹
Mbalenhle	Rural	Mpumalanga
Orange Farm	Urban	Gauteng
Pretoria	Urban	Gauteng
Virginia	Urban	Free State
Vulindlela	Rural	KwaZulu-Natal

¹ Khutsong has subsequently been incorporated in the Northwest Province.

Table C.2: Syphilis prevalence estimates

Study	Year	Sample	Location	n	Prev.	Diagnostic
O'Farrell <i>et al</i> (1989)	1986-7	ANC	Empangeni	193	11.9%	Non-trep. + trep.
Donders <i>et al</i> (1993b)	1988	ANC	Pretoria	256	9.0%	Non-trep. + trep.
Dietrich <i>et al</i> (1992)	-	ANC	Durban	170	7.6%	Non-trep. + trep.
Coetzee (1994)	1990-2	ANC	Cape Town	1973	5.2%	Non-trep. + trep.
Opai-Tetteh <i>et al</i> (1993)	-	ANC	Durban	200	11.0%	Non-trep. + trep.
Bam <i>et al</i> (1994)	1990	ANC	Bloemfontein	971	15.7%	Non-trep. + trep.
Hoosen <i>et al</i> (1996)	-	ANC	Durban	32	12.0%	Non-trep. + trep.
Qolohle <i>et al</i> (1995)	1993	ANC	Durban	363	9.4%	Non-trep. + trep.
Govender <i>et al</i> (1996)	1994	ANC	Durban	168	12.0%	Non-trep. + trep.
Kharsany <i>et al</i> (1997)	1994	ANC	Durban	52	26.9%	Non-trep.
Sturm <i>et al</i> (2003)	1995	ANC	Hlabisa	327	12.0%	Non-trep. + trep.
Sturm <i>et al</i> (1998)	1996	ANC	Hlabisa	327	8.4%	Non-trep. + trep.
Mashiane <i>et al</i> (1999)	1997	ANC	Pretoria	3000	12.4%	Non-trep. + trep.
Dawadi <i>et al</i> (2001)	1997-8	ANC	Hewu	271	8.5%	Non-trep.
Myer <i>et al</i> (2003)	1998- 2000	ANC	Hlabisa	7391	7.5%	Non-trep.
Sturm <i>et al</i> (2003)	1999	ANC	Hlabisa	245	6.0%	Non-trep. + trep.
	2002	ANC	Hlabisa	449	2.0%	Non-trep. + trep.
Ramjee <i>et al</i> (2005)	1996- 2000	CSW	KZN	395	31.4%	Non-trep. + trep.
Steen <i>et al</i> (2000)	1996-7	CSW	Virginia	407	33.8%	Non-trep. + trep.
Dunkle <i>et al</i> (2005)	1996-7	CSW	Johannesburg	295	25.6%	Non-trep. + trep.
Williams <i>et al</i> (2000)	1998	CSW	Khutsong	121	23.3%	Non-trep. + trep.
Williams <i>et al</i> (2003)	2000	CSW	Khutsong	93	34.4%	Non-trep. + trep.
Ndhlovu <i>et al</i> (2005)	2001	CSW	Khutsong	101	21.0%	Non-trep. + trep.
Hoosen <i>et al</i> (1989)	1986	FPC	Durban	50	8.0%	Non-trep. + trep.
Schneider <i>et al</i> (1998)	1994	FPC	Bushbuck- ridge	249	5.0%	Non-trep. + trep.
Wilkinson <i>et al</i> (1997)	-	FPC	Hlabisa	189	8.0%	Non-trep. + trep.
Kharsany <i>et al</i> (1997)	1994	FPC	Durban	55	21.8%	Non-trep.
Hoosen <i>et al</i> (1997)	-	FPC	Durban	40	8.0%	Non-trep. + trep.
Fehler <i>et al</i> (1998)	-	FPC	Johannesburg	210	8.6%	Non-trep. + trep.
Frohlich <i>et al</i> (2003)	2002	FPC	Vulindlela	221	2.2%	Non-trep. + trep.
Cronje <i>et al</i> (1994)	-	HH, F 20-49	Urban FS	403	15.5%	Non-trep. + trep.
		HH, F 20-49	Rural FS	465	12.3%	Non-trep. + trep.
Colvin <i>et al</i> (1998)	1995	HH, F 15-49	Hlabisa	142	8.5%	Non-trep. + trep.
Williams <i>et al</i> (2000)	1998	HH, F 15-59	Khutsong	712	9.7%	Non-trep. + trep.

Table C.2 (continued)

Study	Year	Sample	Location	n	Prev.	Diagnostic
Auvert <i>et al</i> (2001a)	1999	HH, F 15-24	Khutsong	622	4.5%	Non-trep. + trep.
Williams <i>et al</i> (2003)*	2000	HH, F 15-19	Khutsong	893	18.7%	Non-trep. + trep.
Ndhlovu <i>et al</i> (2005)*	2001	HH, F 15-59	Khutsong	878	13.0%	Non-trep. + trep.
Auvert <i>et al</i> (2004)*	2002	HH, F 15-49	Orange Farm	492	9.6%	Non-trep. + trep.
Colvin <i>et al</i> (1998)	1995	HH, M 15-49	Hlabisa	86	9.3%	Non-trep. + trep.
Williams <i>et al</i> (2000)	1998	HH, M 15-59	Khutsong	475	6.1%	Non-trep. + trep.
Auvert <i>et al</i> (2001a)	1999	HH, M 15-24	Khutsong	560	1.8%	Non-trep. + trep.
Williams <i>et al</i> (2003)	2000	HH, M 15-19	Khutsong	606	8.1%	Non-trep. + trep.
Ndhlovu <i>et al</i> (2005)	2001	HH, M 15-59	Khutsong	532	5.0%	Non-trep. + trep.
Auvert <i>et al</i> (2004)	2002	HH, M 15-49	Orange Farm	438	3.2%	Non-trep. + trep.

* Outlier estimates, excluded from analysis due to excessive influence.

ANC = antenatal clinic attenders. CSW = commercial sex workers. F = females. FPC = family planning clinic attenders. FS = Free State. HH = households. KZN = KwaZulu-Natal. M = males. Non-trep. = non-treponemal assay. Prev. = prevalence. Trep. = treponemal assay.

In the case of syphilis, three measurements of syphilis prevalence among women were excluded from the analysis because they were found to have excessive influence on the fitting of the model. All three outlier estimates of syphilis prevalence were from household surveys conducted in townships in Gauteng province between 2000 and 2002. For the sake of comparison, these outliers are included in Table C.2, and are indicated by asterisks. No prevalence estimates were judged to be outliers in the case of other STIs.

Table C.3: Gonorrhoea prevalence estimates

Study	Year	Sample	Location	n	Prev.	Diagnostic
O'Farrell <i>et al</i> (1989)	1987	ANC	Empangeni	193	5.7%	Culture
Donders <i>et al</i> (1993b)	1988	ANC	Pretoria	256	3.9%	Culture
Dietrich <i>et al</i> (1992)	-	ANC	Durban	170	4.1%	Culture
Hoosen <i>et al</i> (1996)	-	ANC	Durban	32	6.0%	Culture
Govender <i>et al</i> (1996)	1994-5	ANC	Durban	168	3.0%	Culture
Kharsany <i>et al</i> (1997)	1994	ANC	Durban	52	5.8%	Culture
Sturm <i>et al</i> (1998)	1996	ANC	Hlabisa	327	7.8%	Culture
Sturm <i>et al</i> (2003)	1999	ANC	Hlabisa	245	7.0%	PCR on swabs
Sturm <i>et al</i> (2004a)	-	ANC	Hlabisa	185	7.6%	- ¹
Sturm <i>et al</i> (2003)	2002	ANC	Hlabisa	449	4.0%	PCR on swabs
Ramjee <i>et al</i> (2005)	1996- 2000	CSW	KZN	387	10.3%	Culture
Steen <i>et al</i> (2000)	1996-7	CSW	Virginia	407	17.3%	LCR on urine
Dunkle <i>et al</i> (2005)	1996-7	CSW	Johannesburg	295	23.3%	LCR on urine
Williams <i>et al</i> (2000)	1998	CSW	Khutsong	121	15.7%	LCR on urine
Williams <i>et al</i> (2003)	2000	CSW	Khutsong	93	16.1%	LCR on urine
Ndhlovu <i>et al</i> (2005)	2001	CSW	Khutsong	101	10.0%	LCR on urine
Hoosen <i>et al</i> (1989)	1986-7	FPC	Durban	50	10.0%	Culture
Schneider <i>et al</i> (1998)	1994	FPC	Bushbuck- ridge	249	3.0%	LCR on urine
Wilkinson <i>et al</i> (1997)	-	FPC	Hlabisa	189	4.0%	Culture
Kharsany <i>et al</i> (1997)	1994	FPC	Durban	55	5.5%	Culture
Hoosen <i>et al</i> (1997)	-	FPC	Durban	40	5.0%	Culture
Fehler <i>et al</i> (1998)	-	FPC	Johannesburg	210	8.6%	LCR on urine
Kleinschmidt <i>et al</i> (2007)	1999- 2001	FPC	Orange Farm	538	3.9%	LCR on urine
Frohlich <i>et al</i> (2003)	2002	FPC	Vulindlela	221	2.2%	PCR on swabs
Colvin <i>et al</i> (1998)	1995	HH, F 15-49	Hlabisa	137	5.8%	LCR on urine
Williams <i>et al</i> (2000)	1998	HH, F 15-59	Khutsong	712	6.9%	LCR on urine
Auvert <i>et al</i> (2001a)	1999	HH, F 15-24	Khutsong	622	10.9%	LCR on urine
Williams <i>et al</i> (2003)	2000	HH, F 15-49	Khutsong	893	8.6%	LCR on urine
Ndhlovu <i>et al</i> (2005)	2001	HH, F 15-59	Khutsong	878	11.0%	LCR on urine
Pettifor <i>et al</i> (2005a)	2002-3	HH, F 15-19	Peri-urban	2624	3.5%	PCR on urine
		HH, F 20-24	townships	2002	3.5%	PCR on urine
Hurkchand <i>et al</i> (2004)	2002	HH, F 20-49	Mbalenhle	399	4.7%	PCR on urine
Colvin <i>et al</i> (1998)	1995	HH, M 15-49	Hlabisa	85	2.4%	LCR on urine
Williams <i>et al</i> (2000)	1998	HH, M 15-59	Khutsong	475	3.4%	LCR on urine

Table C.3 (continued)

Study	Year	Sample	Location	n	Prev.	Diagnostic
Auvert <i>et al</i> (2001a)	1999	HH, M 15-24	Khutsong	560	2.9%	LCR on urine
Williams <i>et al</i> (2003)	2000	HH, M 15-49	Khutsong	606	3.3%	LCR on urine
Ndhlovu <i>et al</i> (2005)	2001	HH, M 15-59	Khutsong	532	4.0%	LCR on urine
Pettifor <i>et al</i> (2005a)	2002-3	HH, M 15-19	Peri-urban	2389	1.1%	PCR on urine
		HH, M 20-24	townships	1455	3.2%	PCR on urine
Hurkchand <i>et al</i> (2004)	2002	HH, M 20-49	Mbalenhle	291	3.9%	PCR on urine

¹ Diagnosed by culture and a series of genetic tests, which in combination would have had very high sensitivity and specificity.

ANC = antenatal clinic attenders. CSW = commercial sex workers. F = females. FPC = family planning clinic attenders. HH = households. KZN = KwaZulu-Natal. LCR = ligase chain reaction test. M = males. PCR = polymerase chain reaction test. Prev. = prevalence.

Table C.4: Vulvovaginal candidiasis prevalence estimates

Study	Year	Sample	Location	n	Prev.	Diagnostic
O'Farrell <i>et al</i> (1989)	1987	ANC	Empangeni	193	26.9%	Culture
Van Rensburg and Odendaal (1992)	1988	ANC	Cape Town	180	20.0%	Culture
Hoosen <i>et al</i> (1996)	-	ANC	Durban	32	59.0%	Microscopy
Kharsany <i>et al</i> (1997)	1994	ANC	Durban	52	55.8%	Culture
Funk <i>et al</i> (1996)	1995	ANC	Pretoria	798	23.6%	Microscopy
Ramjee <i>et al</i> (1998)	1996-7	CSW	KZN	145	40.9%	Microscopy
Dunkle <i>et al</i> (2005)	1996-7	CSW	Johannesburg	295	25.9%	Microscopy
Wilkinson <i>et al</i> (1997)	-	FPC	Hlabisa	189	30.0%	Microscopy
Kharsany <i>et al</i> (1997)	1994	FPC	Durban	55	27.2%	Culture
Fehler <i>et al</i> (1998)	-	FPC	Johannesburg	210	22.9%	Microscopy

ANC = antenatal clinic attenders. CSW = commercial sex workers. FPC = family planning clinic attenders. KZN = KwaZulu-Natal. Prev. = prevalence.

Table C.5: Chlamydial infection prevalence estimates

Study	Year	Sample	Location	n	Prev.	Diagnostic
O'Farrell <i>et al</i> (1989)	1987	ANC	Empangeni	193	11.4%	DIF
Dietrich <i>et al</i> (1992)	-	ANC	Durban	170	4.7%	DIF
Hoosen <i>et al</i> (1996)	-	ANC	Durban	32	41.0%	DIF
Kharsany <i>et al</i> (1997)	1994	ANC	Durban	52	19.2%	DIF
Sturm <i>et al</i> (1998)	1996	ANC	Hlabisa	327	12.9%	DIF
Sturm <i>et al</i> (2003)	1999	ANC	Hlabisa	245	11.0%	PCR on swabs
Sturm <i>et al</i> (2004a)	-	ANC	Hlabisa	185	13.5%	- ¹
Sturm <i>et al</i> (2003)	2002	ANC	Hlabisa	449	11.0%	PCR on swabs
Ramjee <i>et al</i> (1998)	1996-7	CSW	KZN	145	16.4%	DIF
Steen <i>et al</i> (2000)	1996-7	CSW	Virginia	407	14.3%	LCR on urine
Dunkle <i>et al</i> (2005)	1996-7	CSW	Johannesburg	295	8.4%	LCR on urine
Williams <i>et al</i> (2000)	1998	CSW	Khutsong	121	9.1%	LCR on urine
Williams <i>et al</i> (2003)	2000	CSW	Khutsong	93	12.9%	LCR on urine
Ndhlovu <i>et al</i> (2005)	2001	CSW	Khutsong	101	8.0%	LCR on urine
Hoosen <i>et al</i> (1989)	1986-7	FPC	Durban	50	26.0%	DIF
Schneider <i>et al</i> (1998)	1994	FPC	Bushbuck- ridge	249	12.0%	LCR on urine
Wilkinson <i>et al</i> (1997)	-	FPC	Hlabisa	189	8.0%	DIF
Kharsany <i>et al</i> (1997)	1994	FPC	Durban	55	12.7%	DIF
Hoosen <i>et al</i> (1997)	-	FPC	Durban	40	15.0%	DIF
Fehler <i>et al</i> (1998)	-	FPC	Johannesburg	210	18.1%	LCR on urine
Kleinschmidt <i>et al</i> (2007)	1999- 2001	FPC	Orange Farm	539	14.1%	LCR on urine
Frohlich <i>et al</i> (2003)	2002	FPC	Vulindlela	221	8.8%	PCR on swabs
Colvin <i>et al</i> (1998)	1995	HH, F 15-49	Hlabisa	140	6.4%	LCR on urine
Williams <i>et al</i> (2000)	1998	HH, F 15-59	Khutsong	712	8.1%	LCR on urine
Auvert <i>et al</i> (2001a)	1999	HH, F 15-24	Khutsong	622	14.6%	LCR on urine
Williams <i>et al</i> (2003)	2000	HH, F 15-49	Khutsong	893	13.8%	LCR on urine
Ndhlovu <i>et al</i> (2005)	2001	HH, F 15-59	Khutsong	878	12.0%	LCR on urine
Auvert <i>et al</i> (2004)	2002	HH, F 15-49	Orange Farm	492	6.9%	PCR on urine
Pettifor <i>et al</i> (2005a)	2002-3	HH, F 15-19	Semi-urban	2624	9.1%	PCR on urine
		HH, F 20-24	townships	2002	10.8%	PCR on urine
Hurkchand <i>et al</i> (2004)	2002	HH, F 20-49	Mbalenhle	399	6.5%	PCR on urine
Colvin <i>et al</i> (1998)	1995	HH, M 15-49	Hlabisa	90	5.6%	LCR on urine
Williams <i>et al</i> (2000)	1998	HH, M 15-59	Khutsong	475	5.2%	LCR on urine
Auvert <i>et al</i> (2001a)	1999	HH, M 15-24	Khutsong	560	4.8%	LCR on urine
Williams <i>et al</i> (2003)	2000	HH, M 15-49	Khutsong	606	12.4%	LCR on urine

Table C.5 (continued)

Study	Year	Sample	Location	n	Prev.	Diagnostic
Ndhlovu <i>et al</i> (2005)	2001	HH, M 15-59	Khutsong	532	7.0%	LCR on urine
Auvert <i>et al</i> (2004)	2002	HH, M 15-49	Orange Farm	438	6.2%	PCR on urine
Pettifor <i>et al</i> (2005a)	2002-3	HH, M 15-19	Semi-urban	2389	3.5%	PCR on urine
		HH, M 20-24	townships	1455	10.1%	PCR on urine
Hurkchand <i>et al</i> (2004)	2002	HH, M 20-49	Mbalenhle	291	8.2%	PCR on urine

¹ Diagnosed by culture and a series of genetic tests, which in combination would have had very high sensitivity and specificity.

ANC = antenatal clinic attenders. CSW = commercial sex workers. DIF = direct immunofluorescence. F = females. FPC = family planning clinic attenders. HH = households. KZN = KwaZulu-Natal. LCR = ligase chain reaction test. M = males. PCR = polymerase chain reaction test. Prev. = prevalence.

Table C.6: Chancroid prevalence estimates

Study	Year	Sample	Location	n	Prev.	Diagnostic
O'Farrell <i>et al</i> (1991b)	1988-9	GUD, F	Durban	100	14.0%	Culture (ulcers)
Rajagopal <i>et al</i> (1999)	1997	GUD, F	Durban	23	0.0%	Culture (ulcers)
Moodley <i>et al</i> (2003a)	2000	GUD, F	Durban	149	6.0%	PCR (ulcers)
Dangor <i>et al</i> (1989)	1986	GUD, M	Khutsong	240	68.3%	Culture (ulcers)
O'Farrell <i>et al</i> (1991a)	1988-9	GUD, M	Durban	100	22.0%	Culture (ulcers)
Ye <i>et al</i> (2007)	1990	GUD, M	Khutsong	213	62.4%	Culture (ulcers)
Chen <i>et al</i> (2000)	1993-4	GUD, M	Cape Town	180	17.2%	PCR (ulcers)
		GUD, M	Johannesburg	159	21.4%	
		GUD, M	Durban	199	53.3%	
Lai <i>et al</i> (2003)	1993	GUD, M	Khutsong	232	69.4%	PCR (ulcers)
Mathews <i>et al</i> (1998)	1995	GUD, M	Cape Town	40	12.5%	Culture (ulcers)
Lai <i>et al</i> (2003)	1998	GUD, M	Khutsong	186	50.5%	PCR (ulcers)
Kharsany <i>et al</i> (2000)	1998	GUD, M	Durban	400	6.0%	PCR (ulcers)
Moodley <i>et al</i> (2003a)	2000	GUD, M	Durban	438	11.0%	PCR (ulcers)
Muller <i>et al</i> (2007b)	2005-6	GUD, M	Gauteng	450	4.7%	PCR (ulcers)

F = females. GUD = genital ulcer disease patients. M = males. PCR = polymerase chain reaction test. Prev. = prevalence.

Table C.7: Trichomoniasis prevalence estimates

Study	Year	Sample	Location	n	Prev.	Diagnostic
O'Farrell <i>et al</i> (1989)	1987	ANC	Empangeni	193	49.2%	Culture
Donders <i>et al</i> (1993a)	1988	ANC	Pretoria	256	25.4%	Wet mount
Hoosen <i>et al</i> (1996)	-	ANC	Durban	32	19.0%	Wet mount
Govender <i>et al</i> (1996)	1994-5	ANC	Durban	168	21.0%	Wet mount
Kharsany <i>et al</i> (1997)	1994	ANC	Durban	52	51.9%	Culture
Funk <i>et al</i> (1996)	1995	ANC	Pretoria	798	12.3%	Wet mount
Sturm <i>et al</i> (1998)	1996	ANC	Hlabisa	327	41.4%	Culture
Sturm <i>et al</i> (2003)	1999	ANC	Hlabisa	245	32.0%	PCR on swabs
Sturm <i>et al</i> (2004a)	2001	ANC	Hlabisa	185	36.8%	¹
Sturm <i>et al</i> (2003)	2002	ANC	Hlabisa	449	27.0%	PCR on swabs
Ramjee <i>et al</i> (2005)	1996- 2000	CSW	KZN	392	35.7%	Wet mount
Dunkle <i>et al</i> (2005)	1996-7	CSW	Johannesburg	295	16.8%	Wet mount
Hoosen <i>et al</i> (1989)	1986-7	FPC	Durban	50	20.0%	Wet mount
Schneider <i>et al</i> (1998)	1994	FPC	Bushbuck- ridge	249	18.0%	Wet mount
Wilkinson <i>et al</i> (1997)	-	FPC	Hlabisa	189	14.0%	Culture
Kharsany <i>et al</i> (1997)	1994	FPC	Durban	55	25.5%	Culture
Hoosen <i>et al</i> (1997)	-	FPC	Durban	40	20.0%	Culture
Fehler <i>et al</i> (1998)	-	FPC	Johannesburg	210	10.6%	Culture
Kleinschmidt <i>et al</i> (2007)	1999- 2001	FPC	Orange Farm	547	7.5%	Culture
Frohlich <i>et al</i> (2003)	2002	FPC	Vulindlela	221	23.8%	PCR on swabs
Cronje <i>et al</i> (1994)	-	HH, F 20-49	Urban FS	405	29.6%	Wet mount
		HH, F 20-49	Rural FS	470	27.4%	Wet mount
Charumilind <i>et al</i> (2007)	2003	HH ² , M 20-54	Johannesburg	1458	5.6%	PCR on urine

¹ Diagnosed by culture and a series of genetic tests, which in combination would have had very high sensitivity and specificity. ² Sample was drawn from men in hostels, but is treated as a household sample for the purpose of this analysis, as it is the only prevalence estimate for males.

ANC = antenatal clinic attenders. CSW = commercial sex workers. F = females. FPC = family planning clinic attenders. FS = Free State. HH = households. KZN = KwaZulu-Natal. M = males. PCR = polymerase chain reaction test. Prev. = prevalence.

Table C.8: Genital herpes (HSV-2) prevalence estimates

Study	Year	Sample	Location	n	Prev.	Diagnostic
Sturm (2003)	2002	ANC	Hlabisa	417	65.0%	Western blot
Ramjee <i>et al</i> (2005)	1996-2000	CSW	KZN	416	84.0%	ELISA
Ndhlovu <i>et al</i> (2005)	2001	CSW	Khutsong	101	62.0%	ELISA
Mlaba <i>et al</i> (2007)	-	FPC	Johannesburg	210	73.0%	ELISA
O'Farrell <i>et al</i> (1991b)	1988-9	GUD, F	Durban	100	18.0%	Culture (ulcers)
Rajagopal <i>et al</i> (1999)	1997	GUD, F	Durban	23	18.0%	Culture (ulcers)
Moodley <i>et al</i> (2003a)	2000	GUD, F	Durban	149	49.7%	PCR (ulcers)
Auvert <i>et al</i> (2001a)	1999	HH, F 15-24	Khutsong	771	53.3%	ELISA
Ndhlovu <i>et al</i> (2005)	2001	HH, F 15-59	Khutsong	878	71.0%	ELISA
Dangor <i>et al</i> (1989)	1986	GUD, M	Khutsong	240	3.3%	Culture (ulcers)
O'Farrell <i>et al</i> (1991a)	1988-9	GUD, M	Durban	100	10.0%	Culture (ulcers)
Ye <i>et al</i> (2007)	1990	GUD, M	Khutsong	213	3.8%	Culture (ulcers)
Chen <i>et al</i> (2000)	1993-4	GUD, M	Cape Town	180	23.9%	PCR (ulcers)
		GUD, M	Johannesburg	159	49.1%	
		GUD, M	Durban	199	36.2%	
Lai <i>et al</i> (2003)	1993	GUD, M	Khutsong	232	17.2%	PCR (ulcers)
Mathews <i>et al</i> (1998)	1995	GUD, M	Cape Town	40	12.5%	Culture (ulcers)
Lai <i>et al</i> (2003)	1998	GUD, M	Khutsong	186	36.0%	PCR (ulcers)
Kharsany <i>et al</i> (2000)	1998	GUD, M	Durban	400	41.0%	PCR (ulcers)
Moodley <i>et al</i> (2003a)	2000	GUD, M	Durban	438	47.9%	PCR (ulcers)
O'Farrell <i>et al</i> (2007b)	2004	GUD, M	Durban	165	52.7%	PCR (ulcers)
Muller <i>et al</i> (2007b)	2005-6	GUD, M	Gauteng	450	69.3%	PCR (ulcers)
Auvert <i>et al</i> (2001a)	1999	HH, M 15-24	Khutsong	718	17.0%	ELISA
Ndhlovu <i>et al</i> (2005)	2001	HH, M 15-59	Khutsong	532	42.0%	ELISA

ANC = antenatal clinic attenders. CSW = commercial sex workers. ELISA = enzyme linked immunosorbent assay. F = females. FPC = family planning clinic attenders. GUD = genital ulcer disease patients. HH = households. KZN = KwaZulu-Natal. M = males. PCR = polymerase chain reaction test. Prev. = prevalence.

Table C.9: Bacterial vaginosis prevalence estimates, based on Nugent scoring

Study	Year	Sample	Location	n	Prevalence
Hoosen <i>et al</i> (1996)	-	ANC	Durban	32	34.0%
Govender <i>et al</i> (1996)	1994-5	ANC	Durban	168	52.0%
Sturm <i>et al</i> (2003)	1995	ANC	Hlabisa	327	38.0%
	1999	ANC	Hlabisa	245	34.0%
	2002	ANC	Hlabisa	449	31.0%
Wilkinson <i>et al</i> (1997)	-	FPC	Hlabisa	189	15.0%
Fehler <i>et al</i> (1998)	-	FPC	Johannesburg	210	35.1%
Kleinschmidt <i>et al</i> (2007)	1999-2001	FPC	Orange Farm	532	35.9%
Frohlich <i>et al</i> (2003)	2002	FPC	Vulindlela	221	58.4%

ANC = antenatal clinic attenders. FPC = family planning clinic attenders.

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Appendix D: Sensitivity and specificity of STI diagnostic techniques

Table D.1 specifies the assumed sensitivity and specificity of the diagnostic techniques most commonly used for each STI, together with the assumed standard deviation of the sensitivity and specificity parameters when the tests are applied in different conditions by different investigators. In most cases the average sensitivity and specificity are calculated as the unweighted average of the estimates obtained from various studies, and the standard deviation is calculated from the sample variance of the same studies. In cases in which there are fewer than three estimates from which to calculate a sample variance, the standard deviation has been subjectively chosen to be similar to that of the same diagnostic used to detect a different STI, or to that of a related diagnostic used to detect the same STI. In the case of serological tests, estimates of sensitivity and specificity are usually published for males and females combined, and in these cases the same assumptions have been made for males and females. Studies have generally not been included if the 'gold standard' used to calculate the sensitivity and specificity parameters was judged to be insufficiently sensitive. A number of the assumptions are based on published reviews of sensitivity and specificity estimates (Cook *et al*, 2005; Orroth *et al*, 2003a; Wiese *et al*, 2000; Patel *et al*, 2000).

Table D.1: Assumed sensitivity and specificity of different diagnostics

STI	Diagnostic	Sex	Sensitivity		Specificity		Source
			Mean	SD	Mean	SD	
Syphilis	Non-treponemal + treponemal assays	M, F	0.956	0.02	1	0	Bruisten <i>et al</i> (2001) Risbud <i>et al</i> (1999) Behets <i>et al</i> (1999) Castro <i>et al</i> (2003)
	Non-treponemal assay	M, F	0.956	0.02	0.98	0.02	Castro <i>et al</i> (2003) Orle <i>et al</i> (1996) Morse <i>et al</i> (1997) Hooper <i>et al</i> (1994) West <i>et al</i> (2002)
Herpes	ELISA	M, F	0.95	0.03	0.951	0.037	Cusini <i>et al</i> (2000) Turner <i>et al</i> (2002) Eing <i>et al</i> (2002) Gopal <i>et al</i> (2000) Spiezia <i>et al</i> (1990)
	Western blot	M, F	0.914	0.03	1	0	Eing <i>et al</i> (2002) Spiezia <i>et al</i> (1990)
Gonorrhoea	Culture	F	0.742	0.193	0.998	0.005	Orroth <i>et al</i> (2003a)
	LCR on urine	M	0.921	0.029	1	0	van Doornum <i>et al</i> (2001) Buimer <i>et al</i> (1996)
	PCR on urine	F	0.838	0.191	1	0	Orroth <i>et al</i> (2003a)
		M	0.904	0.029	0.997	0.007	Cook <i>et al</i> (2005)
	PCR on swabs	F	0.556	0.202	0.987	0.018	Cook <i>et al</i> (2005)
		F	0.942	0.046	0.992	0.012	Cook <i>et al</i> (2005)
Chlamydial infection	Direct immunofluorescence	F	0.763	0.02	0.988	0.008	Thejls <i>et al</i> (1994) Mills <i>et al</i> (1992) Lefebvre <i>et al</i> (1988)
	LCR on urine	M	0.875	0.121	1	0	Orroth <i>et al</i> (2003a)
		F	0.866	0.121	1	0	Orroth <i>et al</i> (2003a)
	PCR on urine	F	0.833	0.139	0.995	0.007	Cook <i>et al</i> (2005)
	PCR on swabs	F	0.855	0.116	0.996	0.005	Cook <i>et al</i> (2005)

(Continued overleaf)

Table D.1 (continued)

STI	Diagnostic	Sex	Sensitivity		Specificity		Source
			Mean	SD	Mean	SD	
Tricho- moniasis	Wet mount	F	0.59	0.123	0.991	0.021	Wiese <i>et al</i> (2000)
	Culture	F	0.689	0.131	1	0	Wendel <i>et al</i> (2002)
							Mayta <i>et al</i> (2000)
							Madico <i>et al</i> (1998)
						Sturm <i>et al</i> (2004a)	
	PCR on swabs	F	0.95	0.05	0.98	0.024	Patel <i>et al</i> (2000)
	PCR on urine	M	0.95	0.05	0.98	0.024	-
Candidiasis	Culture	F	0.759	0.201	1	0	Bergman <i>et al</i> (1984)
							Giraldo <i>et al</i> (2000)
							Cibley <i>et al</i> (1998)
							Davies and Savage (1975)
							Sobel <i>et al</i> (1990)
	Microscopy	F	0.553	0.227	1	0	Darce-Bello <i>et al</i> (2002)
							Bergman <i>et al</i> (1984)
							Weissberg (1978)
							Sonnex and Lefort (1999)
							Eckert <i>et al</i> (1998)
					Ferris <i>et al</i> (1995)		
					Giraldo <i>et al</i> (2000)		

ELISA = enzyme-linked immunosorbent assay. LCR = ligase chain reaction. PCR = polymerase chain reaction. SD = standard deviation.

Appendix E: Effect of STIs on the detection of HIV in the genital tract

Table E.1 summarizes the results of the studies that estimate the effect of STIs on the detection of HIV in the reproductive tract. Meta-analysis was performed on the results of these studies, and the summary odd ratios are presented in section 5.1.2. The corresponding forest plots are shown in Figure E.1. A more detailed description of this meta-analysis has been published elsewhere (Johnson and Lewis 2008).

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Table E.1: Effects of genital tract infections on HIV-1 detection in the genital tract

Study	Location and period	Population	Study design	Study size	STI/symptom	Diagnosis	No. cases	OR (95% CI)	Measure of HIV shedding				
Clemetson <i>et al</i> (1993)	Nairobi, Kenya 1988-90	Women attending STI clinics	Cross-sectional	97	NG	Culture	6	4.3 (0.7-25.3) ^a	HIV DNA in cervical swabs				
					Cervicitis	≥2 PMNLs/HPF	16	1.6 (0.4-6.2) ^a					
					Cervical mucopus		10	6.2 (0.9-41.4) ^b					
													HIV DNA in vaginal swabs
					TV	Microscopy	15	0.8 (0.2-4.1) ^a					
					Candidiasis	Microscopy	17	0.7 (0.1-3.4) ^a					
								1.4 (0.13-15.8) ^a					
BV	Nugent criteria	50											
								0.5 (0.1-1.8) ^a					
Cohen <i>et al</i> (1997)	Lilongwe, Malawi 1996	Men attending dermatology and STI clinics	Case-control	135	Urethritis	≥5 WBCs/HPF + discharge	86	2.0 (0.7-5.5) ^a	Cell-free HIV-1 RNA in semen				
Cowan <i>et al</i> (2006)	Mashonaland West, Zimbabwe	HSV-2 sero-positive CSWs	Cross-sectional	124	HSV-2	Shedding (PCR)	29	0.8 (0.2-3.3) ^{c,d}	HIV-1 RNA in CVL or DNA in genital swabs				
Cu-Uvin <i>et al</i> (2006)	Providence, USA	Women	Cohort	97	TV	Microscopy	31	2.4 (0.5-11.3) ^{c,d}	HIV-1 RNA in CVL				
					Candidiasis	Culture + abnormal discharge	86	1.6 (0.6-4.1) ^{c,d}					
					BV	Amsel criteria	194	0.8 (0.4-1.6) ^{c,d}					
Cu-Uvin <i>et al</i> (2001)	Providence, USA	Women in HERS	Cohort	108	BV	Amsel criteria	12	5.9 (1.4-25.0) ^{c,d}	HIV-1 RNA in CVL				
					Candidiasis	Culture + abnormal discharge	19	1.0 (0.3-3.0) ^{c,d}					

Table E.1 (continued)

Study	Location and period	Population	Study design	Study size	STI/symptom	Diagnosis	No. cases	OR (95% CI)	Measure of HIV shedding
Cu-Uvin <i>et al</i> (2000)	Providence, USA	Women	Cross-sectional	205	BV	Amsel criteria	12	0.56 (0.06-2.79) ^a	HIV-1 RNA in CVL
Fiore <i>et al</i> (2003)	Bari, Italy 1995-2001	Asymptomatic women	Cross-sectional	122	Candidiasis	Culture	17	0.79 (0.25-2.52) ^a	Cell-free HIV-1 RNA in CVL
Ghys <i>et al</i> (1997)	Abidjan, Côte d'Ivoire 1994-5	CSWs	Cross-sectional	637	NG	Culture	194	1.9 (1.2-3.0) ^c	Cell-free HIV-1 RNA in CVL
					CT	EIA	27	2.5 (1.1-5.8) ^c	
					TV	Microscopy	194	0.9 (0.6-1.4) ^a	
					TP	RPR + TPHA	138	1.3 (0.8-2.0) ^a	
					GUD (CV)		52	3.9 (2.1-7.4) ^c	
					Cervical mucopus		122	2.3 (1.5-3.4) ^a	
					Vaginal discharge		368	1.0 (0.7-1.5) ^a	
Iversen <i>et al</i> (1998)	Copenhagen, Denmark	Women attending outpatient clinics	Cross-sectional	28	Candidiasis	Culture	11	3.9 (0.5-32.1) ^a 1.9 (0.3-13.4) ^a	HIV-1 DNA in vaginal swabs Cell-free HIV-1 RNA in vaginal swabs

Table E.1 (continued)

Study	Location and period	Population	Study design	Study size	STI/symptom	Diagnosis	No. cases	OR (95% CI)	Measure of HIV shedding	
John <i>et al</i> (1997)	Nairobi, Kenya	Pregnant women attending antenatal clinics	Cross-sectional	223	NG	Culture	14	2.2 (0.7-6.4) ^a	HIV-1 DNA in cervical swabs	
					CT	Microtrak/Clearview	17	1.2 (0.4-3.4) ^a		
					TP	RPR + TPHA	11	1.8 (0.5-6.2) ^a		
							Cervical discharge	65	2.1 (1.1-3.9) ^a	HIV-1 DNA in vaginal swabs
							BV	95	0.9 (0.3-2.7) ^a	
							Candidiasis	61	2.0 (0.8-5.2) ^a	
							TV	25	0.9 (0.3-2.7) ^a	
							Vaginal discharge	104	3.3 (1.1-9.4) ^a	
Kovacs <i>et al</i> (2001)	Five cities, USA 1997-8	Women in WIHS	Cross-sectional	311	Candidiasis	Culture	81	1.2 (0.5-2.9) ^d	HIV-1 RNA in CVL or endocervical swabs (PCR), or culture of HIV-1 in CVL/swabs	
						Microscopy	36	5.6 (0.7-45.7) ^d		
						TV	9	4.7 (0.6-37.9) ^a		
						BV	72	0.5 (0.2-1.6) ^d		
						HSV	9	0.2 (0.0-1.8) ^d		
							Shedding (culture)	29		3.1 (0.7-14.5) ^d
							Shedding (PCR)	29		3.1 (0.7-14.5) ^d
							Vaginal discharge	159		2.0 (0.4-9.6) ^d
		Cervical discharge	69	1.0 (0.4-2.7) ^d						
Kovacs <i>et al</i> (1999)	Three cities, USA 1994-5	Women in WIHS	Cross-sectional	56	BV	Amsel criteria	7	6.0 (0.4-217) ^{c,d}	HIV-1 RNA in CVL	

Table E.1 (continued)

Study	Location and period	Population	Study design	Study size	STI/symptom	Diagnosis	No. cases	OR (95% CI)	Measure of HIV shedding
Kreiss <i>et al</i> (1994)	Nairobi, Kenya 1986-90	CSWs	Cohort	92	NG	Culture	86	0.8 (0.4-1.6) ^a	HIV DNA in cervical swabs
					CT	Culture	6	1.4 (0.3-7.4) ^a	
					HD	Culture	4	0.1 (0.0-2.9) ^a	
					TP	RPR or VDRL	18	0.9 (0.3-2.7) ^a	
					Cervicitis	≥2 PMNLs/HPF	87	11.8 (1.5-96.6) ^a	
					GUD (cervical)		6	0.8 (0.2-4.6) ^a	
					Vaginal discharge		7	2.4 (0.5-10.5) ^a	
					Cervical mucopus		76	1.2 (0.6-2.5) ^a	
LeGoff <i>et al</i> (2007)	Bangui, CAR Kumasi & Accra, Ghana 2003-5	Women attending STI clinic with GUD	Cross-sectional	180	HSV-2	Shedding (PCR)	120	2.93 (1.47-5.88) ^a	Cell-free HIV-1 RNA in CVL
Mbopi-Kéou <i>et al</i> (2000)	Bangui, CAR	Women attending STI clinic	Cross-sectional	58	HSV-2	Shedding (PCR)	23	0.3 (0.1-1.3) ^a	Cell-free HIV-1 RNA in CVL
McClelland <i>et al</i> (2002)	Mombasa, Kenya 1996-9	Women starting hormonal contraception	Cross-sectional	200	HSV	Shedding (PCR)	42	1.04 (0.50-2.15) ^a	HIV-1 RNA in cervical swabs
								0.89 (0.42-1.88) ^a	HIV-1 DNA in cervical swabs

Table E.1 (continued)

Study	Location and period	Population	Study design	Study size	STI/symptom	Diagnosis	No. cases	OR (95% CI)	Measure of HIV shedding	
McClelland <i>et al</i> (2001)	Mombasa, Kenya 1996-9	Women attending STI clinic	Cohort	36	Cervicitis	≥30 PMNLs/HPF	13	2.8 (1.3-6.0) ^a	HIV-1 DNA in cervical swabs	
					NG	Culture	16	1.3 (0.4-4.0) ^a		
					CT	EIA	7	3.3 (0.7-14.9) ^a		
Moss <i>et al</i> (1995)	Nairobi, Kenya 1991	Men attending STI clinics	Cohort	106	NG	Culture/microscopy	71	3.2 (1.6-6.4) ^c	HIV DNA in urethral secretions	
					Urethritis	≥5 PMNLs/HPF	80	2.7 (1.3-5.3) ^c		
					NGU	Urethritis, no NG	9	0.2 (0.0-1.9) ^a		
					GUD		23	0.8 (0.3-2.2) ^a		
					TP	RPR + TPHA	6	2.1 (0.3-16.6) ^a		
Mostad <i>et al</i> (2000)	Mombasa, Kenya 1994-6	Women attending STI clinic	Cross-sectional	275	HSV	Shedding (PCR)	46	1.7 (0.8-3.4) ^a	HIV-1 DNA in cervical swabs	
Mostad <i>et al</i> (1997)	Mombasa, Kenya 1994-6	Women attending STI clinic	Cross-sectional	318	NG	Culture	24	3.1 (1.1-9.8) ^a	HIV-1 DNA in cervical swabs	
					CT	EIA	14	1.3 (0.4-4.6) ^a		
					Cervicitis	≥11 PMNLs/HPF	214	2.27 (1.39-3.71) ^a		
					Candidiasis	Microscopy	61	2.6 (1.2-5.4) ^a		HIV-1 DNA in vaginal swabs
					TV	Microscopy	37	0.5 (0.1-1.8) ^a		
Mostad <i>et al</i> (1998)	Mombasa, Kenya	Women attending STI clinic	Cohort	17	BV	Nugent criteria	≥12	0.8 (0.4-2.0) ^a	HIV-1 DNA in vaginal swabs	
					Candidiasis	Microscopy	≥8	0.6 (0.2-2.2) ^a		
					Cervicitis	>30 PMNLs/HPF	≥4	1.3 (0.5-3.6) ^a		HIV-1 DNA in cervical swabs

Table E.1 (continued)

Study	Location and period	Population	Study design	Study size	STI/symptom	Diagnosis	No. cases	OR (95% CI)	Measure of HIV shedding
Neely <i>et al</i> (2007)	Five cities, USA 2000-3	Women in WIHS on HAART	Cross-sectional	290	Candidiasis	Microscopy	28	1.2 (0.4-3.6) ^a	HIV-1 RNA in cervical swabs
					BV	Amsel criteria	59	0.7 (0.3-1.7) ^a	
					TV	Microscopy	11	1.3 (0.1-6.4) ^a	
Seck <i>et al</i> (2001)	Dakar, Senegal 1997	CSWs	Cross-sectional	207	GUD (CV)		62	2.2 (1.1-4.6) ^a	Cell-free HIV-1 RNA in CVL
					Vaginal discharge		149	2.2 (0.9-5.3) ^a	
Spinillo <i>et al</i> (2005)	Pavia, Italy 1999-2003	Women attending STI clinics (cases) or being screened for cervical cancer	Case-control	315	Candidiasis	Culture + vaginitis symptoms	66	1.74 (0.94-3.15) ^a	HIV-1 DNA in CVL HIV-1 RNA in CV swabs: Cell-free Cell-associated
								1.73 (0.89-3.25) ^a	
								1.76 (0.92-3.3) ^a	
Spinillo <i>et al</i> (2001b)	Pavia, Italy 1997-9	Women being screened for cervical cancer	Cross-sectional	122	Candidiasis	Culture	25	2.27 (0.75-6.86) ^d	HIV-1 DNA in CVL
					TV	Culture	10	1.13 (0.24-5.40) ^d	
					BV	Amsel criteria	31	2.47 (0.90-6.79) ^d	Cell-free HIV-1 RNA in CV swabs Cell-associated HIV-1 RNA in CV swabs
					Candidiasis	Culture	25	4.18 (1.29-13.56) ^d	
					TV	Culture	10	0.24 (0.02-2.73) ^d	
					BV	Amsel criteria	31	2.94 (1.00-8.7) ^d	
					Candidiasis	Culture	25	2.92 (0.93-9.16) ^d	
					TV	Culture	10	0.16 (0.02-1.74) ^d	
BV	Amsel criteria	31	3.58 (1.22-10.54) ^d						

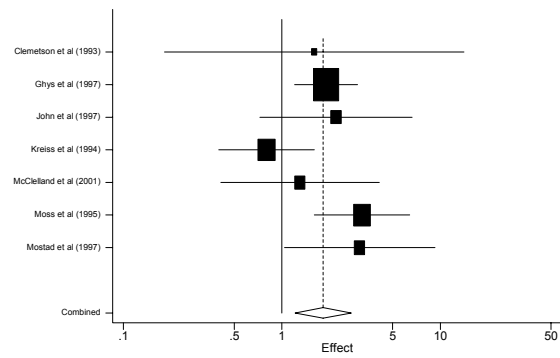
Table E.1 (continued)

Study	Location and period	Population	Study design	Study size	STI/symptom	Diagnosis	No. cases	OR (95% CI)	Measure of HIV shedding
Wang <i>et al</i> (2001)	Mombasa, Kenya 1996-9	Women attending family planning and STI clinics	Cohort	203	Candidiasis	Microscopy	98	2.8 (1.3-6.5) ^a	HIV-1 DNA in vaginal swabs
					TV	Culture/microscopy	67	0.8 (0.3-2.2) ^a	
					BV	Nugent criteria	77	0.8 (0.3-2.0) ^a	
Winter <i>et al</i> (1999)	Birmingham, UK	Asymptomatic men	Cross-sectional	94	Urethritis	≥5 PMNLs/HPF	7	80.2 (2.2-2097) ^{c,d}	Cell-free HIV-1 RNA in semen

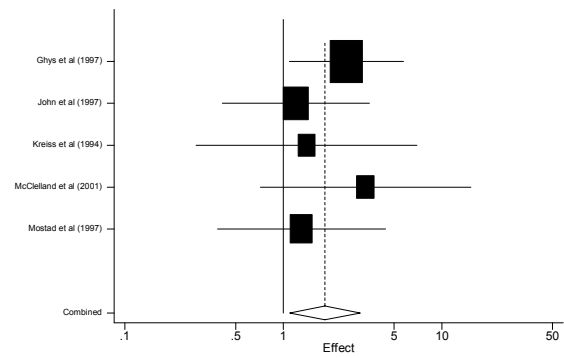
^a Univariate analysis. ^b Multivariate analysis. ^c Multivariate analysis controlling for CD4 count or %. ^d Multivariate analysis controlling for blood plasma viral load.

BV = bacterial vaginosis. CAR = Central African Republic. CSW = commercial sex worker. CT = *Chlamydia trachomatis*. CV = cervicovaginal. CVL = cervicovaginal lavage. EIA = enzyme immunoassay. GUD = genital ulcer disease. HAART = highly active antiretroviral therapy. HD = *Haemophilus ducreyi*. HERS = HIV Epidemiologic Research Study. HPF = high power field. HSV = herpes simplex virus. NG = *Neisseria gonorrhoeae*. NGU = non-gonococcal urethritis. PCR = polymerase chain reaction. PMNL = polymorphonuclear leukocyte. RPR = rapid plasma reagin. TP = *Treponema pallidum*. TPHA = *Treponema pallidum* haemagglutination assay. TV = *Trichomonas vaginalis*. VDRL = Venereal Disease Research Laboratory test. WBC = white blood cell. WIHS = Women's Interagency HIV Study.

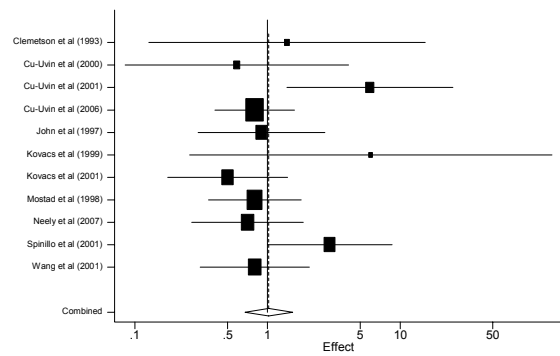
(a) Gonorrhoea



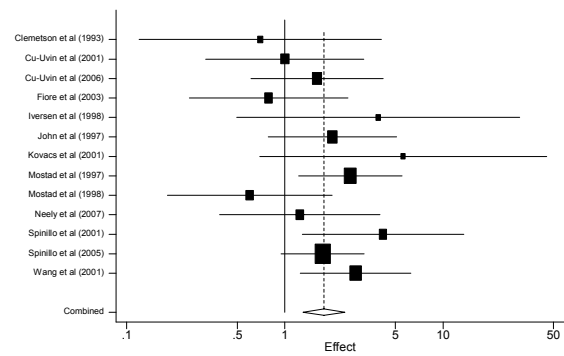
(b) Chlamydial infection



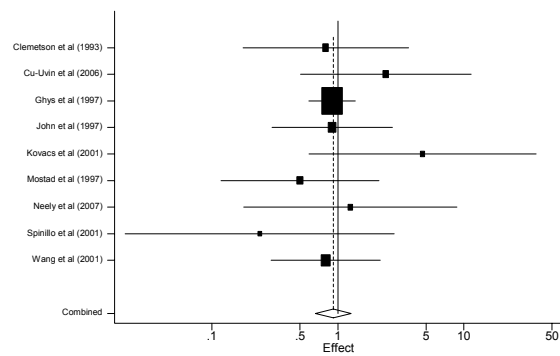
(c) Bacterial vaginosis



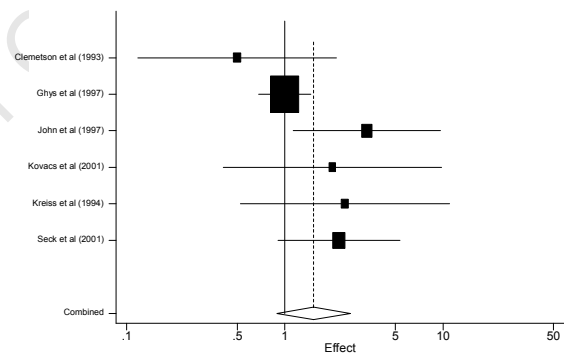
(d) Candidiasis



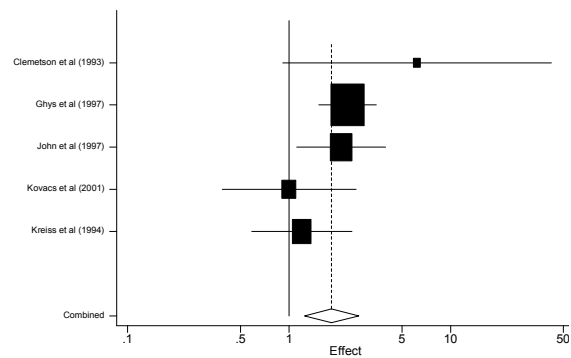
(e) Trichomoniasis



(f) Vaginal discharge



(g) Cervical discharge/mucopus



(h) Cervicitis

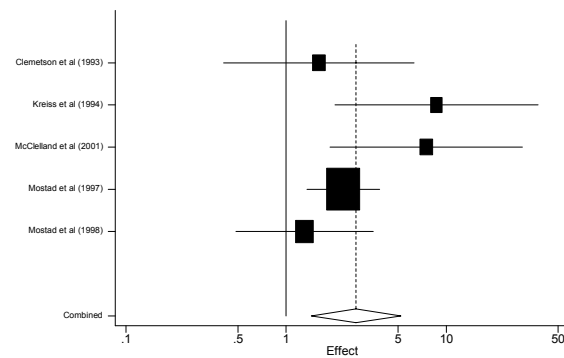


Figure E.1 (continued overleaf)

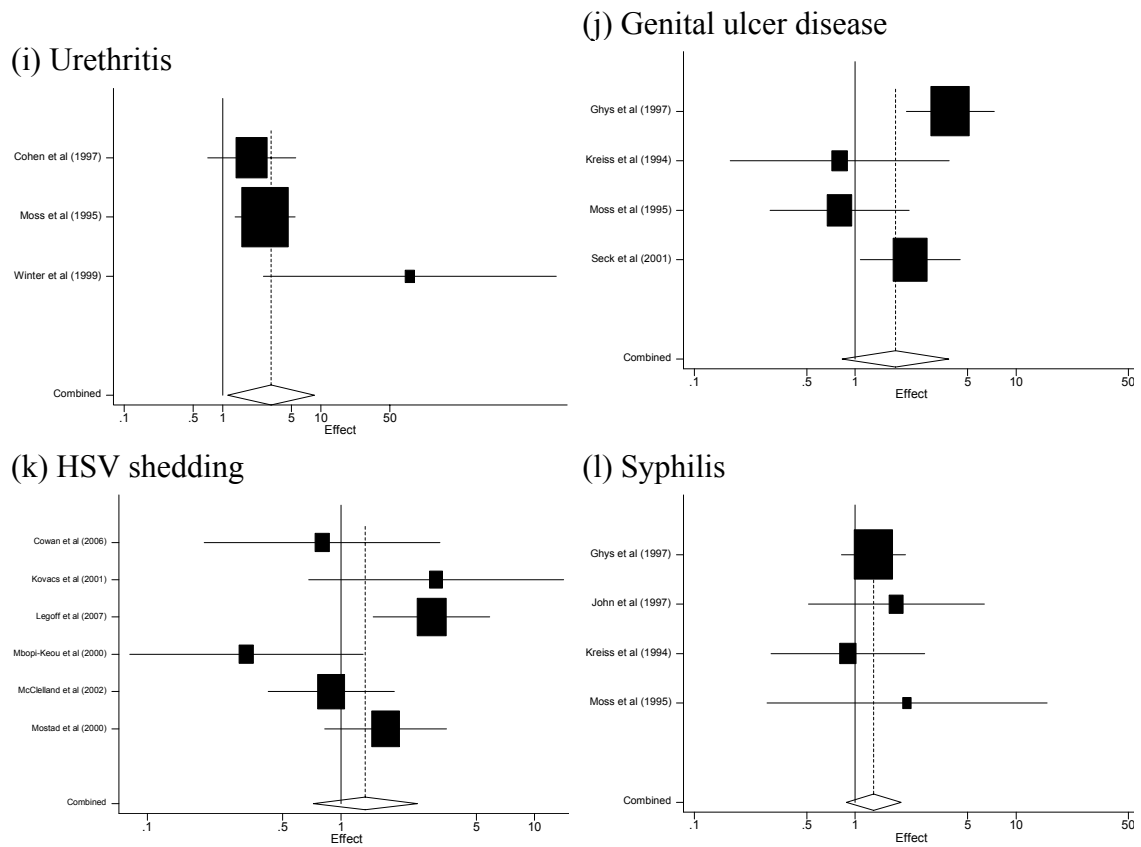


Figure E.1: Forest plots of effects of genital tract infections on the detection of HIV in the genital tract

Squares represent the results of individual studies, with the size of each square representing the weight given to the relevant study. Diamonds represent the combined odds ratios.