

THEMBISA version 1.0:
A model for evaluating the impact of HIV/AIDS in South Africa

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Abstract

This working paper provides a detailed technical description of the THEMBISA model, an integrated demographic and epidemiological model of the South African HIV/AIDS epidemic. The model stratifies the population by demographic characteristics (age and sex), behavioural characteristics (marital status, sexual experience, propensity for concurrent partnerships) and access to HIV prevention (HIV testing history, male circumcision status and receipt of microbicides and pre-exposure prophylaxis). In the HIV-positive population, individuals are further stratified according to their CD4 count, history of HIV diagnosis, receipt of ART and duration of treatment. The model simulates the change in population profile and the spread of HIV over time, starting in 1985. The model is fitted to age-specific HIV prevalence data and recorded death data, as well as self-reported HIV testing history data, using a Bayesian approach. Model results suggest that HIV incidence in South Africa has declined substantially since 2000, and that AIDS mortality rates have declined dramatically since 2005. However, results differ significantly from the two most widely-used HIV models in South Africa, the Spectrum/EPP and ASSA2008 models. Further work is required to refine the demographic parameters in the model and to apply the model to each of South Africa's provinces.

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1. Introduction

South Africa's HIV/AIDS epidemic is one of the most severe in the world. Many mathematical models have been developed to describe this epidemic and to evaluate strategies for its control. In the early phase of the epidemic, most modelling studies focused on trying to predict the future magnitude of the epidemic (Doyle and Millar 1990; Groeneveld and Padayachee 1992; Schall 1990; Lee *et al.* 1996). Other modelling studies focused on explaining variation in HIV prevalence within South Africa by province and population group (Dorrington 2000) and using HIV modelling to explain observed trends in mortality (Dorrington *et al.* 2001). In the last decade, most modelling studies have focused on evaluating the potential impact of HIV prevention and treatment programmes in South Africa. These include strategies such as medical male circumcision (Williams *et al.* 2006b; Verguet 2013; Bärnighausen *et al.* 2012a), pre-exposure prophylaxis (Abbas *et al.* 2013; Pretorius *et al.* 2010; Hallett *et al.* 2011), microbicides (Walensky *et al.* 2012; Williams *et al.* 2011), condom promotion/behaviour change (Nyabadza *et al.* 2011; Johnson *et al.* 2009b), treatment of STIs (Vickerman *et al.* 2006), prevention of mother-to-child transmission (Little *et al.* 2007; Soorapanth *et al.* 2006), vaccines (Hontelez *et al.* 2011; Amirfar *et al.* 2006; Andersson *et al.* 2011) and antiretroviral treatment (Eaton *et al.* 2012; Hontelez *et al.* 2013; Andrews *et al.* 2012; Bacaër *et al.* 2010; Wilson *et al.* 2006; Granich *et al.* 2012; Vijayaraghavan *et al.* 2007; Walensky *et al.* 2010). More recently, there has also been interest in using modelling to perform *ex-post* evaluations of the impact that has been achieved through programmes such as syndromic management for STIs (Johnson *et al.* 2012b) and antiretroviral treatment (April *et al.* 2013).

Although these models have provided important insights into the South African HIV epidemic, many of these models are limited in the range of questions that they can answer. For example, there have been few models that have comprehensively evaluated a broad range of prevention and treatment strategies (Cremin *et al.* 2013; Long and Stavert 2013), making it difficult for policymakers to assess the relative benefits and costs of different strategies. In addition, there have been few models that have integrated demographic and epidemiological modelling, though demographic outputs are important to policymakers when forecasting need for services, and age stratification is important in understanding the dynamics of HIV transmission. Relatively few models are publicly available, which is a problem for individuals needing tailored model outputs or wanting to consider scenarios different from those published.

Of the publicly-available models, the two most widely used in South Africa are the Spectrum/EPP model (Stover *et al.* 2012) and the Actuarial Society of South Africa (ASSA) AIDS and Demographic model (Actuarial Society of South Africa 2011). Both models have been regularly updated as new HIV prevalence data have been published and as scientific understanding of HIV has advanced. The Spectrum/EPP model is used in producing the UNAIDS estimates of the global distribution of HIV, and therefore has the advantage of benefitting from a substantial body of international expertise in HIV epidemiology. However, the separation of the modelling of HIV incidence and demographic impact in this model does limit the ability of the model to make use of age-specific data in model calibration, and the Spectrum model is also limited in its ability to evaluate the impact of HIV prevention strategies and make long-term projections.

The ASSA model has the advantage of being a fully-integrated demographic and epidemiological model, and the Excel interface of the publicly-available model is appealing to many non-modellers. However, several significant problems have emerged in recent years. The model assumes that antiretroviral treatment (ART) initiation can occur only at the time of the first AIDS-defining illness, though guidelines have changed in recent years to recommend ART initiation at earlier stages of disease, and there is increasing interest in early ART initiation as an HIV prevention strategy (World Health Organization 2013). The model also does not make allowance for a number of other new prevention strategies that are of interest, such as medical male circumcision, pre-exposure prophylaxis and WHO options B and B+ for prevention of mother-to-child transmission. The model is based on a clinical staging system for HIV disease, though a CD4 staging system would be more useful for the purpose of quantifying the unmet treatment need. There is also concern that the assumptions regarding sexual behaviour may be unrealistic, with more than half the sexually active population classified as “not at risk of infection” and no allowance for movement between risk groups over time. Lastly, the model allows for mother-to-child transmission only from those mothers who are HIV-positive in early pregnancy, and ignores the substantial transmission risk that occurs if the mother acquires HIV in late pregnancy or while breastfeeding – this can lead to the incidence of HIV in children being substantially under-estimated. In light of these limitations, the AIDS Committee of ASSA has issued a cautionary note regarding the most recently-released ASSA model, ASSA2008, noting that the recent estimates of AIDS mortality and mother-to-child transmission are problematic (Actuarial Society of South Africa 2012). The ASSA2008 model is based only on data published up to 2008, and the model therefore does not reflect new HIV prevalence and mortality data.

To some extent, these limitations have been addressed in recent modelling work by the University of Cape Town (UCT), independent of the ASSA model. For example, the STI-HIV Interaction model is based on a more realistic model of sexual behaviour, which is calibrated to marriage data and cross-sectional data on numbers of partners (Johnson *et al.* 2009b). The UCT Paediatric HIV model includes more detail in modelling the determinants of mother-to-child transmission, and considers most of the new strategies for preventing and treating paediatric HIV (Johnson *et al.* 2012d; Johnson *et al.* 2012a). The NSP ART Need model is based on a CD4 staging system and allows for ART initiation in earlier stages of HIV disease (Johnson 2012). However, these individual models do not provide an integrated framework for comprehensively evaluating the spread of HIV in South Africa and its demographic impact, or for evaluating the range of HIV prevention strategies currently being considered by policymakers.

There is thus a need for a new South African HIV model, which can fulfil the same functions as the ASSA model while overcoming its limitations. We aim to achieve this by integrating the key features of the four previously-described models (the ASSA model, the STI-HIV Interaction model, the UCT Paediatric HIV model and the NSP ART Need model) into a new model, called THEMBISA. In the Xhosa and Zulu languages of South Africa, this means ‘give hope’ or ‘promise’, which reflects the new sense of optimism regarding South Africa’s commitment to HIV prevention and treatment, following a history of controversial leadership.

The objective of this working paper is to provide a comprehensive description of the THEMBISA model assumptions and to present the basic model results up to 2012. Evaluations of intervention impact and projections of the likely future course of the South

African epidemic are beyond the scope of this working paper, but will be presented in future publications. For the sake of completeness, we include here a description of the model assumptions about pre-exposure prophylaxis, microbicides and early ART, even though these do not influence the model results up to 2012. It is anticipated that this paper will be regularly updated in future as the THEMBISA model is refined and improved, and readers are therefore encouraged to suggest improvements to the paper and the model it describes. The results presented are preliminary, to the extent that the demographic parameters still require some refinement. This will only be possible once the unit record data from the 2011 census have been published. This paper therefore focuses on the epidemiological estimates of the THEMBISA model, without providing any detail regarding demographic estimates.

2. Modelling sexual behaviour

The model of sexual behaviour is similar to that in the STI-HIV Interaction model (Johnson *et al.* 2009b), but with several modifications. Briefly, the population is divided into two broad risk groups: a ‘high risk’ group and a ‘low risk’ group. The high risk group is defined as all individuals who have a propensity to engage in concurrent sexual partnerships, while the low risk group consists of individuals who are serially monogamous (i.e. never having more than one partner at a point in time). Within each risk group individuals are further stratified according to whether they are sexually experienced or virgins, married/cohabiting or unmarried, and (if they are married) the risk group of their married partner. Unmarried women in the high risk group are further classified according to whether they are sex workers or not, and men in the high risk group are assumed to have contact with sex workers (individuals in the low risk group are assumed not to engage in commercial sex activity). There are thus three types of relationship considered in the model: long-term relationships (marital/cohabiting), short-term relationships (non-marital and non-cohabiting) and relationships between sex workers and their clients. The model makes various assumptions about the rates at which people move between different relationship states, and patterns of sexual mixing between different groups. Figure 2.1 illustrates the possible transitions for women in the high risk group (similar transitions are defined for women in the low risk group, but the sex worker state is omitted, and the states defined for males are the same as those defined for low risk females). The model in its current form does not consider same-sex relationships, as these are generally considered to account for only a small fraction of adult HIV transmission in the countries of southern Africa (Gouws and Cuchi 2012). The sections that follow describe the model structure and parameter values in more detail.

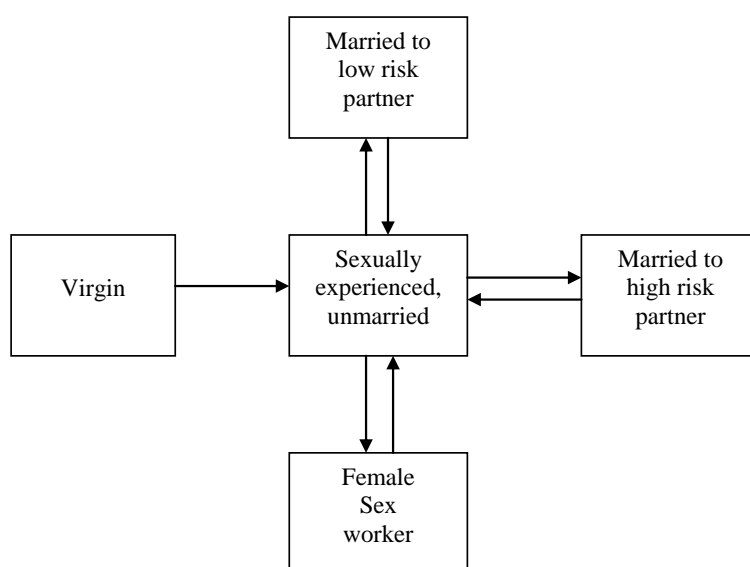


Figure 2.1: Transitions between relationship states

Transitions into and out of sex worker state are relevant only to high risk females.

2.1 Proportion of individuals in the high risk group

Table 2.1 summarizes results from different studies that have attempted to measure the prevalence of concurrency in South Africa. Results of different studies have produced widely different results, largely due to differences in the definition of concurrency, differences in the populations sampled and differences in the form of survey administration. Studies that have evaluated the proportion of adults who have *ever* engaged in concurrent partnerships have estimated proportions of 26% to 51% in women and 55% in men. Studies in individual communities have estimated the proportion of adults who have engaged in concurrent partnerships either during their most recent relationship or during the last 12 months to be between 6% and 33% in women and between 20% and 55% in men. However, these studies are not nationally representative. In a representative survey of youth in four provinces, the proportion who reported concurrent partnerships in the last 12 months was substantially lower: 3.1% in women and 6.8% in men (Seutlwadi *et al.* 2012). Similarly, when comparing studies that have estimated the point prevalence of concurrency, there is a notable difference between studies conducted nationally and studies in individual communities; the proportion of men reporting multiple current partners has been estimated at 21-37% in individual communities, compared to 6-16% in national surveys, and the proportion of women reporting multiple current partners has been estimated at 2-12% in community studies, compared to <2% in national surveys. This suggests that there may be a bias towards conducting studies in communities in which there are high levels of sexual risk behaviour. The high proportions of individuals who report having ever engaged in concurrent partnerships (26-51% in women and 55% in men) are therefore likely to be over-estimates of the proportion of the national population that ever engages in concurrent partnerships, since the data are collected from communities in which there are higher-than-normal levels of risk behaviour. With this bias in mind, we set the assumed high risk proportion (i.e. the proportion of the initial population with propensity for concurrent relationships) to be 35% in men and 25% in women, the same as that assumed in our previous model (Johnson *et al.* 2009b).

Table 2.1: Prevalence of concurrency in South African studies

Study	Year	Location	Sample	Definition of concurrency	% concurrent	
Tanser <i>et al</i> (2011)	2004	Rural KZN	Men aged 15-55	>1 current partner	23.2%	
			Men aged 15-55 ^a		28.9%	
Harrison <i>et al</i> (2008)	2001-2002	Rural KZN	Men aged 15-24	>1 current partner	37%	
			Women aged 15-24		1.5%	
Boulle <i>et al</i> (2008b)	2003-2004	Khayelitsha, WC	Men with current partner	Had sex with someone other than current partner in last 12 months	29%	
			Women with current partner		8%	
Mah <i>et al</i> (2010)	2005	Cape Town metropole, WC	Men aged 16-26 ^a	Had sex with someone other than main partner during most recent partnership	20.4%	
			Women aged 16-26 ^a		6.2%	
Nattrass <i>et al</i> (2012)		Cape Town metropole, WC	Men aged 20-29 ^b	Ever had sex with concurrent partner	54.7%	
			Women aged 20-29 ^b		25.7%	
Jewkes <i>et al</i> (2001)	1995	Cape Town, WC	Women aged <19	>1 current partner	4.8%	
Jewkes <i>et al</i> (2006)	2002-2003	Rural EC	Men aged 15-26 ^a	Had sex with concurrent partner in last 12 months	55.2%	
Jewkes <i>et al</i> (2002)	-	Soweto, Gauteng	Women at antenatal clinics	Had sex with someone other than current partner in last 12 months	24.4%	
				Ever had sex with concurrent partner	51.2%	
Dunkle <i>et al</i> (2004)	2001-2002	Soweto, Gauteng	Participants in Stepping Stones	Had sex with someone other than current partner in last 12 months	41.4%	
					Male	33.3%
					Female	39.6%
Auert <i>et al</i> (2001)	1999	Khutsong, Gauteng	Women at antenatal clinics	Ever had sex with concurrent partner	39.6%	
Seutlwadi <i>et al</i> (2012)	2011	KZN, EC, Gauteng, MP	Men aged 14-24	>1 current partner	21.4%	
			Men aged 14-24 ^a		29.2%	
Johnson <i>et al</i> (2009b)	2005	South Africa	Women aged 14-24	Had sex with concurrent partner in last 12 months	11.5%	
			Women aged 14-24 ^a		15.3%	
Fraser-Hurt <i>et al</i> (2011)	2009	South Africa	Men aged 18-24 ^a	>1 current partner	6.8%	
			Women aged 18-24 ^a		3.1%	
Fraser-Hurt <i>et al</i> (2011)	2009	South Africa	Men aged 15-59	>1 current partner	5.8%	
			Married		15.9%	
Fraser-Hurt <i>et al</i> (2011)	2009	South Africa	Unmarried	>1 current partner	0.4%	
			Women aged 15-59		1.9%	
Fraser-Hurt <i>et al</i> (2011)	2009	South Africa	Married	>1 current partner	0.4%	
			Unmarried		1.9%	
Fraser-Hurt <i>et al</i> (2011)	2009	South Africa	Men aged 16-55 ^b	>1 current partner	12.4%	
			Women aged 16-55 ^b		0.9%	

^a Analysis restricted to individuals who were sexually active. ^b Including only African respondents.

2.2 Rate of starting sexual activity

Table 2.2 summarizes estimates of the proportion of youth who are sexually active, by age, as reported in three different nationally-representative surveys: the 2002 HSRC household survey (Shisana *et al.* 2005), the 2006 National Communication Survey (Health and Development Africa 2007) and the 2009 National Communication Survey (Johnson *et al.* 2010). The average proportions reporting sexual experience, across the three surveys, are

similar in males and females, at most ages. However, it is recognized that young women tend to under-report their sexual experience in face-to-face interviews, while in young men there appears to be less reporting bias (Mensch *et al.* 2003; Hewett *et al.* 2004; Turner *et al.* 1998). The last column in Table 2.2 therefore shows the adjusted female estimates if it is assumed that the odds ratio of true sexual experience to reported sexual experience is 2 (Mensch *et al.* 2003).

Table 2.2: Proportion of South African youth who are sexually experienced, by age

Age	HSRC, 2005		NCS, 2006		NCS, 2009		Average		Adjusted female*
	M	F	M	F	M	F	M	F	
15	11.7%	7.9%	11.3%	8.5%	-	-	11.5%	8.2%	15.2%
16	17.0%	17.5%	22.2%	22.2%	17%	31%	18.7%	23.6%	38.1%
17	29.4%	45.2%	42.5%	38.9%	46%	41%	39.3%	41.7%	58.9%
18	52.0%	55.7%	57.5%	57.8%	57%	56%	55.5%	56.5%	72.2%
19	59.9%	61.7%	61.0%	67.3%	70%	76%	63.6%	68.3%	81.2%
20	74.8%	80.2%	82.5%	83.4%	78%	87%	78.4%	83.5%	91.0%
21	79.6%	88.2%	85.3%	89.8%	87%	86%	84.0%	88.0%	93.6%
22	84.9%	85.0%	87.2%	87.0%	92%	92%	88.0%	88.0%	93.6%
23	84.2%	90.6%	86.7%	90.8%	94%	88%	88.3%	89.8%	94.6%
24	83.5%	91.3%	93.0%	91.0%	94%	95%	90.2%	92.4%	96.1%

* Adjusted on the assumption that the odds ratio relating true sexual experience to reported average sexual experience is 2.

In modelling sexual debut, it is assumed that the youngest age at which sexual activity can begin is age 10, and that the time to starting sexual activity after age 10 is Weibull-distributed. Separate Weibull parameters are specified for males and females, and for the high and low risk groups, with these parameters being set with reference to the average rates of sexual experience shown in Table 2.2 (after adjustment in the case of females). For the high risk group, the median age at the start of sexual activity is assumed to be 17.5 in males and 16.5 in females, and the corresponding shape parameters are 3.5 and 4 respectively. Following our previous modelling work (Johnson *et al.* 2009b), we assume that at each age the rate of starting sexual activity in the low risk group is half of that in the high risk group. These assumptions yield estimates of the proportion sexually experienced at each age roughly consistent with the survey data summarized in Table 2.2, as demonstrated in Figure 2.2.

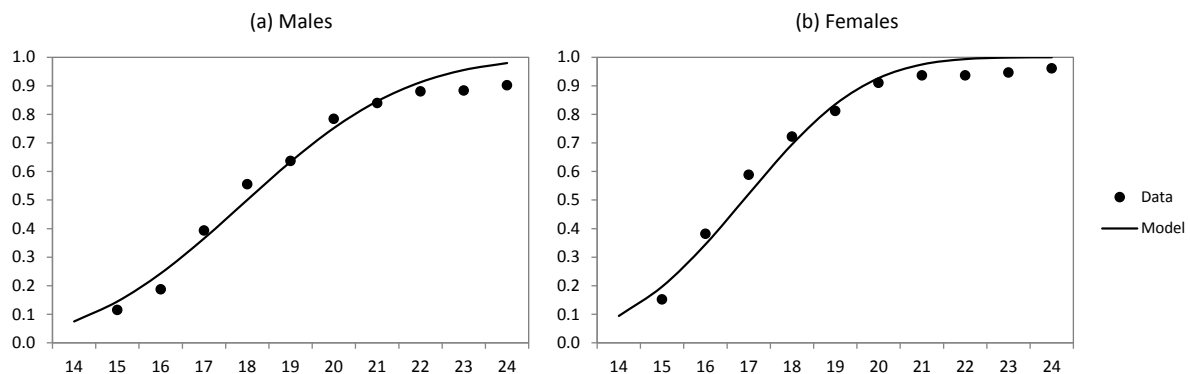


Figure 2.2: Proportion of youth sexually experienced, by age and sex

Data in panel (b) have been adjusted to reflect probable under-reporting of sexual experience by young women.

2.3 Rates at which non-marital partnerships are formed

In setting the assumed rates of non-marital partnership formation, we follow a five-step process: (1) we specify the rate of non-marital partnership formation in unmarried ‘high risk’ women who are aged 20; (2) we specify a gamma function that determines the relative rates of non-marital partnership formation that apply at all other ages; (3) we specify rates of non-marital partnership formation in the ‘low risk’ group as a fraction of those in the high risk group; (4) we specify rates of non-marital partnership formation in married individuals, as a fraction of those in unmarried individuals; and (5) we derive rates of non-marital partnership formation in men from the assumptions made for women.

In the case of the first parameter, the rate of non-marital partnership formation in unmarried ‘high risk’ women who are aged 20, we rely on our previous model estimates (Johnson *et al.* 2009b). The model was fitted to reported numbers of current sexual partners in the 2005 national HSRC household survey (Shisana *et al.* 2005), allowing for social desirability bias in the reporting of numbers of partners, and reconciling male-female differences in reported total numbers of non-marital partnerships. The model was also fitted to age-specific HIV prevalence data from antenatal and household surveys to ensure that the modelled patterns of sexual behaviour by age and sex generated levels of HIV prevalence consistent with those observed in surveys. Based on the parameters fitted in this model, we estimate that unmarried women aged 20 in the high risk group acquire an average of 3.3 new partners per annum (95% CI: 2.8-3.5). The parameter has therefore been fixed at the value of 3.3.

Having specified the partnership formation rates at age 20, our next step is to specify a gamma function that determines the relative rates of non-marital partnership formation that apply at all other ages. In an analysis of partnership formation rates in the 2009 National Communication Survey (Fraser-Hurt *et al.* 2011), a regression model was fitted to determine relative rates of partnership formation in different five-year age groups, expressed relative to rates of partnership formation in the 20-24 age group. The relative rates that were estimated for women (shown in Figure 2.3) suggest that rates of partnership formation are highest in the 20-29 age group, and drop to very low levels at ages 45 and older. A key strength of this analysis is that it controls for marital status, and thus represents the effect of age independent of marital status (which is appropriate to the parameterization of our model, given that the model also assumes separate effects of age and marital status). However, a limitation of this analysis is that women are included in the calculation of the rate of partnership formation even if they are not yet sexually experienced (Emma Slaymaker, personal communication). This may lead to some under-estimation of the rate at which sexually experienced women form new partnerships, particularly in the 15-19 age group.

In modelling the effect of age, we define $c_{g,i,l}(x)$ to be the annual rate of non-marital partnership formation in individuals aged x , of sex g and marital status l , who are in risk group i . The female rates of partnership formation at different ages are modelled using a scaled gamma density of the form

$$c_{2,i,l}(x) = c_{2,i,l}(20) \frac{\lambda^\alpha (x-10)^{\alpha-1} \exp(-\lambda(x-10))}{\lambda^\alpha 10^{\alpha-1} \exp(-10\lambda)}, \quad (2.1)$$

where the λ and α parameters determine the mean and variance of the gamma distribution, and the offset of 10 years is included to prevent sexual activity below age 10. (As noted previously, the $c_{2,i,l}(20)$ value is 3.3 for women in the high risk group ($i = 1$) who are unmarried ($l = 0$.) Setting the mean and standard deviation of the distribution to 29 years and 10 years respectively gives estimates of relative rates of partnership formation consistent with the National Communication Survey data, as shown in Figure 2.3. However, since the assumed number of sex acts per non-marital relationship is the same at all ages, the λ and α parameters also determine the relative frequency of sex in unmarried women at different ages. The *actual* relative frequencies of sex at different ages will differ from the relative rates of partnership formation if in fact the number of sex acts per non-marital relationship is not the same at all ages. It is likely that the number of sex acts per relationship is lower at younger ages than at older ages. For example, Pettifor *et al* (2005a) compared 15-19 year old and 20-24 year old South Africans in terms of both coital frequency and average relationship duration, and found both to be substantially higher among 20-24 year olds. This suggests that some upward adjustment should be made to the mean and standard deviation parameters considered previously (29 and 10 years respectively) in order to obtain realistic estimates of relative frequencies of sex at different ages. To account for uncertainty in these parameters, we assign gamma priors to both the mean and standard deviation of the scaled gamma density function in equation (2.1). The prior for the mean has a mean of 35 years and a standard deviation of 5 years, while the prior for the standard deviation has a mean of 13 years and a standard deviation of 3 years. These priors were chosen to reflect fairly wide ranges of uncertainty around the effect of age on coital frequencies in unmarried women.

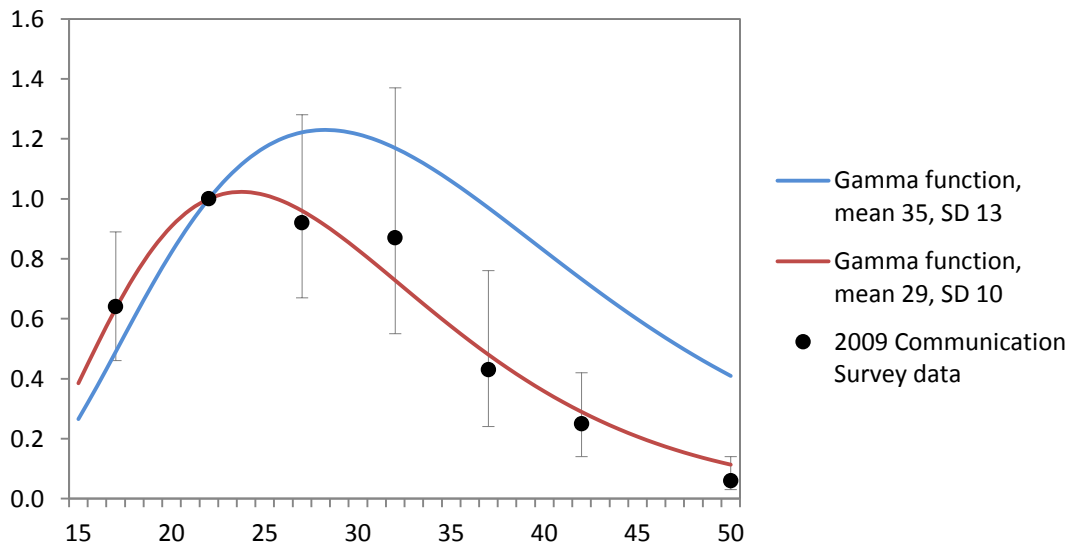


Figure 2.3: Relative rates of short-term partnership formation at different ages
Rates of partnership formation are expressed as multiples of the average rate of partnership formation in the 20-24 age group.

The third step in modelling rates of partnership formation is to specify relative rates of partnership formation in low risk individuals, i.e. $L_g \equiv c_{g,2,0}(x)/c_{g,1,0}(x)$ (the risk group index i is coded 1 for the high risk group and 2 for the low risk group). Because the low risk group is defined to consist of individuals who do not engage in concurrent partnerships, it might be expected that the rate of partnership formation would be lower in the low risk group

than in the high risk group. Due to the lack of data, we assign a vague prior to the relative rate of partnership formation in the low risk group, which is uniform on the interval $[0, 1]$. It should be noted that this relative rate of partnership formation only applies to unmarried individuals, since married low risk individuals would by definition not engage in concurrent partnerships. It should also be noted that separate parameters control the relative rates of partnership formation in the low risk group for males ($g = 1$) and females ($g = 2$), but the relative rates are assumed to be independent of age (x).

The fourth step in modelling rates of non-marital partnership formation is to specify relative rates of partnership formation in high risk married individuals, compared to high risk unmarried individuals, i.e. $R_g \equiv c_{g,1,1}(x)/c_{g,1,0}(x)$ (the marital status index l is coded 1 for married individuals and 0 for unmarried individuals). As before, we lack data to determine this parameter, although Mah *et al* (2010) found that in the Cape Town area, married individuals were significantly less likely to report having engaged in a concurrent relationship during their most recent partnership than unmarried individuals (aOR 0.19, 95% CI: 0.08-0.49). We have therefore fixed the parameters at the posterior means estimated in a previous analysis of the STI-HIV Interaction model, viz. 0.33 for males and 0.14 for females (Johnson *et al.* 2012c).

The final step is to determine the rates of non-marital partnership formation in high risk unmarried men, by age, as a function of (a) the female rates of non-marital partnership formation, (b) female partner age preferences (discussed in section 2.7 below), and (c) the assumed relative rates of partnership formation in low risk males and high risk married males. Mathematical details are provided in Appendix A. It is worth noting here that for the sake of simplicity, we are deriving male rates of non-marital partnership formation from the rates assumed for females. An alternative approach that is commonly used is to specify assumed rates of partnership formation separately for males and females and to apply some ‘balancing factor’ to ensure that the adjusted male and female demand for sex are equal (Garnett and Bowden 2000; Turner *et al.* 2004). Although this balancing factor approach has the advantage of allowing for gender differences in the ability to initiate relationships, it is also more computationally intensive.

2.4 Marriage, divorce and widowhood

As is conventional in demographic analysis, the model defines individuals as ‘married’ if they are legally married or living together with their main partner. Rates of marriage and divorce, by age and sex, are assumed to be the same as those assumed in previous modelling work (Johnson *et al.* 2009b), based on proportions of the population reporting that they are married or living with their main partner, in the 1996 and 2001 censuses and 2007 Community Survey. In our previous model, rates were specified over five-year age groups, rather than at individual ages. In order to obtain a smooth progression of age-specific rates, we use Beer’s ‘ordinary’ formula (Judson and Popoff 2004) to calculate rates of marriage and divorce at each individual age. (Although Beer’s formula is normally applied to population counts rather than event rates, the cumulative hazard function over a particular five-year age group can be regarded as a count.) Further details regarding the modelling of divorce and widowhood are included in section A.5 of Appendix A.

The model does not allow explicitly for polygyny, as studies have found that polygyny is relatively uncommon in South Africa. For example, Tanser *et al* (2011) found that in rural KwaZulu-Natal only 3% of women reported being in a polygynous union. The model also does not allow for changes in rates of marriage over time, although there is evidence of a significant trend towards later marriage in recent decades (Garenne 2004; Hosegood *et al.* 2009).

2.5 Commercial sex

As in our previous work (Johnson *et al.* 2009b), we define sex workers to be individuals who earn all or most of their income by having sex in exchange for money. This definition excludes transactional sex and also excludes so-called ‘indirect sex workers’ (individuals who occasionally have sex for money, but do not regard themselves as sex workers) (Vandepitte *et al.* 2006). The model also considers only female sex workers, though male and transgender sex workers are estimated to comprise approximately 8-9% of sex workers in South Africa (Richter *et al.* 2013; Sex Worker Education and Advocacy Taskforce 2013a).

Although a few South African studies have reported rates at which miners and military recruits visit sex workers (Ijsselmuiden *et al.* 1990; Williams *et al.* 2000a; Van der Ryst *et al.* 2001), only one national survey has estimated the rate at which men in the general population visit sex workers. In this survey, conducted by the HSRC in 2008, only 0.4% of men aged 15 and older reported having had sex with a sex worker in the last year (Fraser-Hurt *et al.* 2011). This is almost certainly an under-estimate, as it is well recognized that men tend to under-report sex worker contact in face-to-face interviews (Des Jarlais *et al.* 1999; Morison *et al.* 2001). In other southern African surveys, the proportion of men reporting sex with a sex worker in the last 12 months has been between 1.6% and 13.2% (Caraël *et al.* 2006).

In light of the substantial uncertainty regarding the accuracy of male self-reported data, it is perhaps more appropriate to work backwards from estimated numbers of sex workers in South Africa and their reported frequencies of client contact, to determine what these imply about rates of male contact with sex workers. To date there has been only one national study that has aimed to estimate the number of sex workers in South Africa, in 2012 (Sex Worker Education and Advocacy Taskforce 2013b). In this study, attempts were made to estimate the number of sex workers in 12 different South African centres, and these results were extrapolated to the rest of the country, based on the demographic characteristics of each centre. In each centre, a convenience sample of known sex worker ‘hotspots’ was drawn, and at each hotspot key informants were asked for estimates of numbers of sex workers operating in the relevant hotspot. Estimates were then extrapolated to unsampled hotspots. Although the authors argue that there could be some under-estimation due to unknown hotspots, there could also be over-estimation, as the convenience sample was drawn based on which sites were busiest and easiest to visit. This potential for over-estimation is evident in Cape Town, for example, where the study team estimated a total of 5 000 sex workers, in contrast to a previous study that estimated only 1 200 sex workers (Gould and Fick 2008). In the 8 centres with populations of more than 200 000, the estimated number of sex workers, expressed as a percentage of the number of woman aged 15-64, varied between 0.17% in East London and 0.38% in Cape Town, with an average of 0.26%. In the 4 smaller centres, sex worker prevalence was more variable, ranging between 0.13% in Thohoyandou and 2.4% in Pongola on the South Africa-Swaziland border. It is difficult to extrapolate from this limited sample of

smaller sites, as the survey team sampled disproportionately from towns on major trucking routes and at international border posts. The study team therefore relied on a previous review of sex worker prevalence levels in other African countries (Vandepitte *et al.* 2006), in extrapolating from the sampled centres to other South African centres. Based on this approach, the authors estimated that there were roughly 153 000 sex workers in South Africa. However, the review of Vandepitte *et al.* is likely to overestimate the proportion of women who are sex workers (according to our model definition) in South Africa, as many of the studies included in the review used very broad definitions of commercial sex that included transactional sex or indirect sex work. This is evident in the low median numbers of clients per week reported by sex workers in these studies, for example, 1 in Kisumu, 2 in Yaoundé, 3 in Ndola and 7 in Cotonou (Morison *et al.* 2001), in contrast to the medians of 12-24 clients per week in South African studies (Richter *et al.* 2013; Dunkle *et al.* 2005). We therefore consider the estimate of 153 000 sex workers to be a probable upper bound on the true number of sex workers.

Little is known regarding the age distribution of male clients of sex workers in South Africa. In a study of 310 truck drivers who were clients of sex workers, Ramjee and Gouws (2002) found the average age to be 37 years (standard deviation 9 years). In another small study of 20 men visiting sex workers in a large mining town, it was reported that most of the men were aged 25 to 35 (Jochelson *et al.* 1991). Interviews with sex workers and brothel owners in Cape Town suggest that most clients are “between 35 and 80” (Gould and Fick 2008).

There is also little local data on the effect of marital status on the rate at which men visit sex workers. However, in the 2001 Zambian Demographic and Health Survey, the proportion of men reporting having paid for sex in the last 12 months was 6.7% and 29.3% in married and unmarried men respectively (Leclerc and Garenne 2008). This suggests that the rate of sex worker contact in married men is only about a quarter of that in unmarried men.

In our model of male contact with sex workers, we assume that HIV-negative, sexually experienced men in the high risk group visit sex workers at annual rate $w_l(x)$, which depends on their age (x) and marital status (l). It is assumed that the rate of visiting sex workers is reduced by a factor of 0.25 in men who are married ($l = 1$) and that the effect of age is determined by a gamma scaling function with parameters λ_1 and α_1 . The formula used to determine the rate of male contact with sex workers is thus

$$\begin{aligned} w_l(x) &= K \frac{\lambda_1^{\alpha_1} (x-10)^{\alpha_1-1} \exp(-\lambda_1(x-10))}{\lambda_1^{\alpha_1} (21.5-10)^{\alpha_1-1} \exp(-\lambda_1(21.5-10))} 0.25^l \\ &= K \times \left(\frac{x-10}{11.5} \right)^{\alpha_1-1} \exp(-\lambda_1(x-21.5)) \times 0.25^l, \end{aligned}$$

where K is a constant scaling factor, corresponding to the rate at which unmarried men aged 21.5 visit sex workers. (The offset of 10 is applied to age x to prevent boys below age 10 from having contact with sex workers, and the age of 21.5 was chosen previously because it corresponded to the average age of male military recruits who were asked about their rate of contact with sex workers (Van der Ryst *et al.* 2001).) The parameters λ_1 and α_1 are set at 0.37 and 11.1 respectively. With these parameters, the model simulates a client age distribution in 1995 that has a mean of 35.0 years and a standard deviation of 7.9 years. This

is roughly consistent with observed client age distributions in the early stages of South Africa's HIV epidemic.

If we set the value of K to 7, the model simulates sufficient male demand for commercial sex to match the roughly 153 000 sex workers estimated to be working in South Africa in 2012, given the model assumptions about sex workers' frequencies of client contact (discussed below). However, as discussed previously, we consider the estimate of 153 000 a likely upper bound, and have therefore set parameter K to 3.5. Figure 2.4 shows the simulated age-specific rates of male contact with sex workers for unmarried men in the high risk group, at different values of K . It is worth noting here that although the frequencies of male contact with sex workers are low in young men (<25), the modelled rates are substantially higher at older ages.

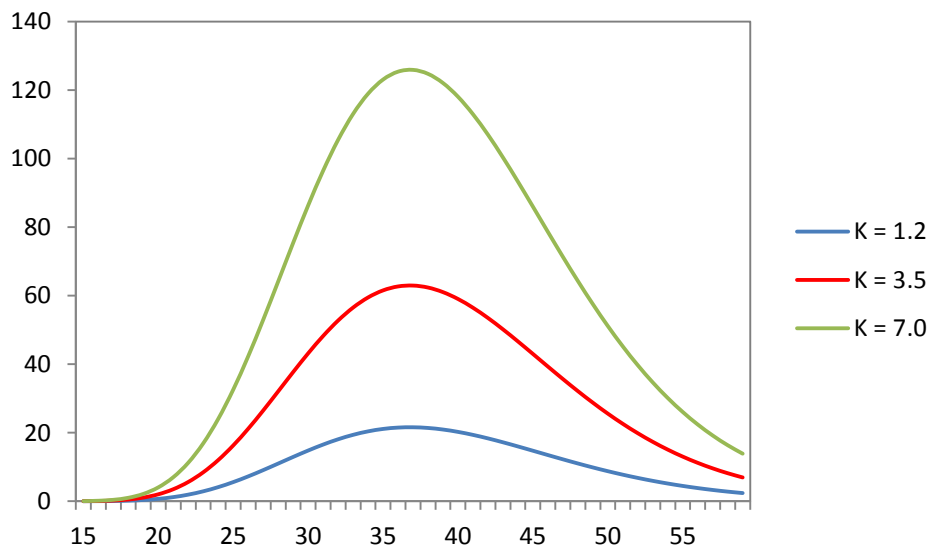


Figure 2.4: Annual rates at which unmarried high risk males visit sex workers, by age

In order to determine the rates at which women enter commercial sex, we assume a constant age distribution of sex workers. This age distribution is estimated from data collected in various South African surveys of sex workers, summarized in Table 2.3. The weighted average of the sex worker ages reported in these studies is 29.2 years, and many of these studies provide additional information on proportions of women in each 5-year age group. Based on these data, we assume that sex worker ages are gamma-distributed, with a mean of 29 years and a standard deviation of 9 years. The modelled proportions of sex workers who are younger than age 18 and older than 25 are 5% and 63% respectively, consistent with the age distribution in a national sex worker survey conducted in 2012 (3% and 62% respectively) (Sex Worker Education and Advocacy Taskforce 2013a).

Sex workers are assumed to leave commercial sex at a rate of 0.33 per annum, so that the average duration of commercial sex work is 3 years. This is consistent with South African sex workers' reports of their average times spent active as sex workers: 2.1 years in 295 sex workers in Johannesburg (Dunkle *et al.* 2005), 3.0 years in 145 sex workers at truck stops between Durban and Gauteng (Ramjee *et al.* 1998), and 5.7 years in 70 sex workers in Tzaneen and Phalaborwa (Peltzer *et al.* 2004).

Table 2.3: Female sex worker age distributions

Study	Location	Year	n	Mean age
Rees <i>et al</i> (2000)	Johannesburg	1996-8	247	24
Williams <i>et al</i> (2000a)	Carletonville	1998	121	32.5
Luseno & Wechsberg (2009)	Pretoria	2004-7	425	28.0
Peltzer <i>et al</i> (2004)	Tzaneen, Phalaborwa		70	26.6
Ramjee <i>et al</i> (1998)	KwaZulu- Natal	1996	145	25
Van Loggerenberg <i>et al</i> (2008)	Durban	2004	775	31.3
Varga <i>et al</i> (2001)	Durban		100	25.5
Richter <i>et al</i> (2013)	Sandton, Hillbrow, Cape Town, Rustenburg	2010	1653	29.7
Delva <i>et al</i> (2011)	-	2010	210	28.6
Gould and Fick (2008)	Cape Town	2006-7	118	29
Weighted average				29.2

Sex workers are assumed to have an average of 750 contacts with clients per annum. The majority of South African studies have suggested that average numbers of client contacts per week are between 19 and 25 (Varga 1997; Abdool Karim *et al.* 1995; Ramjee *et al.* 1998; Dunkle *et al.* 2005; Gould and Fick 2008), but other studies suggest lower frequencies in women who only engage in commercial sex for a few days each week (Peltzer *et al.* 2004; van Loggerenberg *et al.* 2008) and sex workers who advertise online (Delva *et al.* 2011). The assumption of 750 contacts per annum (equivalent to about 15 clients per week) is a compromise that takes into account that some women engage in commercial sex intermittently, and that ‘regular’ sex workers will occasionally take holidays from sex work.

The numbers of women who are recruited into commercial sex in each period are assumed to be just sufficient to meet the male demand for commercial sex. The number entering at each age is calculated to be such that the same age distribution of commercial sex workers is maintained over time. It is assumed, in the interests of simplicity, that sex workers are recruited only from unmarried women in the high risk group, though evidence suggests that as many as 30% of sex workers may in fact be married or in cohabiting relationships (Luseno and Wechsberg 2009; Peltzer *et al.* 2004). Further details regarding the modelling of movements into and out of sex work are included in section A.4 of Appendix A.

2.6 Preferences regarding partner risk group

Mixing between the high and low risk groups is determined by a ‘degree of assortative mixing’ parameter, ϵ . This parameter takes on values between 0 and 1, 0 implying completely assortative sexual mixing (i.e. individuals only choose sexual partners from their own risk group), and 1 implying random sexual mixing (i.e. individuals have no preferences regarding the risk group of their partners and choose partners in proportion to their availability). The formulas used to calculate mixing between risk groups are presented in Appendix A.

As noted in our previous modelling work (Johnson *et al.* 2009b), this parameter is difficult to determine based on empirical data, and we have therefore fixed this parameter at a value of 0.47, the posterior mean estimated in a previous analysis of the STI-HIV Interaction model (Johnson *et al.* 2012c). This parameter determines proportions of women choosing their partners from different risk groups. The proportions of men who choose their partners from different risk groups are calculated to be consistent with these.

2.7 Preferences regarding partner age

Studies conducted in Africa suggest that age preferences differ according to the type of relationship, with young women reporting greater age differences between themselves and their spouses than between themselves and their non-spousal partners. For example, Clark (2004) found that married adolescent females in Kenya and Zambia reported a significantly greater average age difference than did unmarried adolescent females, by 4.5 years. Nnko *et al.* (2004) also found that in Tanzanian adolescents the average age difference between married women and their spouses (7.0 years) was greater than that between women and their non-marital partners (5.3 years). It is therefore important to set the assumptions about partner age distributions separately for different relationship types.

In South Africa, the chief source of data on age preferences in marital unions is the 1998 DHS. Table 2.4 shows the average ages of spouses (and standard deviations), for married women in different age groups. Average age differences are around 6 years in young women, with smaller age differences at older ages. The large age differences at young ages are roughly consistent with the mean age differences of 6 to 9 years, in marital relationships, which have been measured in other southern and eastern African DHSs (Wellings *et al.* 2006). The somewhat lower age differences between older married women and their partners are likely to reflect higher mortality in older men.

Table 2.4: Distribution of spouse ages, for women in each age band

	Age of married women						
	15-19	20-24	25-29	30-34	35-39	40-44	45-49
Average age of male spouse	24.31	28.84	32.95	37.63	42.69	47.04	51.45
Average age difference*	6.81	6.34	5.45	5.13	5.19	4.54	3.95
Standard deviation of married partner ages	4.45	5.17	7.14	7.55	8.53	8.27	7.59

Source: 1998 DHS (extracted by Ria Laubscher, Medical Research Council)

* Crude approximation, based on subtracting midpoint of female age interval from average partner age.

Consistent with studies elsewhere in Africa, South African data show that young women report smaller age differences between themselves and their non-marital partners than between themselves and their husbands. Williams *et al.* (2000a) fitted linear functions relating male and female ages in casual relationships, among youth in Carletonville. The function fitted to the data predicts that the average age of a male partner, for a woman aged 18 in a casual relationship, is 20.9 years – an age difference of only three years. Other South African surveys do not distinguish between marital and non-marital partners when asking questions about ages of partners, but do nevertheless suggest that at young ages overall age preferences are very different from those represented in Table 2.4 (probably because in South Africa, relatively few young women are married). For example, only 18 to 28% of sexually

experienced female adolescents report having partners more than four years older than themselves (Shisana *et al.* 2005; Shisana *et al.* 2009; Kelly 2000), and fewer than 6% report having partners 10 or more years senior (Kelly 2000; Reproductive Health Research Unit 2004). In a household survey conducted in KwaZulu-Natal, the median age difference between female youth (aged 14 to 24) and their male partners was three years (Hallman 2004), similar to the age difference observed by Williams *et al* among young women in casual relationships.

In our model, the symbol $f_{g,l}(y | x)$ represents the probability that for an individual of sex g and age x , in a relationship of type l , the partner's age is y . We model female age preferences regarding married partner ages using a gamma distribution. Based on the data in Table 2.4, we assume that if there were equal numbers of sexually-experienced men at each age, the distribution of spousal partner ages, for women aged x , would be gamma distributed with a mean of $(x + 6)$ and a standard deviation of 5. The standard deviation of 5 is less than that shown in Table 2.4 for most ages, but this is because the estimates from the DHS are based on combining women of different ages, which leads to exaggeration of the variance when considering women of a single age. We also introduce a minimum partner age (which is $\min(x) = 17 + (x - 17)/2$ for $x \geq 17$), so that the origin of the gamma distribution is at this minimum age and not at zero, in order to prevent unrealistically low married male ages. Expressed mathematically, the probability that a married woman aged x has a husband between the ages of y and $y + 1$ is

$$\int_y^{y+1} \frac{\lambda_2(x)^{\alpha_2(x)} (t - \min(x))^{\alpha_2(x)-1} \exp(-\lambda_2(x)(t - \min(x)))}{\Gamma(\alpha_2(x))} dt,$$

where $\lambda_2(x)$ and $\alpha_2(x)$ are the parameters of the gamma distribution, calculated from the mean, variance and minimum age. This formula is modified to take into account that there might not be equal numbers of sexually experienced men at all ages, i.e. women's preferred male partner age distribution may be modified if the actual numbers of men available at older ages are less than at younger ages. Suppose that over the male age range $[x, x + 10)$, the average rate of decline in the number of men available is $\xi(x)$ per year of increase in age, and assume that this rate of decline is constant over the age range from which women aged x are likely to select their partners. Then the modified probability that a married woman aged x has a husband between the ages of y and $y + 1$ is

$$\frac{\int_y^{y+1} \frac{\lambda_2(x)^{\alpha_2(x)} (t - \min(x))^{\alpha_2(x)-1} \exp(-\lambda_2(x)(t - \min(x))) \exp(-\xi(x)(t - \min(x)))}{\Gamma(\alpha_2(x))} dt}{\int_0^{\infty} \frac{\lambda_2(x)^{\alpha_2(x)} (t - \min(x))^{\alpha_2(x)-1} \exp(-\lambda_2(x)(t - \min(x))) \exp(-\xi(x)(t - \min(x)))}{\Gamma(\alpha_2(x))} dt},$$

which simplifies to

$$f_{2,1}(y | x) \equiv \int_y^{y+1} \frac{(\lambda_2(x) + \xi(x))^{\alpha_2(x)} (t - \min(x))^{\alpha_2(x)-1}}{\Gamma(\alpha_2(x)) \exp((\lambda_2(x) + \xi(x))(t - \min(x)))} dt,$$

i.e. the same gamma distribution but with $(\lambda_2(x) + \xi(x))$ in place of $\lambda_2(x)$. The $\xi(x)$ values are calculated from the simulated male population age distribution in each year. Because there are generally declining numbers of men at older ages ($\xi(x) > 0$), this modified gamma distribution has a lower mean than is implied by the assumed age difference of 6 years, and this modified mean is more consistent with the mean partner ages for older women in Table 2.4.

A similar approach is adopted when modelling women's preferences regarding the ages of their non-spousal partners. The means of the gamma distributions for non-spousal partnerships are assumed to be equal to the women's age plus 3 years, consistent with the average age difference of 3 years noted previously. The standard deviation of the gamma distribution for non-spousal ages is assumed also to be 3 years, and the same standard deviation is assumed at all female ages. This yields estimates of fractions of male partners aged ≥ 5 years older and ≥ 10 years older within the ranges of 18-28% and $< 6\%$ noted previously. The adjustment for the number of available men at each age is similar to that performed in respect of marital relationships, except that the calculation of $\xi(x)$ is based on all men (not just sexually experienced men), and the rate of decline is calculated over the range $[x, x + 5)$, reflecting the slightly younger distribution of non-spousal partner ages.

Proportions of men who choose their partners from different ages ($f_{1,l}(y|x)$) are calculated to be consistent with the distributions specified for women, taking into account the relative rates of partnership formation at different ages, and relative numbers of men and women at different ages. Further mathematical detail is provided in Appendix A.

2.8 Coital frequencies

The average number of sex acts per non-spousal relationship is assumed to be 18. This is based on previous modelling work, in which we assumed that (a) the average frequency of sex was 3 acts per month in non-spousal relationships (Johnson *et al.* 2009b), based on data collected in South African surveys (Kelly 2000; Shisana *et al.* 2005); and (b) the average duration of non-spousal relationships is 6 months. In spousal relationships, the frequency of sex is assumed to vary in relation to individuals' age and sex. For married women who are aged 20, the average number of spousal sex acts per month is assumed to be 5, and this number is assumed to halve for each 20-year increase in age (Johnson *et al.* 2009b). Coital frequencies in married men are calculated to be consistent with these assumptions, based on the assumed patterns of age mixing described previously.

2.9 Condom usage

The method used to model condom usage is similar to that in the STI-HIV Interaction model, with some modifications to the method described previously (Johnson *et al.* 2012c). Rates of condom use are assumed to depend on age, sex, type of relationship and (as described in section 2.11 below) knowledge of HIV-positive status. Rates of condom usage are also assumed to increase over time, but the model also allows for a potential reduction in condom use in recent years. This time-dependency represents the effect of HIV communication

programmes and condom promotion campaigns, which were introduced in the 1990s and early 2000s, but which have since seen a decline in funding (Scalway 2010). The time dependency could also potentially reflect reduced concern about HIV since the rollout of ART (Shafer *et al.* 2011; Cohen *et al.* 2009; de Walque *et al.* 2012). The parameter $\gamma_{2,l}(x,t)$ represents the probability that an HIV-negative woman aged x uses a condom in an act of sex with a partner of type l at time t . This parameter is calculated in relation to an arbitrary ‘baseline’ rate of condom usage, γ^* , which is the probability of condom use for a woman aged 20 in a short-term relationship in 1998. The following formula is used to calculate $\gamma_{2,l}(x,t)$:

$$\ln\left(\frac{\gamma_{2,l}(x,t)}{1-\gamma_{2,l}(x,t)}\right) = \ln\left(\frac{\gamma^*}{1-\gamma^*}\right) + \chi_l + \nu_l(x-20) + \left[\kappa_l^1 + (\kappa_l^2 - \kappa_l^1) \left(1 - 0.5^{(t/M_l^1)^{Q_l}}\right) - (\kappa_l^2 - \kappa_l^3) \left(1 - 0.5^{(t/M_l^2)^{2Q_l}}\right) \right] \quad (2.2)$$

where

$\exp(\chi_l)$ = the odds of using a condom in relationship type l , relative to that in short-term relationships ($l = 0$), in 1998;

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

$\exp(\kappa_l^1)$ = the initial odds of using a condom in relationship type l , in 1985 (before the onset of behaviour change), relative to the odds in 1998;

$\exp(\kappa_l^2)$ = the maximum odds of using a condom in relationship type l , once behaviour change is at its maximum, relative to the odds in 1998;

$\exp(\kappa_l^3)$ = the ultimate odds of using a condom in relationship type l , after reductions in condom promotion and/or risk compensation, relative to the odds in 1998;

M_l^1 = 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 maximum levels (in years since 1985);

M_l^2 = the median time to reversal of behaviour change in relationships of type l , i.e. the time at which the log odds of condom use is half-way between its maximum and ultimate levels (in years since 1985);

Q_l = the Weibull shape parameter controlling the speed of behaviour change in relationships of type l .

The logistic transformation prevents rates of condom use greater than 100%, and facilitates a ‘logistic regression’ interpretation of the condom parameters. The term in square brackets represents the difference in condom usage (on a logit scale) between year t and 1998. Figure 2.5 illustrates the interpretation of the κ_l and M_l parameters.

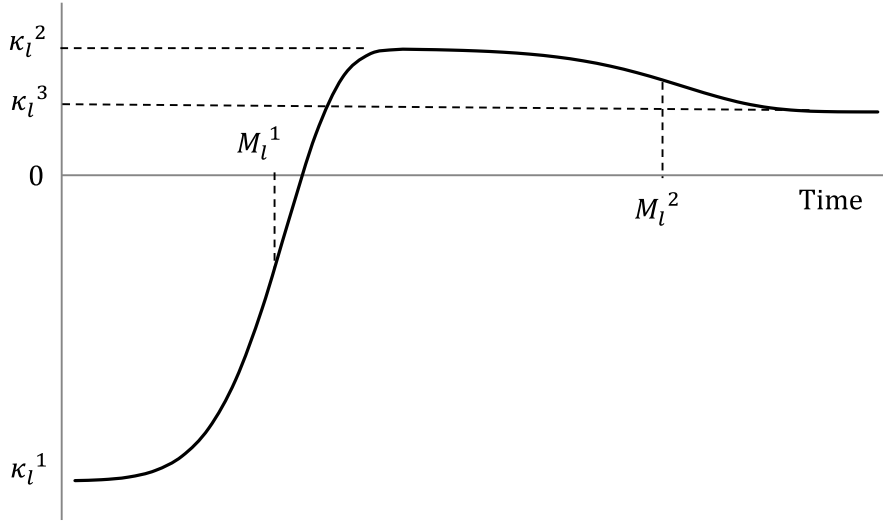


Figure 2.5: Ratio of the odds of condom use in year t to that in 1998 (y axis on log scale), for HIV-negative females

In women who have been diagnosed HIV-positive and are ART-naïve, the probability of condom use is assumed to be

$$\gamma_{2,t}^+(x,t) = 1 - (1 - \gamma_{2,t}(x,t))(1 - \delta),$$

where δ is the reduction in unprotected sex following HIV diagnosis (see further discussion in section 2.11).

For all relationship types, the median parameter M_l^1 is calculated by noting that the ‘baseline’ parameters relate to 1998, and hence when $t = 13$ (i.e. in 1998)

$$\kappa_l^1 + (\kappa_l^2 - \kappa_l^1) \left(1 - 0.5^{(t/M_l^1)^{Q_l}} \right) - (\kappa_l^2 - \kappa_l^3) \left(1 - 0.5^{(t/M_l^2)^{2Q_l}} \right) = 0.$$

This equation is solved to determine M_l^1 as a function of the remaining parameters:

$$M_l^1 = 13 \left\{ \left(\ln \left[\kappa_l^3 + (\kappa_l^2 - \kappa_l^3) 0.5^{(13/M_l^2)^{2Q_l}} \right] - \ln(\kappa_l^2 - \kappa_l^1) \right) / \ln(0.5) \right\}^{-1/Q_l}$$

Based on logistic regression models fitted to data on condom usage in the 1998 and 2003 South African DHSs (Department of Health 1999; Department of Health 2004), it is assumed that the age parameter ν_l is -0.025 for both spousal and non-spousal relationships, and that the odds of condom usage in spousal relationships relative to that in non-spousal relationships ($\exp(\chi_l)$) is 0.46 in 1998. The proportion of African women reporting condom usage for contraceptive purposes was found to be 0.13% in the 1987-89 DHS (Kaufman 1996), compared to 1.8% in the 1998 DHS, and on the basis of this information, the ratio of the

initial odds of condom use to that in 1998 ($\exp(\kappa_1^1)$) is assumed to be 0.07 for both spousal and non-spousal relationships. Taking into account the slight reduction in reported condom use in recent surveys (Shisana *et al.* 2013; Johnson *et al.* 2010), we have set $\kappa_1^3 = 0.5 \times \kappa_1^2$ and have set $M_1^2 = 26$ (corresponding to 2011), for both spousal and non-spousal relationships. Although these assumptions are to some extent arbitrary, we later show (Figure 2.6, panels a and b) that this leads to results reasonably consistent with reported trends in condom use.

In interactions between sex workers and their clients, levels of condom usage were around 60% in 1998 (Rees *et al.* 2000; Williams *et al.* 2000a), compared with levels of around 20% in women aged 15-19 in the 1998 DHS. Based on this evidence, it is assumed that in 1998 the ratio of the odds of condom use in sex worker–client interactions to that in non-spousal relationships ($\exp(\chi_2)$) was 6.0. In the absence of information regarding age differences in condom use by sex workers, no age effect is assumed ($\nu_3 = 0$). A study conducted in 1988 found that condom usage was reported by only about 20% of sex workers and their clients (Jochelson *et al.* 1991), and the odds ratio for condom use in 1985, relative to that in 1998 ($\exp(\kappa_2^1)$), is therefore set at 0.17. For sex workers, there is little evidence of any reduction in condom use in recent years (Richter *et al.* 2013; Sex Worker Education and Advocacy Taskforce 2013a), and the parameter $\exp(\kappa_2^3)$ has therefore been set to $\exp(\kappa_2^2)$.

The remaining parameters - γ^* , κ_0^2 , κ_1^2 , κ_2^2 , Q_0 , Q_1 and Q_2 - have been set separately for two scenarios: a scenario in which women are assumed to report accurately on their levels of condom use, and a scenario in which women are assumed to overstate their levels of condom use substantially. A condom reporting bias parameter, θ , is used to interpolate linearly between the parameter values in these two scenarios, with $\theta = 0$ corresponding to the scenario in which there is no bias and $\theta = 1$ corresponding to the scenario in which there is substantial over-reporting of condom use. The assumed parameter values for the two scenarios are summarized in Table 2.5, and the modelled trends in condom use for different values of θ are shown in Figure 2.6 below. Parameters in the ‘no bias’ scenario were chosen so that the modelled proportions of women using condoms were reasonably consistent with proportions of women in the general population reporting having used a condom the last time they had sex (Department of Health 1999; Human Sciences Research Council 2002; Reproductive Health Research Unit 2004; Shisana *et al.* 2005; Shisana *et al.* 2009; Shisana *et al.* 2013; Johnson *et al.* 2010; Johnson *et al.* 2014; Health and Development Africa 2007). Parameters in the ‘high bias’ scenario were chosen so that the modelled proportions of women reporting condoms were consistent with proportions of sexually active women who reported using condoms for contraceptive purposes in the Demographic and Health Surveys (on the assumption that these would be less affected by social desirability bias and would represent a minimum on the true rate of condom use). In the case of sex workers, only two nationally representative surveys have measured condom use at last sex (Richter *et al.* 2013; Sex Worker Education and Advocacy Taskforce 2013a), and we have therefore relied also on smaller local studies that are not nationally representative, both for estimates of condom use at last sex (Jochelson *et al.* 1991; Peltzer *et al.* 2004) and for proportions of sex workers using condoms for contraceptive purposes (Abdool Karim *et al.* 1995; van Loggerenberg *et al.* 2012).

Table 2.5: Differences in condom usage parameters between scenarios

Parameter	Symbol	No bias scenario ($\theta = 0$)	High bias scenario ($\theta = 1$)
Probability of condom use in women aged 15-19, in short-term relationships, in 1998	γ^*	0.20	0.08
Maximum odds of condom use in short-term relationships, relative to the odds of condom use in 1998	$\exp(\kappa_0^2)$	15	2
Maximum odds of condom use in long-term relationships, relative to the odds of condom use in 1998	$\exp(\kappa_1^2)$	6	1.2
Maximum odds of condom use in sex worker-client contacts, relative to the odds of condom use in 1998	$\exp(\kappa_2^2)$	7	3
Shape parameter controlling the speed of behaviour change in short-term relationships	Q_0	2.8	3.8
Shape parameter controlling the speed of behaviour change in long-term relationships	Q_1	1.8	3.6
Shape parameter controlling the speed of behaviour change in sex worker-client contacts	Q_2	3	4

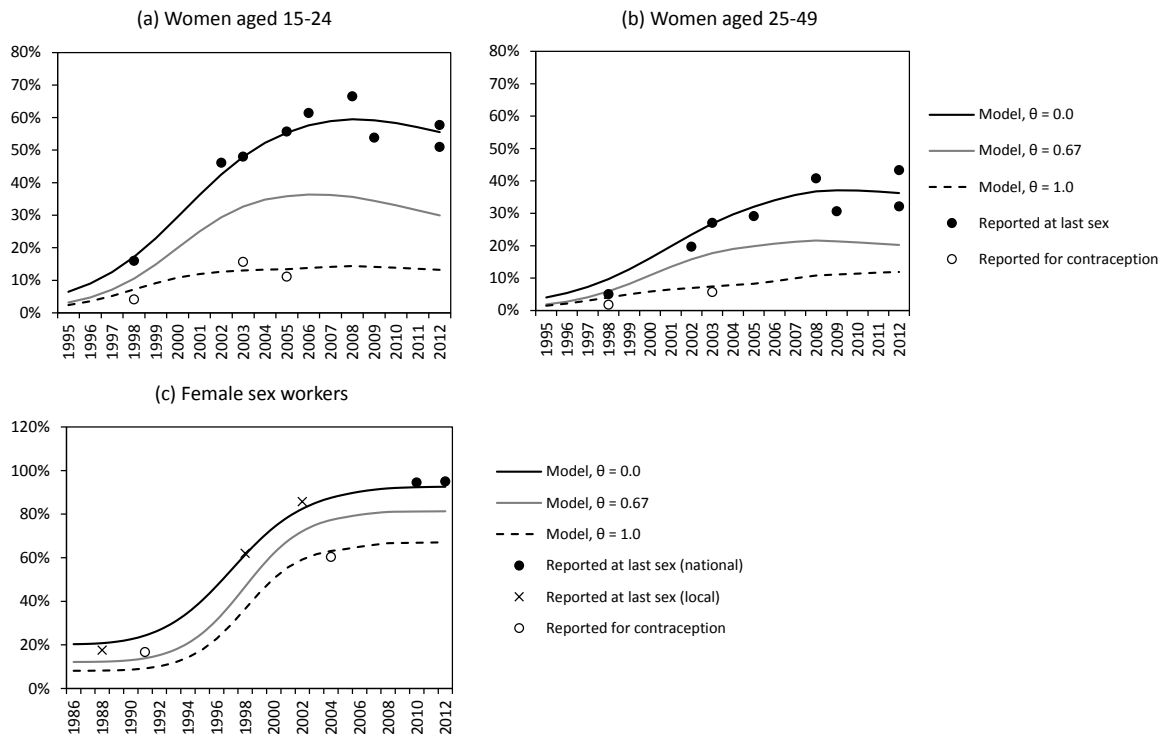


Figure 2.6: Calibration of model of condom use to reported condom use data

The ‘condom bias’ parameter (θ) has been set at a value of 0.8, the same as the mean estimated in a previous analysis of the STI-HIV Interaction model (Johnson *et al.* 2012c).

To ensure that male and female assumptions are consistent, the probability that an HIV-negative male uses a condom in a short-term or long-term relationship is calculated as

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

where $f_{1,l}(y|x)$ is the probability that a female partner is aged y , if the male partner 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.

2.10 The effect of CD4 count on level of sexual activity

Several studies have suggested that the frequency of unprotected sex may be lower in individuals with reduced CD4 counts, possibly as a result of poorer health. The precise mechanisms underlying this association are unclear, and may differ between settings; some studies suggest that individuals with low CD4 counts are less likely to be in sexual relationships (Hankins *et al.* 1998; Greenblatt *et al.* 1999), while other studies suggest that even after controlling for whether or not individuals are sexually active, coital frequency is reduced at low CD4 counts (McClelland *et al.* 2006b). Table 2.6 summarizes the evidence from various studies that have assessed the frequency of unprotected sex at different CD4 levels. As there are very few studies that have evaluated this directly, we have included African studies that evaluated the incidence of pregnancy by CD4 level, as this is a crude approximation to the effect of CD4 count on the frequency of unprotected sex. It should be noted, however, that HIV and low CD4 count are significantly associated with pregnancy loss (Brocklehurst and French 1998; Ross *et al.* 2004), and differences in the incidence of pregnancy by CD4 count may therefore exaggerate the differences in the frequency of unprotected sex by CD4 count. Table 2.6 also includes studies that have assessed the effect of CD4 count on being sexually active, and CD4 effects measured in these studies may understate the effect of CD4 count on the frequency of unprotected sex because these studies do not measure the effects of CD4 count on the frequency of sex and the level of condom use in those individuals who are sexually active. With two exceptions (Myer *et al.* 2010; McGrath *et al.* 2013), all of the studies relate to women's sexual behaviour in the pre-HAART era, and there is thus limited information to assess whether the effect of CD4 count is different in men and treated patients. The study of Myer *et al.* (2010) included data from both pre-HAART women and women receiving HAART, but did not find the effect of CD4 count to be significantly different in the two groups. The study of McGrath *et al.* (2013) found that reductions in coital frequencies, in individuals who were in partnerships, were similar for males and females. In all of the studies, women were aware of their HIV status, and the CD4 effects shown in Table 2.6 therefore reflect the effects of CD4 count on the frequency of unprotected sex, independent of knowledge of HIV status.

Table 2.6: Relative frequencies of sexual activity, at different CD4 levels

Study	Location	Measure of sexual activity	HIV/CD4 category	RR/OR (95% CI)
Hankins <i>et al</i> (1998)	11 cities in Canada	Any sex in last 6 months	CD4 \geq 500	1
			CD4 200-499	0.69 (0.45-1.05) ^a
			CD4 <200	0.43 (0.28-0.67) ^a
Greenblatt <i>et al</i> (1999)	6 centres across USA	Any sex partners in last 6 months	CD4 \geq 500	1
			CD4 200-499	0.97 (0.76-1.23) ^a
			CD4 <200	0.59 (0.47-0.77) ^a
Sedgh <i>et al</i> (2005)	Dar es Salaam, Tanzania	Incidence of pregnancy	CD4 >500	1
			CD4 250-500	1.06 (0.79-1.43) ^b
			CD4 <250	0.54 (0.36-0.81) ^b
Loko <i>et al</i> (2005)	Abidjan, Côte d'Ivoire	Incidence of pregnancy	CD4 \geq 500	1
			CD4 350-499	1.02 (0.63-1.66) ^b
			CD4 200-349	0.55 (0.31-0.98) ^b
			CD4 <200	0.41 (0.20-0.85) ^b
Myer <i>et al</i> (2010)	6 African countries	Incidence of pregnancy	CD4 \geq 500	1
			CD4 350-499	0.83 (0.67-1.02) ^b
			CD4 200-349	0.68 (0.44-1.05) ^b
			CD4 <200	0.68 (0.41-1.14) ^b
McClelland <i>et al</i> (2006b)	Mombasa, Kenya	Any unprotected sex in last week	Uninfected	1
			CD4 \geq 500	0.93 (0.62-1.39) ^b
			CD4 200-499	0.58 (0.41-0.82) ^b
			CD4 <200	0.45 (0.25-0.82) ^b
McGrath <i>et al</i> (2013)	Hlabisa, South Africa	Any sex in last month	CD4 >500	1
			CD4 <200	0.49 (0.31-0.76) ^b

^a Univariate analysis. ^b Multivariate analysis.

In our model, it is assumed that the frequency of sex in undiagnosed HIV-positive adults with CD4 counts \geq 500/ μ l is the same as would be expected in HIV-negative adults with the same characteristics. After controlling for whether or not HIV status is known and whether individuals are receiving ART, the frequency of unprotected sex is assumed to be reduced by 8% in individuals with CD4 counts of 350-499/ μ l, by 24% in individuals with CD4 counts of 200-349/ μ l, and by 45% in individuals with CD4 counts of <200/ μ l (relative to individuals with CD4 counts of \geq 500/ μ l in all cases). These assumptions are based on the data presented in Table 2.6; the 45% reduction at CD4 <200/ μ l is the result obtained from a random effects meta-analysis of the RRs and ORs presented in this CD4 category. A similar meta-analysis applied to the data in the CD4 200-499/ μ l category yielded an average reduction of 16%, which is the average of the reductions that we have assumed for the CD4 350-499/ μ l and 200-349/ μ l categories. Figure 2.7 below shows that the assumed relative frequencies of unprotected sex in the different CD4 categories all lie within the 95% confidence intervals around the empirical estimates obtained from Table 2.6. The assumed relative frequencies are also consistent with those in a Ugandan cohort, which included both treated and untreated individuals (Shafer *et al.* 2011); relative to individuals with CD4 >500, the frequency of sex was reduced by 10% in those with CD4 351-500, by 16% in those with CD4 201-350 and by 40% in those with CD4 of 200 or less.

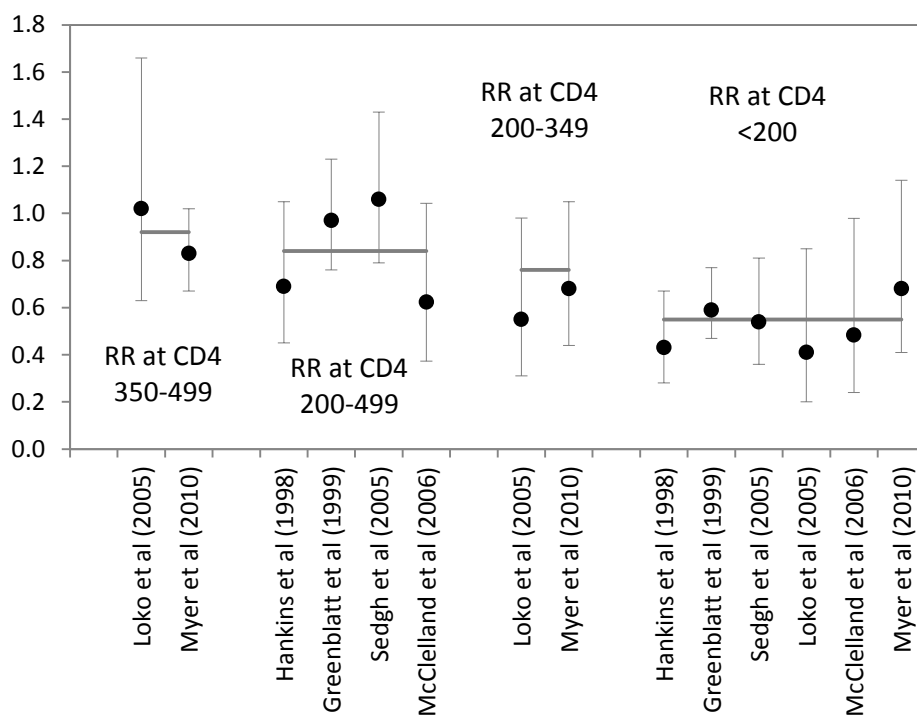


Figure 2.7: Comparison of model assumptions about relative frequency of unprotected sex at different CD4 levels and empirical estimates

Model assumptions are represented by horizontal grey lines. Empirical estimates are represented by dots (error bars represent 95% confidence intervals). Note that the model assumption for the CD4 200-499/ μl is taken as the average of that in the 350-499/ μl and 200-349/ μl categories. For convenience, we have treated the Sedgh *et al* (2005) estimates as if they are based on CD4 cut-offs of 200 and 500 (not 250 and 500).

It is assumed that the frequency of sex is the only sexual behaviour parameter that changes in relation to the CD4 count in HIV-infected adults. In the interests of simplicity, we do not model the possible effect of the CD4 count on rates at which new partnerships are formed, rates of partnership dissolution or rates of condom usage. However, in high risk women, we do assume that rates of entry into commercial sex are reduced by 12% at CD4 counts of 350-499, by 35% at CD4 counts of 200-349 and by 60% at CD4 counts of <200 cells/ μl . Rates of exit from commercial sex are increased by factors that are inversely related to these reduction factors (for example, a sex worker with a CD4 count <200/ μl is assumed to cease commercial sex at a rate that is $1/(1 - 0.6) = 2.5$ times that in HIV-negative sex workers). These assumptions are consistent with data from sex workers in Kenya (McClelland *et al.* 2006a), who were found to be significantly more likely to abstain from sex at lower CD4 counts (OR 1.70 for CD4 counts of 200-499 and 2.39 for CD4 counts of <200). It is also assumed that the frequency at which men visit sex workers is reduced by the same factors as those used to reduce coital frequencies in short-term and long-term relationships.

2.11 The effect of knowledge of HIV status on sexual behaviour

In reviewing the literature on the effectiveness of HIV testing and counselling, we exclude studies that have involved simple comparisons of behaviour before and after HIV testing. In the absence of any control for whether or not people are tested for HIV or diagnosed HIV-

positive, these studies are likely to exaggerate the effect of HIV testing on sexual behaviour, due to the Hawthorne effect. We also focus primarily on evidence from developing countries.

HIV testing is likely to lead to different changes in sexual behaviour depending on whether individuals test positive or negative, and it is therefore important to review separately the evidence for positive and negative diagnoses. In general, there is little conclusive evidence to suggest that individuals who test negative modify their sexual behaviour. For example, in a meta-analytic review, Weinhardt *et al* (1999) found that individuals who tested HIV-negative did not modify their behaviour by more than individuals who remained untested. In a study conducted in Uganda (Matovu *et al.* 2005), it was found that when VCT was offered to all individuals in a community, subsequent HIV incidence was no lower in those who accepted VCT and tested negative (1.6 per 100 PYO) than in those who refused the offer of VCT (1.4 per 100 PYO). In a randomized controlled trial in which individuals received VCT or received only health information, unprotected sex with non-primary partners was significantly reduced in those individuals who received VCT (adjusted OR 0.68, 95% CI: 0.56-0.82) but there was no significant reduction in unprotected sex with primary partners (adjusted OR 1.09, 95% CI: 0.92-1.29) when individuals receiving VCT were compared to individuals who received only health information (Voluntary HIV-1 Counselling and Testing Efficacy Study Group 2000). In this study the reported odds ratios combined HIV-positive and HIV-negative diagnoses, and may therefore exaggerate the effect of HIV-negative diagnosis. In another study conducted in Zimbabwe (Cremin *et al.* 2010; Sherr *et al.* 2007), community members who received VCT and tested negative did not significantly reduce inconsistent condom use with regular partners when compared to HIV-negative individuals who did not receive VCT (adjusted OR of 1.04 (95% CI: 0.48-2.22) in males and 0.72 (95% CI: 0.42-1.23) in females). Pooling the adjusted odds ratios from the randomized trial and the Zimbabwean study in a random-effects meta-analysis yields an OR of 0.85 (95% CI: 0.61-1.19), suggesting that VCT in HIV-negative individuals has minimal impact – if any – on condom use.

Studies that have evaluated the impact of HIV diagnosis on unprotected sex in developing countries are summarized in Table 2.7. There is marked variation in estimates of the effect of HIV diagnosis on the frequency of unprotected sex, with adjusted odds ratios lying between 0.05 and 0.9. Combining these results in a random-effects meta-analysis yields a pooled OR with wide confidence intervals (OR 0.32, 95% CI: 0.15-0.67). Some of these differences may be due to differences in survey design; other differences may reflect differences in study population or differences in definition of risk behaviour.

Table 2.7: Studies evaluating the effect of HIV diagnosis on sexual risk behaviour in developing countries

Study	Location	Definition of risk behaviour	Controls	Effect on risk behaviour in HIV-diagnosed (OR, 95% CI)
Mwangi <i>et al</i> (2011)	Kenya	Any unprotected sex with a partner who was HIV-negative or of unknown HIV status	Individuals who were HIV-positive but undiagnosed	0.05 (0.02-0.12)
Voluntary HIV-1 Counselling and Testing Efficacy Study Group (2000)	Kenya, Tanzania, Trinidad	Any unprotected sex with primary partner	Individuals who tested HIV-negative	0.60 (0.40-0.89)
		Any unprotected sex with non-primary partner: Women Men		0.90 (0.49-1.66) 0.19 (0.05-0.81)
Müller <i>et al</i> (1995)	Thailand	<100% condom use in last 3 sex acts	Individuals who were HIV-positive but undiagnosed	0.15 (0.09-0.24)
Cremin <i>et al</i> (2010)	Zimbabwe	Inconsistent condom use with regular partners: Women	Individuals who were HIV-positive but undiagnosed	0.53 (0.24-1.16)
		Men		0.61 (0.25-1.47)
Pooled OR				0.32 (0.15-0.67)

In all studies, with the exception of Müller *et al*, the odds ratio presented is based on multivariate analysis (Müller *et al* did not employ multivariate analysis, but did select controls who were age- and sex-matched to the cases.)

These studies may exaggerate the impact of HIV diagnosis on sexual risk behaviour for two reasons. Firstly, social desirability bias means that individuals who have been diagnosed HIV-positive are less likely to report having unprotected sex than individuals who are either untested or HIV-negative. Secondly, these studies use the odds ratio as a summary measure, though this is likely to be biased away from 1 when compared with the risk ratio, which is the parameter that we wish to estimate (for example, if the proportion reporting unprotected sex is 0.25 in the diagnosed group and 0.5 in the undiagnosed group, the OR would be 0.33 but the RR would be 0.5). On the other hand, there are also reasons why these studies might under-estimate the effect of HIV diagnosis on the extent of sexual risk behaviour. Firstly, we have focused exclusively on the effect of HIV diagnosis on the reporting of unprotected sex. It is possible that HIV-diagnosed individuals may change their behaviours in ways that are not captured by simple reporting of unprotected sex (for example, by reducing their number of partners or by sero-sorting behaviour) (Cremin *et al.* 2010). Secondly, we have conservatively included studies that have used as the control group individuals who are diagnosed HIV-negative. Although we believe that testing HIV-negative has little effect on sexual behaviour (as discussed previously), if it were the case that testing HIV-negative led to a significant reduction in risk behaviour, we would be under-estimating the effect of an HIV diagnosis by using individuals who have tested negative as controls.

In our model, we assume that the only form of behaviour change associated with HIV-positive diagnosis is increased condom usage. Although this is undoubtedly an oversimplification, we make this assumption in the interests of mathematical simplicity. We define the parameter δ to be the reduction in unprotected sex following HIV diagnosis. To represent the uncertainty regarding this parameter, we assign a beta prior distribution with a mean of 68% and a standard deviation of 15%, roughly consistent with the mean and range of estimates summarized in Table 2.7.

2.12 The effect of ART on sexual behaviour

In our model, ART is assumed to affect the sexual behaviour of treated individuals in two ways. Firstly, by bringing about an improvement in CD4 count and restoring individuals' health and sexual desire (Wamoyi *et al.* 2011), ART is assumed to cause an increase in the frequency of sexual activity. Secondly, because of their greater contact with health services and greater exposure to prevention messages, sexually active ART patients are assumed to have a higher level of condom usage when compared with sexually active ART-naïve patients who are HIV-diagnosed. We therefore aim to review studies that have quantified either the changes in sexual activity or changes in condom use associated with ART.

African studies that have evaluated changes in the frequency of sexual activity in ART patients are summarized in Table 2.8. In all studies, the outcome of interest is the proportion of subjects reporting any sexual activity within some reference period. In a random-effects meta-analysis of these studies, ART patients did not have a significantly increased likelihood of recent sexual activity (OR 1.06, 95% CI: 0.84-1.33). However, when analysis was restricted to those studies that did not control for any recent measure of disease severity, ART patients did have a significantly increased likelihood of recent sexual activity (OR 1.23, 95% CI: 1.02-1.47), and when analysis was restricted to the studies in which recent disease severity was controlled for, no significant effect of ART was estimated (OR 0.95, 95% CI: 0.70-1.27). This is consistent with the results of two of the studies that found that odds ratios relating ART to recent sexual activity reduced after controlling for CD4 count (Venkatesh *et al.* 2010; McClelland *et al.* 2010). This suggests that any observed increase in sexual activity in ART patients can be explained entirely by improvements in overall health status.

Table 2.8: African studies of the association between ART use and recent sexual activity

Study	Location	Population	Definition of sexual activity	Measures of disease severity controlled for	Effect of ART (OR, 95% CI)
Bunnell <i>et al</i> (2006)	Tororo, Uganda	Men and women	Any sex in last 3 months	None	1.2 (1.0-1.5)
McClelland <i>et al</i> (2010)	Mombasa, Kenya	Female sex workers	Any sex in last week	CD4 count	1.08 (0.85-1.35)
Moatti <i>et al</i> (2003)	Côte d'Ivoire	Men	Any sex in last 6 months	CD4 count and score of physical abilities	1.67 (0.84-3.33) 0.65 (0.31-1.39)
Bateganya <i>et al</i> (2005)	Kampala, Uganda	Men and women	Any sex in last 6 months	None	2.0 (0.3-9.9)
Luchters <i>et al</i> (2008)	Mombasa, Kenya	Men and women	Any sex in last 12 months	None	1.30 (0.86-1.96)
Venkatesh <i>et al</i> (2010)	Mpumalanga and Soweto, South Africa	Men and women	Any sex in last 6 months	CD4 count and needing assistance with daily activities	0.78 (0.67-0.93)
Pooled OR					1.06 (0.84-1.33)

African studies that have compared levels of condom usage in patients receiving ART and ART-naïve HIV-positive patients are summarized in Table 2.9. In all studies, the analysis was limited to individuals who reported recent sexual activity, and the outcome of interest was the proportion of these sexually active individuals who reported inconsistent condom use or unprotected sex. In all of these studies, ART users were significantly less likely to report inconsistent condom use. When a random-effects meta-analysis was performed on these studies, the pooled OR for the association between ART use and recent unprotected sex was 0.46 (95% CI: 0.37-0.57).

Table 2.9: African studies of the association between ART use and inconsistent condom use, in sexually active HIV-positive adults

Study	Location	Population	Design	Controls for recency of diagnosis	Effect of ART (OR, 95% CI)
Bunnell <i>et al</i> (2006)	Tororo, Uganda	Men and women	Longitudinal	None	0.3 (0.2-0.6)
Andia <i>et al</i> (2009)	Mbarara, Uganda	Women	Cross-sectional	None	0.28 (0.12-0.65)
McClelland <i>et al</i> (2010)	Mombasa, Kenya	Female sex workers	Longitudinal	Minimal bias due to monthly measurements	0.65 (0.45-0.93)
Donnell <i>et al</i> (2010)	Multicentre study	Men and women	Longitudinal	Minimal bias due to monthly measurements	0.63 (0.41-0.96)
Moatti <i>et al</i> (2003)	Côte d'Ivoire	Men	Cross-sectional	Controlled for time since HIV diagnosis	0.52 (0.29-0.93)
Luchters <i>et al</i> (2008)	Mombasa, Kenya	Men and women	Longitudinal	None	0.52 (0.32-0.87)
Venkatesh <i>et al</i> (2010)	Mpumalanga and Soweto, South Africa	Men and women	Longitudinal	None	0.32 (0.23-0.44)
Dia <i>et al</i> (2010)	Cameroon	Men and women	Cross-sectional	No bias due to exclusion of those diagnosed during the reporting period	0.44 (0.31-0.61)
Pooled OR					0.46 (0.37-0.57)

Although these studies suggest that the initiation of ART is associated with a significant increase in condom use (in those who are sexually active), there are a number of reasons why these studies may exaggerate the impact of ART on condom use. Firstly, several of the studies do not control for time since diagnosis, and this is potentially problematic if the period over which risk behaviour is reported may overlap with the period prior to HIV diagnosis. Since individuals receiving ART will generally have been diagnosed for longer than individuals who are ART-naïve, the untreated individuals reporting on whether they had unprotected sex in the last 6 months are more likely to be reporting on unprotected sex prior to diagnosis than the treated individuals. This means that the effect of ART on condom usage is conflated to some extent with the effect of HIV diagnosis on condom usage – a problem for us in parameterizing our model, since we wish to estimate the two effects separately. When the random-effects meta-analysis was restricted to those studies in Table 2.9 that either controlled for time since diagnosis or minimized the overlap between the period of reporting and the period since diagnosis, the pooled OR for the association between ART use and inconsistent condom use was 0.55 (95% CI: 0.45-0.67) – significantly greater than the pooled OR when considering the other studies (0.35, 95% CI: 0.28-0.45). This suggests that there is indeed substantial bias if periods prior to HIV diagnosis are not excluded or controlled for when evaluating the effect of ART on condom use.

A second reason why the studies in Table 2.9 may exaggerate the impact of ART on condom use is that most published studies have considered patients on ART for relatively short durations. It is possible that the observed increases in condom usage in these studies may reflect transient changes in behaviour associated with the intensive counselling that occurs just prior to ART initiation, and that these changes might not be sustained at longer ART durations. For example, Apondi *et al* (2011) found that among Ugandan ART patients who reported relationships with partners of unknown HIV status, the proportion who reported consistent condom use increased from 58% at baseline to almost 80% at months 6 and 12, but then dropped down to around 60% at longer ART durations. In another Ugandan study, Kembabazi *et al* (2013) found that although male risk behaviour reduced over early ART durations, it increased over longer ART durations.

The longitudinal studies summarized in Table 2.9 may also exaggerate the impact of ART on condom usage, as longitudinal studies tend to observe greater reductions in risk behaviour at longer follow-up durations, independent of the treatment that individuals receive (McClelland *et al.* 2010; Donnell *et al.* 2010). Since individuals receiving ART will generally have been followed for longer than individuals not receiving ART, the lack of adjustment for differences in risk behaviour by follow-up duration may lead to the effect of ART on condom usage being exaggerated.

In our model we assume that the change in coital frequency after ART initiation is determined entirely by the effect of restored CD4 counts, so that it is not necessary to make any additional assumptions beyond those that have already been made about the effect of CD4 count on coital frequencies (section 2.10) and those that are made about increases in CD4 counts after ART initiation (described in Appendix C). However, we do make additional assumptions about the effect of ART on condom usage. The proportion of sex acts that are protected in year t , in an HIV-treated adult of age x and sex g , of marital status l , is

$$1 - (1 - \gamma_{g,l}(x,t))(1 - \delta)(1 - h) ,$$

where $\gamma_{g,l}(x,t)$ is the corresponding rate of condom use in HIV-negative individuals, δ represents the reduction in unprotected sex following diagnosis (discussed in section 2.11), and h represents the reduction in unprotected sex following ART initiation. This effect of ART on the fraction of sex acts that are unprotected is derived from the studies in Table 2.9, using the equation

$$h = 1 - 0.46^u ,$$

where 0.46 is the reduction factor estimated in Table 2.9, and u is an adjustment factor to reflect the sources of bias discussed above. Since 0.46 is likely to be an under-estimate, we have set $u = 0.5$, which yields $h = 0.32$. Given the uncertainty regarding the likely extent of the bias, it might be considered appropriate to include parameter h in the uncertainty analysis. However, this parameter has little influence on the model results, as the δ parameter is a much more important determinant of condom use, and individuals on ART have relatively low levels of infectiousness even if they do not use condoms.

3. Modelling adult HIV survival

The model of HIV survival in adults is summarized in Figure 3.1. Individuals who acquire HIV are assumed to enter an ‘acute HIV’ state in which they are highly infectious. After having progressed to chronic HIV infection, HIV-positive adults are stratified according to their current CD4 count and knowledge of their HIV status/HIV testing history. All infected adults are assumed to have initial CD4 counts above 500 (based on the CD4 distributions observed in HIV-negative South Africans (Avert *et al.* 2004; Coutsooudis *et al.* 2010)), which decline over the course of HIV infection. After having started ART, individuals are stratified according to their baseline CD4 category and time since ART initiation. Although the model structure also allows for a distinction between individuals who are interrupting ART and individuals who are currently on ART, we do not include this differentiation in the current model parameterization (research quantifying the extent of ART interruptions in the South African context is currently being conducted, and the model will be updated once this research has been completed). The sections that follow describe the assumptions made in parameterizing this model. Details regarding the assumed rates of HIV testing and diagnosis are deferred to section 6.1.

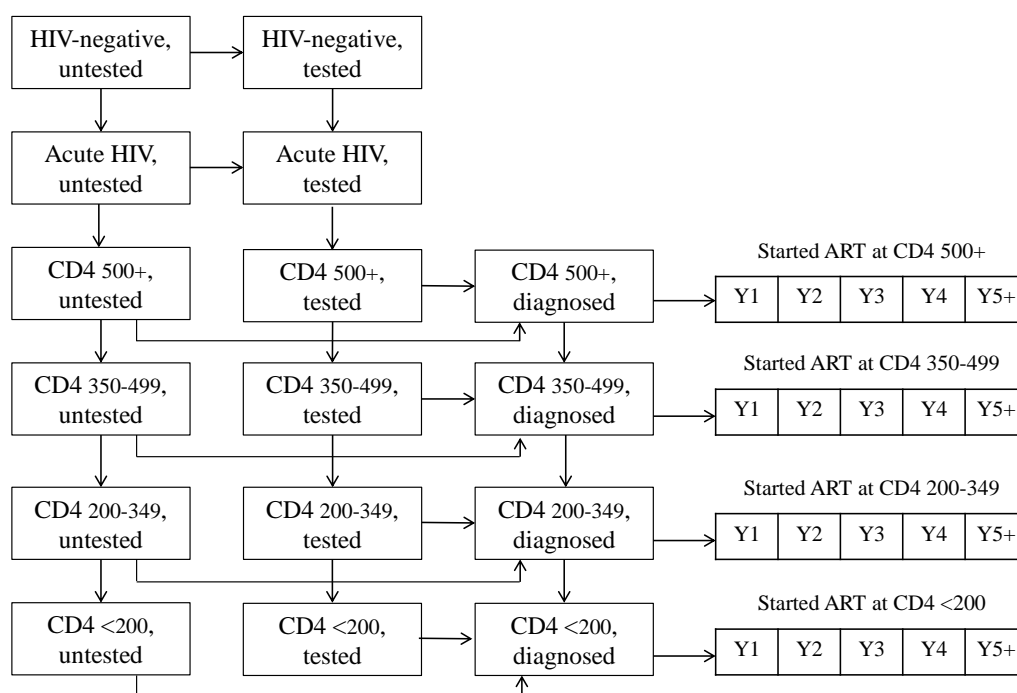


Figure 3.1: Multi-state model of survival in HIV-positive adults

AIDS mortality from all untreated states with CD4 <350 cells/ μ l and all treated states is included (not shown).

3.1 Rates of CD4 decline and mortality in the absence of antiretroviral treatment

For the purpose of setting the model parameters, consider first a simplified model in which there is no ART, and rates of HIV disease progression are independent of age and sex. This model is illustrated in Figure 3.2. In this simplified model, λ_s represents the annual rate of transition from state s to state $s + 1$, and parameter μ_s represents the annual AIDS mortality rate in state s . As HIV-related mortality rates above CD4 350 cells/ μl appear to be very low, we set $\mu_1 = \mu_2 = \mu_3 = 0$.

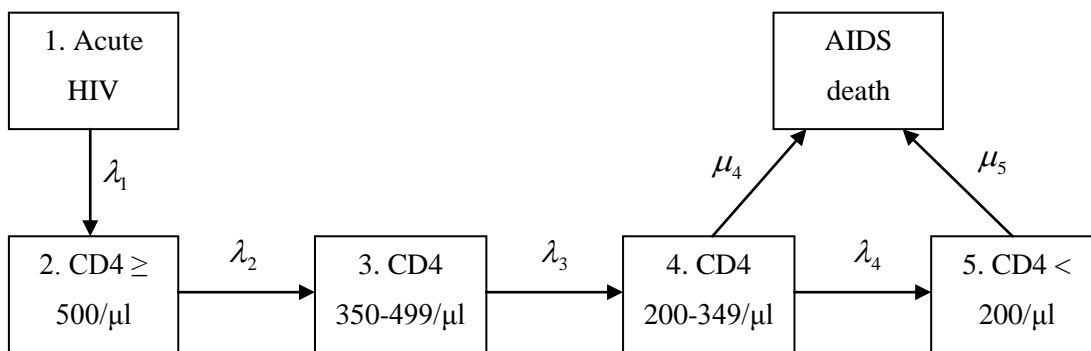


Figure 3.2: Simplified model of CD4 decline and mortality in the absence of ART

The mean survival time in the absence of ART is

$$\pi = \frac{1}{\lambda_1} + \frac{1}{\lambda_2} + \frac{1}{\lambda_3} + \frac{1}{\lambda_4 + \mu_4} + \frac{\lambda_4}{\lambda_4 + \mu_4} \times \frac{1}{\mu_5}. \quad (3.1)$$

In a previous modelling exercise (Johnson 2012), which involved fitting a South African HIV model to survey estimates of CD4 distributions in HIV-infected adults, the parameters λ_2 , λ_3 and λ_4 were estimated to be 0.30, 0.48 and 0.32 respectively,¹ although the λ_2 parameter was defined differently in that analysis as the model did not include an acute stage of HIV infection. If we use the symbol $\hat{\lambda}_s$ to represent the empirical estimates corresponding to the model in Figure 3.2 and assume that the average duration of the acute HIV infection stage is 3 months (Wawer *et al.* 2005; Lavreys *et al.* 2006), then $\hat{\lambda}_1 = 1/0.25$ and $\hat{\lambda}_2 = 1/((1/0.30) - 0.25)$. The estimates of the mortality parameters in the same analysis, $\hat{\mu}_4$ and $\hat{\mu}_5$, were estimated at 0.034 and 0.26 respectively. Substituting these estimated values into equation (3.1) yields an estimated mean survival time of $\hat{\pi} = 11.72$ years in the absence of ART.

¹ In some cases we use the prior means and in other cases we use the posterior means, as the prior means in some cases yield CD4 distributions more consistent with those observed in surveys (see section 10.8).

Although these previous estimates are useful as a starting point, the model on which they are based was not calibrated to South African mortality data. As we wish to allow for uncertainty regarding the mean survival time in South Africa when fitting the model to recorded numbers of deaths in South Africa, we specify a prior distribution to represent uncertainty regarding the parameter π . Previous studies have estimated that for HIV-positive men in South Africa the median time from HIV infection to death, in the absence of ART, is 11.6 years (Todd *et al.* 2007; Glynn *et al.* 2007), though this could be an under-estimate of π , as mean survival time usually exceeds median survival time. In a pooled analysis of African studies of untreated HIV survival, the sum of the average survival times before and after reaching different CD4 thresholds ranged between 13.7 and 14.6 years, depending on the CD4 threshold used (Eligibility for ART in Lower Income Countries Collaboration 2008). However, these estimates may be over-estimates, as patient follow-up time was censored at the point of starting ART, which can introduce a positive bias. To represent our uncertainty regarding the parameter π we have therefore chosen a gamma prior distribution with a mean of 12 years and a standard deviation of 1 year. For a chosen π value, we obtain the values λ_s and μ_s using the equations

$$\lambda_s = \hat{\lambda}_s \times \hat{\pi} / \pi$$

and

$$\mu_s = \hat{\mu}_s \times \hat{\pi} / \pi.$$

3.1.1 The effect of age and sex on CD4 count

In modelling CD4 declines, it is important to consider potential age and sex differences in rates of immune deterioration, as well as age and sex differences in CD4 counts at the time of HIV acquisition. Several studies have found that CD4 counts are typically higher in HIV-negative females than in HIV-negative males (Malaza *et al.* 2013; Gorter *et al.* 1992; Maini *et al.* 1996; Ohta *et al.* 1986; Rezza *et al.* 1997), suggesting that women start out with higher CD4 counts than men at the time they acquire HIV. However, it is unclear whether age affects CD4 counts. One study found that CD4 counts were higher in pre-menopausal women than in post-menopausal women (van Benthem *et al.* 2002), and Lodi *et al.* (2011) found that in patients from industrialized countries, with known dates of seroconversion, the initial CD4 count (soon after seroconversion) was lower in older patients. However, a South African study in HIV-negative adults found that CD4 count tended to increase with respect to age, both in men and women (Malaza *et al.* 2013). Other studies have failed to detect any association between age and CD4 count in HIV-negative adults (Rezza *et al.* 1997; Maini *et al.* 1996). There is thus limited evidence of an effect of age on CD4 counts in HIV-negative individuals, suggesting that the initial CD4 count at the time of HIV acquisition is independent of age.

It is uncertain whether there are sex differences in the rate of CD4 decline following HIV acquisition. Although there is some evidence to suggest that the pace of CD4 decline may be more rapid in females than in males (Prins *et al.* 2005), Lessells *et al.* (2011) found that among adults enrolled in pre-ART programmes in rural South Africa, the rate of CD4 decline was significantly higher in men than in women. A faster rate of CD4 decline in males might be expected, given that many studies have shown HIV viral load levels in males to be higher

than in females (Touloumi *et al.* 2006; Hughes *et al.* 2012; Prins *et al.* 2005). Other studies suggest no clear sex differential in the rate of CD4 decline. Using a mixed-effects model of CD4 decline in HIV-positive individuals in industrialized countries, Lodi *et al.* (2011) found no significant sex difference in the rate of CD4 decline. In a South African study, Holmes *et al.* (2006) also found no significant difference in rates of CD4 decline between males and females.

Age appears to have a significant influence on the rate of CD4 decline. Lodi *et al.* (2011) found that in patients from industrialized countries, with known dates of seroconversion, older patients tended to experience a more rapid CD4 decline. The same conclusion was reached when the data were combined with data from a cohort of HIV-positive individuals enrolled in a randomized controlled trial, whose dates of seroconversion were not known (Lodi *et al.* 2010).

In modelling the effect of sex differences in CD4 counts, two possible approaches are possible. The first is to assume that at the point of HIV acquisition, a certain proportion of individuals are already in the CD4 <500 category, and to allow for sex differences in this proportion. The second is to allow for sex differences in the rates of CD4 decline. Although there appears to be stronger evidence of a sex difference in CD4 counts at seroconversion than in the rate of CD4 decline, South African data suggest that almost all HIV-negative adults have CD4 counts above 500 cells (Coutsoudis *et al.* 2010; Williams *et al.* 2006a; Malaza *et al.* 2013), so that it may be unrealistic to assume that there is a substantial proportion of individuals who have CD4 counts <500 at the point of seroconversion. (To the extent that surveys such as that in rural KwaZulu-Natal (Malaza *et al.* 2013) do find HIV-negative adults with CD4 counts below 500, this could simply be due to random variation in CD4 measurements (Malone *et al.* 1990; Hughes *et al.* 1994).) We have therefore favoured the second approach over the first approach. The second approach is also the more parsimonious approach, as it requires a single parameter (the relative rate of CD4 decline in females, which we represent by the symbol ϖ) rather than two parameters (male and female proportions with CD4 <500 at seroconversion). This relative rate of CD4 decline in females has been set at 0.9, to be consistent with the assumed effect of female sex on the rate of HIV mortality (discussed in section 3.1.3).

3.1.2 The effect of age on HIV mortality in the absence of ART

In individuals with known dates of seroconversion, AIDS mortality is significantly related to age, with older individuals experiencing more rapid disease progression and higher mortality than younger individuals, in the pre-ART era. For example, a regression model fitted to untreated HIV survival data from several high income countries (Collaborative Group on AIDS Incubation and HIV Survival 2000) suggests that the median time to death increases by a factor of 1.19 for each 10-year decrease in age at seroconversion, and the median time to AIDS increases by a factor of 1.15 for each 10-year decrease in age at seroconversion. A similar effect on mortality (HR 1.20, 95% CI: 0.89-1.63, per 10-year increase in age) was observed in rural Zimbabwe (Erikstrup *et al.* 2007). However, higher estimates of the increase in the rate of progression to AIDS per 10-year increase in age have been estimated in US haemophiliacs (HR 1.61, 95% CI: 1.29-2.04) and in gay men in high income countries (HR 1.36, 95% CI: 0.90-1.97) (Rosenberg *et al.* 1994). High estimates of the increase in mortality per 10-year increase in age have also been observed in rural Tanzania (HR 1.72)

(Isingo *et al.* 2007), Canada (HR 1.37) (Hogg *et al.* 1994) and Italy (HR 1.55, 95% CI: 1.31-1.83) (Pezzotti *et al.* 1996).

In our model, we assume that the previously-specified mortality rates and rates of transition between CD4 states are multiplied by an age adjustment factor, since it is clear that age affects both the rate of CD4 decline and the mortality rate. This age adjustment factor, for an individual aged x , is

$$(1+k)^{(x-30)/10}$$

A base age of 30 is chosen since this is roughly midway between the median age at which adult HIV acquisition occurs in generalized epidemics (Stover *et al.* 2010) and the median age at which ART is initiated in South Africa (Cornell *et al.* 2009), i.e. it is likely to be close to the median age in most of studies on which our mortality and CD4 decline parameters are based. In view of the variability in age effects between studies, we assign a gamma prior distribution to represent the uncertainty regarding the parameter k . This distribution has a mean of 0.40 and a standard deviation of 0.20. The resulting factor $(1+k)$ has a mean of 1.40 (close to the average of the estimates reported in the previous paragraph), a 2.5 percentile of 1.11 and a 97.5 percentile of 1.88.

As the evidence reviewed here includes estimates of rates of progression to AIDS (which may be immunologically defined) and as previous studies have also shown a significant effect of age in the rate of CD4 decline (as discussed in the previous section), the same age adjustment factors that we have applied to the mortality rates are applied also to the assumed rates of CD4 decline.

3.1.3 Sex differences in survival in the absence of ART

In the absence of ART, higher mortality might be expected in HIV-positive males than in HIV-positive females. This is mainly because men tend to become infected at older ages than women (and hence have more rapid disease progression), and is also partly due to non-HIV mortality rates being higher in men than in women. However, relatively few studies have evaluated whether there are sex differences in mortality after controlling for age and after removing the effects of background mortality. Using data from the CASCADE Collaboration, Bhaskaran *et al.* (2008) found that after controlling for age differences and removing non-HIV mortality, mortality rates were lower in women than in men prior to 1996 (HR 0.76, 95% CI: 0.63-0.93). Using the same data set and controlling for age differences, but not controlling for non-HIV mortality, Jarrin *et al.* (2008) found that prior to 1997 mortality rates were lower in women, although this difference was not statistically significant (HR 0.89, 95% CI: 0.76-1.05). In yet another analysis of the CASCADE data, it was found that although mortality rates were lower in women (HR 0.77, 95% CI: 0.67-0.89), this was not significant after controlling for route of HIV transmission (HR 0.89, 95% CI: 0.74-1.07) (Collaborative Group on AIDS Incubation and HIV Survival 2000). In a review of gender differences in HIV mortality, which included mainly data from high income countries, Prins *et al.* (2005) noted that although no individual study found a significant difference between males and females, studies consistently estimated a slightly lower mortality risk in females.

Few relevant studies have been conducted in developing countries. Isingo *et al.* (2007) found that after controlling for age at HIV infection, HIV-positive women in rural Tanzania had

lower mortality than their male counterparts (HR 0.62, 95% CI: 0.34-1.15) prior to the availability of ART, although this analysis did not remove the effect of non-HIV mortality. However, in an analysis that combined these data with data from other African demographic surveillance sites (Todd *et al.* 2007), the effect of female sex on mortality, after controlling for age, was found to be much weaker (HR 0.91, 95% CI: 0.71-1.16).

The finding of a moderately lower mortality rate in HIV-infected females is consistent with the previously-discussed findings of higher CD4 counts in HIV-positive females, and we therefore apply the same female adjustment factor to the untreated HIV mortality rates as are applied to the rates of CD4 decline. This means that the parameter ϖ , which represents the ratio of the rate of CD4 decline in females to that in males, also represents the ratio of the HIV mortality rate in untreated females to that in untreated males. The assumed ratio of 0.90 is consistent with the estimates of 0.91 and 0.89 in collaborative studies by the ALPHA Network and CASCADE Collaboration respectively (Todd *et al.* 2007; Collaborative Group on AIDS Incubation and HIV Survival 2000).

3.1.4 Mathematical model

We define the symbol $\lambda_{g,s}(x)$ to be the annual rate of transition from HIV state s to state $(s + 1)$ in untreated HIV-positive individuals of sex g ($1 = \text{males}$, $2 = \text{females}$) who are aged x . This is calculated from the previously-specified parameters as follows:

$$\lambda_{g,s}(x) = \lambda_s \varpi^{g-1} (1+k)^{(x-30)/10}.$$

Similarly, we define the symbol $\mu_{g,s}(x)$ to be the annual mortality rate in HIV state s in untreated individuals of sex g who are aged x . This is calculated as

$$\mu_{g,s}(x) = \mu_s \varpi^{g-1} (1+k)^{(x-30)/10}.$$

3.2 Rates of ART initiation

We model ART initiation as occurring either in the month of HIV diagnosis, or else at longer durations since HIV diagnosis. (In reality relatively few adults start ART within a month of being diagnosed, but we use ‘in the same month’ as a convenient model approximation to represent individuals who are linked to care and started on ART shortly after HIV diagnosis.)

3.2.1 Modelling of ART initiation immediately after diagnosis

The modelling of HIV diagnosis is described in detail in section 6.1. Briefly, we model three ways in which HIV diagnosis can occur: through antenatal HIV screening, through HIV testing in individuals with opportunistic infections (OIs) and through other VCT programmes. For each of these three groups, eligibility to start lifelong ART depends on the individual’s CD4 count, and guidelines have changed over time (Department of Health 2003; Department of Health 2010; Mureithi *et al.* 2012). We therefore allow for changes over time in the assumed proportions of individuals in each group who are eligible to start ART. These assumptions are summarized in Table 3.1 below. Note that ‘eligibility to receive ART’ here

means only that the relevant guidelines recommended ART initiation in these patients – this does not reflect the actual proportion of patients who started ART when they became eligible. In some of the periods we have set the assumed proportion to 50% because the change in guideline occurred midway through the relevant period. Assumptions for the post-2012 period can be changed when assessing potential alternative future scenarios.

Table 3.1: Proportions of adult patients assumed to be eligible to receive lifelong ART

	1999- 2003*	2003- 2009	2009- 2010	2010- 2011	2011- 2012	Post- 2012
WHO stage IV or CD4 <200	100%	100%	100%	100%	100%	100%
Pulmonary TB, CD4 200-349	0%	0%	50%	100%	100%	100%
Pulmonary TB, CD4 350+	0%	0%	0%	0%	0%	100%
WHO stage III (excl. pulmonary TB)	0%	0%	0%	0%	0%	0%
Pregnant women, CD4 200-349	0%	0%	50%	100%	100%	100%
Pregnant women, CD4 350+	0%	0%	0%	0%	0%	0%
Asymptomatic, non-pregnant, CD4 200-349	0%	0%	0%	0%	100%	100%
Asymptomatic, non-pregnant, CD4 350-499	0%	0%	0%	0%	0%	0%
Asymptomatic, non-pregnant, CD4 500+	0%	0%	0%	0%	0%	0%

Calendar periods are defined to run from the middle of the first year quoted to the middle of the second year.

* Applies only to rollout in private sector and NGO-run programmes.

ART eligibility criteria differ depending on whether patients have WHO stage III or IV symptoms or pulmonary TB (extrapulmonary TB is a stage IV condition and is therefore automatically included in the eligibility criteria, but pulmonary TB is a stage III condition). In modelling ART uptake we therefore set assumptions about the incidence of each of these symptom categories. These assumptions are summarized in Table 3.2, and are based on the average incidence rates observed in a Cape Town study (Holmes *et al.* 2006) and a study conducted in Abidjan (Anglaret *et al.* 2012). (Pulmonary TB incidence assumptions have also been checked for consistency with data from the Gauteng and Mpumalanga provinces of South Africa (Golub *et al.* 2009; Hanrahan *et al.* 2010).) The probability of HIV testing being conducted in OI patients is assumed to be the same for all OIs, and the assumed rates of OI testing are specified in section 6.1.²

Table 3.2: Assumed annual incidence of opportunistic infections (OIs) in HIV-positive adults

	CD4 count				
	Acute HIV	500+	350-499	200-349	<200
All WHO stage III and IV	0.05	0.05	0.12	0.27	0.90
WHO stage IV	0.01	0.01	0.02	0.06	0.28
Pulmonary TB	0.01	0.01	0.015	0.04	0.07

In pregnant women, the proportion of newly-diagnosed ART-eligible women who start ART has been set at rates assumed previously (Johnson *et al.* 2012d), which increase from 5% in 2003 (when the ART rollout in the public sector was in its early stages and access was limited) to 80% in 2012. Although this assumption of 80% may appear optimistic relative to South African data sources, which generally suggest proportions of 30-75% (Hussain *et al.*

² Although this assumption is made in the model, we recognize when setting the assumptions based on rates of HIV testing in TB patients that rates of HIV testing may be higher in TB patients than in patients with other OIs. This issue is further discussed in section 6.1.

2011; Orié *et al.* 2009; Horwood *et al.* 2010; Stinson *et al.* 2010; van der Merwe *et al.* 2006), recent changes in guidelines, which include greater integration of ART in PMTCT services and switching to WHO option B for PMTCT, should mean fewer barriers to future initiation of ART during pregnancy. Recent data from the Western Cape suggest that after integrating ART and antenatal services the proportion has increased to 85% (Cox 2013).

In a recent review of sub-Saharan African studies that have examined linkages between HIV diagnostic services and ART services, half of studies included were from South Africa (Rosen and Fox 2011). Restricting attention to those studies conducted in South Africa, the median proportion of patients who received CD4 testing following HIV diagnosis was around 75% and the median proportion of those receiving CD4 testing who collected their test results was around 80%. Of those who were determined to be ART-eligible, the average proportion who started ART was around 67%. This suggests that of all individuals who are newly diagnosed and ART-eligible, the proportion who actually start ART within a few months of diagnosis is only about 40% ($0.75 \times 0.80 \times 0.67$). However, this is likely to be an underestimate, because many of the studies included in the review were unable to establish the extent to which patients sought treatment or CD4 testing from other services. In addition, there is likely to be substantial variation in rates of linkage to ART services when comparing different groups of newly-diagnosed patients (Kranzer *et al.* 2010b; Larson *et al.* 2010b; Govindasamy *et al.* 2011). For example, patients who are newly diagnosed with WHO stage IV-defining symptoms are likely to be more motivated to start ART immediately than patients who are asymptomatic, and are likely to be fast-tracked through the patient preparation process (since CD4 testing is not required prior to ART initiation). We therefore assume that the proportion of newly-diagnosed symptomatic patients who start ART soon after diagnosis is the same as the proportion of pregnant women who start ART soon after diagnosis (i.e. reaching 80% by 2012), but that the proportion of asymptomatic non-pregnant patients who initiate ART (if they are eligible) is only half of that in pregnant women (i.e. reaching 40% by 2012). This is supported by South African data showing that the leading reason for refusing ART initiation following diagnosis is ‘feeling healthy’ (Katz *et al.* 2011).

3.2.2 Modelling of ART initiation in previously-diagnosed individuals

In modelling the rate of ART initiation in individuals who were previously diagnosed with HIV (i.e. excluding the individuals who were started on ART immediately after HIV diagnosis), the method used to calculate the rate of ART initiation changes after 2012. In the period up to mid-2012, the rates are calculated directly from previously-published estimates of numbers of patients starting ART in each period (Johnson 2012; Department of Health 2012), while in the period after mid-2012 the rates of ART initiation are calculated with reference to some assumed average delay between diagnosis and ART initiation.

Suppose that in the period up to mid-2012, $S_g(t)$ is the estimated number of adults of sex g starting ART in month t , calculated from previously-published estimates (Johnson 2012; Department of Health 2012). Further suppose that $S_g^0(t)$ is the number who started ART immediately after HIV diagnosis, calculated as described in the previous section. Let $N_{g,s}(x,t)$ be the number of HIV-diagnosed individuals in CD4 category s , who are ART-naïve at time t , of age x and sex g . Let $\mu_{g,s}(x,t)$ be the monthly HIV mortality rate that applies in these individuals, and let $J_s(t)$ be the relative rate of ART initiation in stage s relative to that in the CD4 <200/ μl category ($s = 5$). In most periods $J_s(t)$ will be zero for $s < 5$, since South African ART guidelines have only recently changed to allow for ART initiation at CD4 counts above

200/ μl . In the hypothetical scenario where all individuals are eligible for ART, we set $J_s(t)$ to 0.40 for CD4 of 500 or higher, 0.50 for CD4 of 350-499, 0.70 for CD4 of 200-349 and 1 for CD4 <200. (These assumptions are based on the observed relative rates at which individuals enrolled in pre-ART care return for regular CD4 testing (Lessells *et al.* 2011; Larson *et al.* 2010a) and initiate ART (Geng *et al.* 2013), and reflect the reluctance of many HIV-positive individuals to start therapy at high CD4 counts (Heffron *et al.* 2012).) We wish to estimate the monthly rate at which HIV-diagnosed individuals in the CD4 <200/ μl category initiate ART, $\rho_g(t)$. We estimate this by noting that

$$\begin{aligned} S_g(t) - S_g^0(t) &= \sum_{x=15}^{90} \sum_{s=1}^5 N_{g,s}(x,t) \int_0^1 \rho_g(t) J_s(t) \exp\left(-(\mu_{g,s}(x,t) + \rho_g(t) J_s(t))u\right) du \\ &\approx \sum_{x=15}^{90} \sum_{s=1}^5 N_{g,s}(x,t) \rho_g(t) J_s(t) (1 - 0.5(\mu_{g,s}(x,t) + \rho_g(t) J_s(t))) \end{aligned}$$

This is a quadratic in $\rho_g(t)$, and the smaller of the two roots is the rate of ART initiation that we wish to estimate.

In the period after mid-2012, we specify an assumed ‘ultimate’ delay in the time to starting ART, in individuals who have previously been HIV-diagnosed and who have CD4 counts below 200/ μl (it is ‘ultimate’ in the sense that this is the level at which the delay is assumed to stabilize in future). Individuals who do not start ART immediately after HIV diagnosis should return for CD4 testing at 6-monthly intervals, which means that the average time between reaching the eligibility threshold and starting ART should be 3 months on average in a perfect scenario. However, the assumed ultimate delay is set to 6 months, to take into account that many individuals who have been diagnosed positive do not return for regular CD4 testing, or do not start ART immediately even if they know they are ART-eligible. The ultimate delay is assumed to apply from mid-2016 onwards, and the parameter $\rho_g(t)$ is set at the inverse of this delay. In the period between mid-2012 and mid-2016, the $\rho_g(t)$ parameter is estimated by interpolating linearly between the value estimated in the period prior to mid-2012 and the value estimated in the period following mid-2016.

A limitation of this approach to modelling ART initiation is that it does not allow for the possibility that the rate of ART initiation may be related to age. A recent study in two clinics in Malawi found that the rate of ART initiation in ART-eligible adults over the age of 45 was double that in ART-eligible adults aged 15-24 (Feldacker *et al.* 2012), and similar results have been observed in Uganda (Geng *et al.* 2013). A South African study has also shown that older age is significantly associated with retention in pre-ART care (Lessells *et al.* 2011), which suggests that previously-diagnosed individuals are more likely to start ART when they reach the eligibility threshold if they are older.

3.3 Survival after ART initiation

3.3.1 The effect of age and sex on mortality after ART initiation

A number of studies have assessed the effect of baseline age on AIDS-related mortality. In the ATHENA Cohort, the HIV-related mortality rate was found to increase by a factor of 1.029 (95% CI: 1.012-1.046) for each year of increase in age (van Sighem *et al.* 2003), after controlling for baseline CD4. Braithwaite *et al.* (2005) also found, when fitting a model to mortality data from the CHORUS Collaboration in the US, that regardless of the current CD4 or viral load after ART initiation, HIV-related mortality was higher in older individuals than in younger individuals. Data from the CASCADE Collaboration also suggest that after removing non-HIV mortality, mortality in older HIV-infected adults is substantially greater than that in younger HIV-infected adults, even after controlling for the greater duration of HIV infection in older individuals (Bhaskaran *et al.* 2008). An analysis of data from the IeDEA Southern Africa collaboration also found that HIV-related mortality was associated with age, with the increase in mortality per 10-year increase in age varying between 1.07 and 1.13 (Johnson *et al.* 2013). A similar association between age and excess HIV mortality has been observed in China (Zhu *et al.* 2013). This age effect may be explained by lower rates of CD4 recovery in older individuals, following ART initiation (Micheloud *et al.* 2008; Nash *et al.* 2008; Mutevedzi *et al.* 2011), and an associated higher incidence of AIDS-defining conditions (Sterne *et al.* 2007; Sabin *et al.* 2008).

Men generally appear to experience higher mortality after starting ART than women, even after controlling for age differences and after controlling for differences in baseline characteristics. Using data from the CASCADE Collaboration, Bhaskaran *et al.* (2008) found that in all periods following 1996 (the start of the HAART era), HIV-related mortality (after controlling for age) was lower in women than in men, with hazard ratios varying between 0.55 and 0.95. Similarly, data from the IeDEA Southern Africa collaboration suggest a hazard ratio of 0.76 (95% CI: 0.71-0.82), although some of this difference was found to be attributable to differences between males and females in levels of non-HIV mortality (Cornell *et al.* 2012). To the extent that HIV-specific mortality explains this difference, this may be due to lower rates of CD4 recovery in males (Nglazi *et al.* 2011; Cornell *et al.* 2012) and higher rates of ART discontinuation (Kranzer *et al.* 2010a; Fatti *et al.* 2010; Vella *et al.* 2010; Nglazi *et al.* 2011; Cornell *et al.* 2012).

3.3.2 Modelling survival after ART initiation

Our model of survival after ART initiation is based on a model that has been fitted to mortality data from six different ART programmes operating in South Africa and participating in the IeDEA Southern Africa collaboration (Johnson *et al.* 2013). This relative survival model stratifies mortality rates by age, sex, baseline CD4 category and time since ART initiation. The model also allows for heterogeneity in mortality rates between the six treatment programmes, and estimates HIV-specific mortality by subtracting non-HIV mortality rates estimated in the ASSA2008 model from the crude mortality rates. For those patients who were lost to follow-up, information from the national population register was incorporated to obtain 'corrected' estimates of mortality. This relative survival model estimated significant differences in HIV-specific mortality by age and sex (consistent with the literature reviewed previously), as well as by baseline CD4 count and duration of ART.

In applying the coefficients estimated in this relative survival model to our demographic model, a number of adjustments have been made:

- The relative survival model estimates mortality over four treatment durations (0-12, 12-24, 24-36 and >36 months), which differ from the treatment durations used in the demographic model (0-6, 6-18, 18-30, 30-42 and >42 months). We have set the assumed mortality rate in the first 6 months to be 1.5 times that estimated in months 0-12 in the relative survival model, and we have set the assumed mortality rate in months 6-18 to be the average of half the mortality rate in months 0-12 and the mortality rate in months 12-24. The implicit assumption here is that the mortality rate in the first 6 months on ART is approximately three times the mortality rate in the second 6 months of ART (Cornell *et al.* 2012). The assumed mortality rates in the 18-30 and 30-42 month periods are similarly set at the average of the mortality rates estimated over the corresponding durations in the relative survival model.
- Although the relative survival model calculates rates of mortality for four baseline CD4 categories (<50, 50-99, 100-199 and 200+), our demographic model uses these to estimate mortality rates in only 2 CD4 categories (<200 and 200-349). Over time we would expect a change in the distribution of baseline CD4 counts among individuals starting ART at CD4 <200, as rates of ART initiation increase and as there are fewer untreated individuals remaining at CD4 counts below 50 (IeDEA and ART Cohort Collaborations 2014; Cornell *et al.* 2009). We have therefore created a sub-model to evaluate the likely change in the disease severity of patients with CD4 <200 over time, as a function of the average rate of ART initiation. This sub-model is used to derive adjustments both to the rate of untreated mortality at CD4 <200 and to the rate of mortality in patients who started ART with CD4 <200. A detailed description of this sub-model is provided in Appendix B.
- In the data set to which the relative survival model was fitted, relatively few patients started ART with CD4 counts above 200, because the South African treatment guidelines in place at the time recommended ART initiation at CD4 counts above 200 only if the patient had WHO stage IV symptoms. As symptomatic patients are likely to have higher mortality than asymptomatic patients, even after controlling for CD4 count (Brinkhof *et al.* 2009; Egger *et al.* 2002), the relative survival model estimates of mortality in the baseline CD4 200+ category are likely to exaggerate the future mortality rates in asymptomatic patients starting ART with CD4 counts of 200-349. We have therefore multiplied the relative survival model estimates by factors of 0.2 and 0.5 in the periods up to and after the first 6 months of ART respectively. These multiples are derived from a South African study of ART mortality, which found that after controlling for baseline CD4 count, the ratio of mortality in patients with baseline WHO stage IV to that in patients with no symptoms at baseline dropped from 5.82 in the first 4 months of ART, to 2.78 in months 4-12 and to 1.98 after the first 12 months of ART (Cornell *et al.* 2010).

The relative survival model estimates cannot be used to estimate the likely mortality rates in patients starting ART with CD4 counts above 350 in future, as there were too few patients starting ART at these high CD4 counts, and those few patients who did would in any case not be representative of the patients starting ART at high CD4 counts if future guidelines were to allow earlier ART initiation in asymptomatic individuals. Randomized controlled trials are currently being conducted to assess the therapeutic benefit of starting ART at these higher CD4 counts (Geffen 2011), and a few trials that have been published to date do provide ‘low-

quality' evidence of a lower mortality rate in patients starting ART at CD4 >350 (World Health Organization 2013). Given the current lack of data, an accurate model of the impact on mortality of earlier ART initiation is not possible. In our demographic model it is assumed that adults with CD4 counts above 350 do not face any immediate HIV-related mortality risk in the absence of ART, and we therefore assume that for patients starting ART at high CD4 counts, mortality rates are very low and unrelated to the duration of ART. These rates have been set just below the minimum rates assumed for patients starting ART with CD4 counts of 200-349. The annual HIV mortality rates assumed for patients starting ART with CD4 counts of 350-499 are 0.004 in males and 0.0025 in females, and those assumed for patients starting ART with CD4 counts above 500 are 0.0025 and 0.0015 in males and females respectively.

A limitation of our approach to estimating mortality in patients with baseline CD4 <350/ μ l is that it relies on the IeDEA-SA estimates of excess HIV mortality, though these estimates may be biased. The IeDEA-SA estimates could understate average mortality levels in South Africa if the clinics participating in the IeDEA-SA collaboration are better resourced than clinics not participating in the collaboration, or if the socioeconomic status of patients in these clinics (mostly in urban areas) is higher on average than that in other clinics. However, it is also possible that the IeDEA-SA estimates may overstate average mortality levels, because the relative survival model was fitted on the assumption of piecewise-constant hazards over different ART durations, which will tend to exaggerate mortality rates if follow-up times are short (Johnson *et al.* 2013).

Another limitation of this modelling approach is that it does not allow for possible improvements in mortality over time, which may occur independently of changes in CD4 distributions of patients starting ART. Evidence of such improvements has been noted in our previous analysis of the IeDEA-SA data (Johnson *et al.* 2013). This could be a reflection of increasing integration of HIV care into primary care over time (Uebel *et al.* 2013), or improvements in patient management and adoption of better drugs with fewer side effects (e.g. tenofovir in place of stavudine).

For the purpose of modelling changes in CD4 distributions over time, it is necessary to estimate the proportion of ART patients currently in a particular CD4 category, based on the baseline CD4 category and the time since ART initiation. Our approach to estimating these proportions is described in Appendix C.

4. Modelling heterosexual transmission of HIV

The model of heterosexual HIV transmission is based on assumptions about the probability of HIV transmission per act of sex between an infected individual and a susceptible partner. These transmission probabilities are adjusted to take into account the effect of various factors including HIV disease stage, type of relationship, age and risk group. The sections that follow describe the derivation of the base transmission probabilities and the adjustments to these probabilities, though the discussion of the effect of male circumcision is deferred to section 6.2. The chapter concludes with some mathematical detail on the modelling of heterosexual transmission rates.

4.1 The effect of sex and relationship type

Male-to-female transmission probabilities in young women have been estimated in two South African studies. In the first study, Pettifor *et al* (2007) estimated the transmission probability per partnership to be 0.74 when assuming high levels of HIV prevalence in male partners, but making minimal allowance for bias in female reporting of numbers of partners. They also estimated an average of 82 sex acts per partnership, which implies an average transmission probability per sex act of 0.0163. In the second study, Auvert *et al* (2001) estimated the transmission probability per partnership to be 0.49 if women under-reported their lifetime number of partners by half. If the same assumption is made about the average number of sex acts per partnership (82), this implies an average transmission probability per sex act of 0.0082. The advantage of using these two studies is that they are locally relevant and – because rates of marriage in young women are low – they are likely to be representative of transmission rates in non-marital relationships. However, the estimates are not adjusted for the effects of condom use (we would expect a higher transmission probability per unprotected sex act) or for the effect of higher HIV susceptibility in young women (discussed in section 4.5 below). Adjusting for the latter would lead to lower estimates of HIV transmission probabilities per act of sex in older women. In light of the uncertainties, we assign a beta distribution to represent our uncertainty regarding the HIV transmission probability per unprotected sex act between an HIV-positive male and a susceptible female in a short-term relationship. This prior has a mean of 0.012 and a standard deviation of 0.005.

Estimates of the female-to-male HIV transmission probability per sex act in non-commercial short-term relationships, when the male is uncircumcised, have been estimated to be 0.016 in South Africa (Mahiane *et al.* 2009) and 0.0128 in Kenya (Baeten *et al.* 2005). In the latter study, estimates were adjusted to take into account the effects of condom use, while in the former study the average of 0.016 was the average for all sex acts (protected and unprotected) and therefore a likely under-estimate of the probability per unprotected sex act. Given the lack of reliable data, we represent our uncertainty regarding the female-to-male transmission probability using the same beta prior distribution as that assumed for the male-to-female transmission probability (i.e. mean of 0.012, standard deviation of 0.005). Although it may seem unrealistic to assign the same prior mean to the male-to-female and female-to-male transmission parameters, it should be noted that the female-to-male parameter is adjusted downward for circumcised men, so that the average female-to-male transmission probability is lower than the average male-to-female transmission probability.

Probabilities of HIV 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). In another study of cohabiting couples in Rwanda, HIV transmission probabilities per act of unprotected sex were approximately 0.0028 (6/2099) if the initially infected partner was male and 0.0035 (2/572) if the initially infected partner was female (Allen *et al.* 1992). In a more recent study of HIV transmission rates in serodiscordant couples in eastern and southern Africa (almost all of whom were married or cohabiting), the probability of transmission per unprotected sex act was 0.0019 if the initially infected partner was male and 0.0010 if the initially infected partner was female (Hughes *et al.* 2012). As there does not appear to be a substantial difference between female-to-male and male-to-female transmission probabilities in these studies, we use the average of these transmission probabilities (0.002) as our prior mean for the probability of transmission per act of sex in spousal relationships. This transmission probability is substantially lower than the transmission probabilities estimated in short-term relationships, which is probably a reflection of the selection biases inherent in studies of transmission in long-term serodiscordant relationships (if transmission has not occurred in the early stages of a relationship, this is likely to be because either the infected individual has low infectiousness or the susceptible partner has low susceptibility).

Few studies have estimated the probability of HIV-1 transmission from an infected client to a susceptible sex worker, in African settings. In a study of Senegalese sex workers, Gilbert *et al.* estimated that the average probability of HIV-1 transmission per act of sex with an infected client was between 0.00031 and 0.00056, depending on the approach to dealing with missing data on numbers of clients (Gilbert *et al.* 2003). A similarly low probability of transmission per unprotected sex act with an infected client, 0.00063, was estimated in a cohort of Kenyan sex workers (Kimani *et al.* 2008). Data from a South African study of sex workers in KwaZulu-Natal can also be used to estimate the probability of transmission per sex act. In this study, an HIV incidence rate of 14.7 per 100 person years was observed (Ramjee *et al.* 2005) in sex workers who reported an average of 23.3 sex acts with clients per week, of which 20.3 were protected (Ramjee *et al.* 1999). HIV prevalence in truck driver clients was estimated to be 56% (Ramjee and Gouws 2002). If β is the probability of transmission per act of unprotected sex, and condoms are assumed to reduce this transmission probability by 90% (Weller and Davis 2004), we can crudely estimate the average weekly rate of HIV acquisition as

$$0.56 \times \beta \times (20.3 \times (1 - 0.9) + 3.0).$$

Setting this expression to 0.147/52 and solving for β yields a β estimate of 0.0010. Although this is higher than the estimates from Senegal and Kenya, we use this as our model assumption as it is likely to be more locally applicable. The assumed rate of transmission is low when compared with the previously-estimated probabilities of transmission in young unmarried women in the South African context, possibly because some sex workers acquire a degree of immunity through regular exposure to HIV (Rowland-Jones *et al.* 1998).

Estimates of the probability of transmission from infected sex workers to susceptible clients are highly variable. In a Kenyan study of men with a single exposure to a sex worker, the cumulative proportion who seroconverted was 13%, which suggests an extremely high transmission probability (Cameron *et al.* 1989). However, men were recruited into the study from an STI clinic, suggesting likely over-estimation of the transmission probability, given that STIs substantially increase HIV transmission probabilities. Another study in Thai military conscripts estimated the probability of HIV transmission from an infected sex worker to a susceptible client to be between 0.031 and 0.056 (Mastro *et al.* 1994). This assumed, however, that there was no under-reporting of past contacts with sex workers, and that sex workers were the only potential source of infection – assumptions that are both likely to lead to exaggeration of the HIV transmission risk. In light of the limitations associated with both studies, we set the female-to-male transmission probabilities in commercial sex to the same levels as those assumed for female-to-male transmission in short-term non-spousal relationships.

Table 4.1 summarizes the beta prior distributions that have been chosen to represent the uncertainty regarding the HIV transmission probabilities.

Table 4.1: Assumed probabilities of HIV transmission per act of sex

Relationship type	Symbol	Male-to-female		Female-to-male ^c	
		Mean	Std dev.	Mean	Std dev.
CSW-client relationships	$\beta_{g,2}$	0.001 ^a	-	0.012 ^b	-
Short-term relationships	$\beta_{g,0}$	0.012	0.005	0.012	0.005
Long-term relationships	$\beta_{g,1}$	0.002	0.00075	0.002	0.00075

CSW = commercial sex worker.

^a Fixed parameter, not included in Bayesian analysis. ^b Parameter value is assumed to be the same as in short-term relationships. ^c For a male partner who is uncircumcised.

4.2 The effect of risk group

Sexually transmitted infections (STIs) have been shown to have a significant effect on HIV transmission probabilities, both when present in the HIV-susceptible partner (Røttingen *et al.* 2001; Sexton *et al.* 2005) and when present in the HIV-infected partner (Johnson and Lewis 2008). Although we do not model other STIs explicitly, we would expect the prevalence of other STIs to be higher in high risk groups than in low risk groups, and for this reason, some adjustment to the previously-stated HIV transmission probabilities may be appropriate, depending on the risk groups of the HIV-infected partner and the HIV-susceptible partner.

In a previous modelling study, which defined risk groups and relationship types in the same way that we have defined them here, the effect of STIs on HIV transmission in South Africa was simulated dynamically (Johnson *et al.* 2012b). Three possible sets of STI cofactors were considered to represent the range of possible multiples by which STIs increase HIV transmission risk; we consider here only the ‘base cofactors’, which were closest to the odds ratios estimated in meta-analytic reviews. Based on these assumed cofactors and the estimated levels of STI prevalence in different types of relationship, it is possible to estimate the ratios of average HIV transmission probabilities in high-risk interactions to average HIV

transmission probabilities when both partners are in the low risk group. These ratios are summarized in Table 4.2.

Table 4.2: Ratios of average HIV transmission probabilities in partnerships involving high-risk individuals to transmission probabilities in partnerships involving only low-risk individuals

	1985	1990	1995	2000	2005	2010	Average 1985-2010
Short-term relationships							
Infected male, susceptible female							
High risk male, low risk female	1.16	1.16	1.15	1.13	1.13	1.12	1.14
Low risk male, high risk female	1.11	1.11	1.09	1.07	1.07	1.07	1.09
High risk male, high risk female	1.25	1.25	1.22	1.16	1.17	1.17	1.20
Infected female, susceptible male							
High risk male, low risk female	1.28	1.27	1.25	1.24	1.24	1.24	1.25
Low risk male, high risk female	1.11	1.11	1.09	1.06	1.06	1.06	1.08
High risk male, high risk female	1.27	1.27	1.24	1.19	1.21	1.21	1.23
Long-term relationships							
Infected male, susceptible female							
High risk male, low risk female	1.37	1.41	1.38	1.31	1.29	1.29	1.35
Low risk male, high risk female	1.27	1.30	1.27	1.21	1.20	1.20	1.24
High risk male, high risk female	1.42	1.46	1.42	1.34	1.31	1.31	1.38
Infected female, susceptible male							
High risk male, low risk female	1.63	1.65	1.61	1.52	1.51	1.50	1.57
Low risk male, high risk female	1.40	1.41	1.37	1.28	1.27	1.28	1.33
High risk male, high risk female	1.70	1.72	1.67	1.57	1.54	1.53	1.62

These ratios are generally highest when both partners are in the high risk group. The ratios are more strongly influenced by the risk group of the male partner than the risk group of the female partner; this is partly because the prevalence of reproductive tract infections in women is much higher than in men, which means that the relative difference between high risk women and low risk women is small (even though the absolute difference may be larger than in men). It is also partly because the assumed STI cofactors are generally higher when the STI occurs in the male partner than when the STI occurs in the female partner. Ratios are higher in long-term (marital) relationships than in short-term relationships, and this is likely to be because STI prevalence in short-term relationships is much higher than in long-term relationships (meaning that relative differences between low risk and high risk are small in short-term relationships). Ratios tend to diminish over time; this is likely to be due to the substantial reduction in the prevalence of certain curable STIs (syphilis, chancroid and gonorrhoea, which occur mainly in the high risk group) in the mid- to late 1990s (Johnson *et al.* 2012b).

In our model, we adjust the HIV transmission probabilities using the average of the ratios estimated over the 1985-2010 period (shown in the last column of Table 4.2). The transmission probabilities specified in the previous section are assumed to apply to partnerships in which both partners are in the low risk group (except in the case of interactions between sex workers and clients, in which both partners are assumed to be high risk). The parameter $\Theta_{g,i,l,j}$ is therefore defined to represent the ratio of the transmission probability from an infected individual of sex g and risk group i to a partner of type l in risk

group j , to the transmission probability that would be expected if both partners were low risk. Although it would be possible to allow for time-varying multiples, it is worth noting that the ratios do not depart substantially from the average over time, and allowing the multiples to change over time would therefore not change the model results materially. It is also worth noting that even when both partners are in the high risk group, transmission probabilities are only of the order of 1.20-1.62 times those in low-risk partnerships. This is in contrast to the ASSA AIDS and Demographic model, which assumes HIV transmission probabilities in the high risk group to be 3.5-5 times the HIV transmission probabilities in the intermediate risk group (Actuarial Society of South Africa 2011).

4.3 The effect of HIV stage and antiretroviral treatment

HIV viral load has been shown to be a significant determinant of HIV transmission. In a recent meta-analysis, it was estimated that the HIV transmission rate from untreated HIV-positive individuals to their HIV-negative partners varies from 0.16 per 100 person years when the viral load is less than 400 RNA copies/ml, to 9.03 per 100 person years when the HIV viral load is more than 50 000 RNA copies/ml (Attia *et al.* 2009). Quinn *et al.* (2000) estimated that for every unit increase in the logarithm of the HIV viral load in blood plasma, there was a 2.45-fold increase in the odds of HIV transmission occurring within heterosexual unions, and a similar effect was estimated in the Partners in Prevention trial (Lingappa *et al.* 2010). Even stronger associations have been estimated between HIV transmission and the concentration of HIV in semen (Chakraborty *et al.* 2001).

Although viral load is the principal determinant of HIV-1 transmission, our model does not stratify individuals according to their viral load, and it is therefore necessary to consider the effect of CD4 count on HIV transmission. Donnell *et al.* (2010) estimate that in untreated HIV-infected adults, the rate of HIV transmission to susceptible partners varies from 1.77 per 100 person years in individuals with CD4 >350, to 2.79 per 100 person years in individuals with CD4 between 200 and 350, to 8.79 per 100 person years in individuals with CD4 counts less than 200. As discussed in section 2.10, the frequency of unprotected sex may be reduced at lower CD4 counts, which would imply a greater difference in HIV transmission probabilities *per act of sex* than is suggested by the quoted *per period* transmission rates. Combining the relative frequencies of unprotected sex estimated in section 2.10 with the relative infectiousness per period estimated by Donnell *et al.*, we estimate that the average infectiousness per act of unprotected sex, expressed as a multiple of that in the CD4 $\geq 500/\mu\text{l}$ category, is 1.02 in the CD4 350-499 category, 2.13 in the CD4 200-349 category, and 9.47 in the CD4 <200 category.

It is also possible to derive crude estimates of the relative transmission risks in different CD4 categories based on known distributions of viral load levels by CD4 count. For example, Abu-Raddad *et al.* (2013) report average viral load levels for HIV-infected South Africans in the same four CD4 categories as defined previously, based on a systematic review. If it is assumed that the transmission rate from an infected individual increases by a factor of 2.89 for each unit increase in the log of the viral load (Hughes *et al.* 2012), the risk of transmission calculated from the systematic review is 2.52 times higher in individuals with CD4 <200 than in individuals with CD4 of 500 or greater, and the risk of transmission is 1.74 times higher in individuals with CD4 of 200-349 than in individuals with CD4 of 500 or greater. These differences in infectivity are less substantial than those observed by Donnell *et al.* (2010). It is

likely that viral load is not the only determinant of infectiousness, and that HIV disease stage may have an effect on transmission rates independent of viral load (Wawer *et al.* 2005). This means that estimating levels of infectiousness in different CD4 categories based only on viral load is likely to lead to underestimation of differences in infectiousness between CD4 categories. In a meta-analysis of studies of HIV transmission probabilities, the effect of advanced disease was estimated to be much greater, with the transmission probability per act of sex in advanced disease being estimated at 7.3 (95% CI: 4.5-11.9) times that in asymptomatic infection (Boily *et al.* 2009). These estimates are more consistent with the estimates of Donnell *et al.*

Based on these various data sources, we have assumed that I_5 , the ratio of infectiousness in untreated individuals with CD4 counts <200 cells/ μ l to that in untreated individuals with CD4 counts >500/ μ l, is 7. This is in line with the meta-analysis of Boily *et al.* The ratio of infectiousness in untreated individuals with CD4 counts 200-349 cells/ μ l to that in untreated individuals with CD4 counts >500/ μ l is assumed to be $I_5 = 2$, based on the relative differences in viral load estimated by Abu-Raddad *et al.* (2013) and based on the adjusted estimates of Donnell *et al.* (2010). As viral load levels tend to be relatively stable at higher CD4 counts, and as Donnell *et al.* (2010) found the HIV transmission risk to be similar in the CD4 >500 and 350-500 categories, it is assumed that the ratio of infectiousness in the former group to the latter (I_3) is 1.

The HIV transmission risk is also extremely high during the acute stage of HIV infection. Wawer *et al.* (2005) estimated that the average HIV transmission risk in Rakai (Uganda) was 0.0082 per sex act during the first 2.5 months of infection, 0.0015 per sex act during the period from 6 to 15 months after seroconversion, and 0.0007 per sex act when the duration of infection in the infected partner is unknown. A limitation of this study is that it included all sex acts in the calculation of the denominators (including sex acts after the date of transmission), leading to some under-estimation of the true transmission probability per sex act. When the same data were used in a model that accounted more accurately for the sex acts that could lead to transmission, the level of infectiousness in the acute stage of infection was estimated to be 26 times that in the asymptomatic stage of HIV infection (Hollingsworth *et al.* 2008). Although this multiple of 26 may be realistic, the use of such high multiples in frequency-dependent models is problematic, as frequency-dependent models assume that susceptible individuals can interact with newly-infected individuals immediately after they become infected – when in reality newly-infected individuals in monogamous partnerships would be unlikely to have sex with anyone other than the partner who infected them during the short acute phase (Johnson and Geffen 2013). As our model is frequency-dependent, some downward adjustment to the multiple of 26 might be considered appropriate. Brian Williams and Christopher Dye argue that it would be more appropriate – given the small sample size of the Rakai study – to base the assumed difference in infectiousness on the observed viral load difference (about 2 log) between acute and chronic infection (Cohen *et al.* 2012), which would imply a multiple of 8.4 if it is assumed that infectiousness per sex act increases by a factor of 2.89 per unit increase in viral load (Hughes *et al.* 2012). Based on the available evidence, we set the I_1 parameter to 10.

Antiretroviral treatment reduces HIV viral load levels considerably, and therefore reduces substantially the probability of HIV transmission. Donnell *et al.* (2010) found that in heterosexual HIV-discordant couples, the probability of HIV transmission per period was 92% lower (95% CI: 43-100%) when the index partner was receiving ART than when the

index partner was untreated, after controlling for CD4 count. Attia *et al* (2009) found the same percentage reduction in the transmission rate per period in a meta-analytic review of studies in heterosexual serodiscordant couples, although this analysis did not adjust for CD4 count. However, both studies report on the effect of HAART on the probability of HIV transmission per period, rather than the effect on the HIV transmission probability per act of unprotected sex. To the extent that individuals receiving HAART are more likely to be using condoms than untreated HIV-positive individuals, the 92% estimate may overstate the true reduction in infectiousness per act of unprotected sex. In a recent randomized controlled trial, Cohen *et al* (2011) found that individuals who were randomized to start ART when their CD4 counts were between 350 and 550 were 96% less likely (95% CI: 73-99%) to transmit HIV to their sexual partners than individuals who were randomized to start ART only when their CD4 count had fallen below 250. However, a number of recent studies from field settings in developing countries suggest that ART may in fact be substantially less effective than has been estimated in clinical trials and in high income countries. Jia *et al* (2013) found that in a large cohort of serodiscordant couples in China, the transmission rate when the index partner was on ART was only 26% lower (95% CI: 16-35%) than when the index partner was not on ART. Even more concerning, Birungi *et al* (2012) found no significant difference in transmission rates when comparing index partners on ART and index partners not on ART in Uganda. We have set the assumed reduction in infectiousness after ART initiation to 80%. Although most modelling studies assume more substantial reductions in infectiousness, we have chosen 80% as it is closer to the efficacy levels implied by the recent studies in China and Uganda. It is also important to note that our current model does not distinguish between individuals who are actively receiving ART and individuals who have interrupted ART, and as the latter would have a relatively high rate of infectiousness, it is appropriate to assume an average transmission rate somewhat higher than what might be expected in individuals actively receiving ART.

It is likely that the infectiousness of individuals receiving HAART is to some extent dependent on their CD4 count. Individuals who have lower baseline CD4 counts at the time of starting HAART are significantly more likely to experience virological failure (Datay *et al.* 2010; Tuboi *et al.* 2007; Boulle *et al.* 2010; Tarwater *et al.* 2001; Nglazi *et al.* 2011; Fox *et al.* 2012). In addition, individuals with higher baseline CD4 counts are also more likely to resuppress viraemia after experiencing virological failure (Hoffmann *et al.* 2009). Individuals starting HAART at high CD4 counts are therefore likely to be less infectious than individuals starting HAART at low CD4 counts. In our model we assume that infectiousness after ART initiation depends on CD4 count at the time of ART initiation, with the percentage reduction in infectiousness being the same regardless of the CD4 count at the time of ART initiation.

4.4 Condom effectiveness

In a pooled analysis, based on a systematic review of HIV transmission studies, Weller and Davis (2004) estimated that the average rate of HIV transmission in serodiscordant couples always using condoms was 1.14 per 100 PY, which compared with 5.75 per 100 PY in serodiscordant couples never using condoms. This suggests condoms are about 80% effective in preventing HIV transmission. This is consistent with data from a recent randomized trial in serodiscordant couples (Hughes *et al.* 2012), which recorded detailed data on numbers of protected and unprotected sex acts in each period, estimating an effectiveness of 78% (95% CI: 58-89%). However, both estimates are probably under-estimates, since it is likely that

some individuals who report ‘always’ using condoms do not use them as consistently as they claim (Holmes *et al.* 2004; Meekers and Van Rossem 2005). In the model it is therefore assumed that condoms have a 90% chance of preventing HIV transmission per sex act.

4.5 Age-related factors

Young women appear to be biologically more susceptible to HIV than older women. For example, in a study which controlled for a large number of known risk factors for HIV transmission, Mackelprang *et al.* (2012) found that each 10-year increase in age was associated with 60% reduction in the rate of HIV acquisition (equivalent to a roughly 10% reduction in HIV acquisition risk per additional year of age). In another study of Kenyan sex workers, HIV transmission probabilities per act of sex decreased by 3.5% per year of age, equivalent to a 30% reduction in HIV risk per 10-year increase in age (Kimani *et al.* 2008). In a study of Ugandan women married to HIV-positive men (Carpenter *et al.* 1999), the rate of seroconversion in women aged 25-34 was 43% lower than that in women aged 13-24 (again corresponding to a roughly 10-year age difference).

There are a number of possible explanations for the high risk of HIV acquisition in young women. Firstly, there is a high prevalence of cervical ectopy in adolescence and early adulthood. Several studies have shown that the presence of cervical ectopy is significantly associated with HIV risk (Plourde *et al.* 1994; Myer *et al.* 2006; Moss *et al.* 1991), although other studies have not confirmed this (Ghys *et al.* 2001; Mati *et al.* 1995; Moscicki *et al.* 2001). It is also possible that the high risk of HIV acquisition at young ages is a reflection of other sources of variation in HIV susceptibility, with the most susceptible women being infected soon after starting sexual activity and the less susceptible women remaining uninfected until their mid-20s. This variation in susceptibility could be due to variation in genetic factors or levels of immune activation, which have been linked to the risk of HIV acquisition (Kaul *et al.* 2011; He *et al.* 2008; Lajoie *et al.* 2006).

In our model we allow for the age effect by assuming that for each year of age below age 25, susceptibility to HIV in individuals of sex g increases by Z_g , so that the ratio of HIV transmission risk (per sex act with an infected partner) in women aged 30 to that in women aged 20 is

$$(1 + Z_g)^5.$$

We have set the Z_2 parameter equal to 0.15. Substituting this value into the above equation gives a 30- to 20-year old susceptibility ratio of 0.50, roughly consistent with the relative rates of transmission estimated from the literature (Mackelprang *et al.* 2012; Kimani *et al.* 2008; Carpenter *et al.* 1999). It should be noted, however, that our model of the age effect is not the same as the standard exponential model used in most statistical analyses, and our model would estimate different ratios if we were to use reference ages other than 20 and 30 (we chose the 20-30 age range as it is the age range in which HIV-negative women are most frequently recruited and followed (Carpenter *et al.* 1999)). The function $Z_g(x)$ is defined as

$$Z_g(x) = \begin{cases} (1 + Z_g)^{25-x} & \text{for } x < 25 \\ 1 & \text{for } x \geq 25 \end{cases}$$

For males, there does not appear to be strong evidence of age variation in the risk of HIV acquisition per sex act (Hughes *et al.* 2012; Carpenter *et al.* 1999). We have therefore set the Z_1 parameter to zero.

4.6 Mathematical model

We define $\Gamma(s)$ to be the relative frequency of sex in untreated HIV disease stage s , relative to that in uninfected individuals (these parameters are estimated in section 2.10). We further define $\beta_{g,l}$ to be the average transmission probability per act of sex in relationships of type l , when the infected partner is of sex g (the prior distributions for these parameter values are specified in Table 4.1). These transmission probabilities are assumed to be weighted averages of the probabilities from all untreated disease stages, where the weights are calculated from the expected numbers of unprotected sex acts in each stage. If we define $\beta_{g,l}^*$ to be the transmission probability from chronically-infected individuals who have CD4 counts ≥ 500 cells/ μl ($s = 2$), then

$$\beta_{g,l} = \beta_{g,l}^* \frac{\sum_{s=1}^3 \frac{I_s \Gamma(s)}{\lambda_s} + \frac{I_4 \Gamma(4)}{\lambda_4 + \mu_4} + \frac{\lambda_4}{\lambda_4 + \mu_4} \times \frac{I_5 \Gamma(5)}{\mu_5}}{\sum_{s=1}^3 \frac{\Gamma(s)}{\lambda_s} + \frac{\Gamma(4)}{\lambda_4 + \mu_4} + \frac{\lambda_4 \Gamma(5)}{(\lambda_4 + \mu_4) \mu_5}},$$

where the I_s factors are as defined in section 4.3, and the CD4 decline parameters (λ_s) and mortality parameters (μ_s) are those specified in section 3.1. We define I_s^* to be the ratio of infectiousness in stage s to average infectiousness, from which it follows that

$$I_2^* = \beta_{g,l}^* / \beta_{g,l},$$

and hence

$$I_2^* = \frac{\sum_{s=1}^3 \frac{\Gamma(s)}{\lambda_s} + \frac{\Gamma(4)}{\lambda_4 + \mu_4} + \frac{\lambda_4 \Gamma(5)}{(\lambda_4 + \mu_4) \mu_5}}{\sum_{s=1}^3 \frac{I_s \Gamma(s)}{\lambda_s} + \frac{I_4 \Gamma(4)}{\lambda_4 + \mu_4} + \frac{\lambda_4}{\lambda_4 + \mu_4} \times \frac{I_5 \Gamma(5)}{\mu_5}}.$$

For other values of s , $I_s^* = I_2^* \times I_s$. Lastly, we define $I_s^*(a)$ to be the relative infectiousness for individuals with ART status a (0 implying untreated and 1 implying treated), where s is either the current HIV stage (for $a = 0$) or the HIV stage at the time ART was initiated (for $a = 1$). For treated individuals who started ART in HIV disease stage s , the relative infectiousness is simply $I_s^*(1) = I_s^*(1 - 0.8)$, while for untreated individuals $I_s^*(0) = I_s^*$.

We define $G(v,a)$ to be the ratio of the proportion of sex acts that are unprotected in individuals with testing history v and ART status a , to that in individuals who are HIV-negative. The HIV testing history v is coded as 0 if the individual has never been tested, 1 if the individual has been tested but not diagnosed positive, and 2 if the individual has been diagnosed positive. For all values of $v < 2$, we set $G(v,a) = 1$, while for $v = 2$ we set

$$G(v,a) = (1 - \delta)(1 - h)^a,$$

where the δ and h parameters represent the reductions in unprotected sex due to HIV diagnosis and ART initiation respectively (see sections 2.11 and 2.12).

We define $Y(a,s,d)$ to be the ratio of the frequency of sex in individuals with ART status a and CD4 stage s , who have been on ART for d years, to the frequency of sex in HIV-negative individuals. In the case of untreated individuals ($a = 0$ and $d = 0$), $Y(0,s,0) = \Gamma(s)$. In the case of treated individuals, we define

$$Y(1,s,d) = \sum_{s'=2}^5 \psi_d(s' | s) \Gamma(s'),$$

where $\psi_d(s' | s)$ is the proportion of ART patients with current CD4 count in category s' , in the cohort of patients who started ART with a CD4 count of s and who have been on ART for d years (as defined in Appendix C). The frequency of sex is thus assumed to be a function only of the *current* CD4 count.

For the purpose of calculating average transmission probabilities, we define $N_{g,i,l,j}^r(x)$ to be the total number of individuals aged x and of sex g , who are in risk group i , in relationship state l (0 for unmarried, 1 for married/cohabiting and 2 for sex workers) with a partner in risk group j (the j subscript is omitted in the case of unmarried individuals, i.e. for $l = 0$ or $l = 2$) and circumcision status r (1 for circumcised males, 0 otherwise). Within this group we define $X_{g,i,l,j}^r(x,a,s,v,d)$ to be the proportion who are in HIV stage s , with ART status a , HIV testing history v and ART duration d . In total there are 35 possible HIV-positive states, summarized in Table 4.3.

Table 4.3: Definitions of HIV-positive states

ART status (<i>a</i>)	HIV stage (<i>s</i>)	Testing history (<i>v</i>)	ART duration (<i>d</i>)	Description
0	1	0	0	Acutely infected, never tested
0	2	0	0	CD4 ≥500, never tested
0	3	0	0	CD4 350-499, never tested
0	4	0	0	CD4 200-349, never tested
0	5	0	0	CD4 <200, never tested
0	1	1	0	Acutely infected, previously tested but undiagnosed
0	2	1	0	CD4 ≥500, previously tested but undiagnosed
0	3	1	0	CD4 350-499, previously tested but undiagnosed
0	4	1	0	CD4 200-349, previously tested but undiagnosed
0	5	1	0	CD4 <200, previously tested but undiagnosed
0	1	2	0	Acutely infected, diagnosed but not yet treated*
0	2	2	0	CD4 ≥500, diagnosed but not yet treated
0	3	2	0	CD4 350-499, diagnosed but not yet treated
0	4	2	0	CD4 200-349, diagnosed but not yet treated
0	5	2	0	CD4 <200, diagnosed but not yet treated
1	2	2	0	Started ART with CD4 ≥500 in current year
1	2	2	1	Started ART with CD4 ≥500 in previous year
1	2	2	2	Started ART with CD4 ≥500 2 years previously
1	2	2	3	Started ART with CD4 ≥500 3 years previously
1	2	2	4	Started ART with CD4 ≥500 4 years previously or earlier
1	3	2	0	Started ART with CD4 350-499 in current year
1	3	2	1	Started ART with CD4 350-499 in previous year
1	3	2	2	Started ART with CD4 350-499 2 years previously
1	3	2	3	Started ART with CD4 350-499 3 years previously
1	3	2	4	Started ART with CD4 350-499 4 years previously or earlier
1	4	2	0	Started ART with CD4 200-349 in current year
1	4	2	1	Started ART with CD4 200-349 in previous year
1	4	2	2	Started ART with CD4 200-349 2 years previously
1	4	2	3	Started ART with CD4 200-349 3 years previously
1	4	2	4	Started ART with CD4 200-349 4 years previously or earlier
1	5	2	0	Started ART with CD4 <200 in current year
1	5	2	1	Started ART with CD4 <200 in previous year
1	5	2	2	Started ART with CD4 <200 2 years previously
1	5	2	3	Started ART with CD4 <200 3 years previously
1	5	2	4	Started ART with CD4 <200 4 years previously or earlier

* Only relevant in the case of individuals who seroconvert while receiving PrEP, microbicides or regular HCT – all other infections are assumed to be diagnosed following acute infection.

For an HIV-positive individual with state covariates (a, s, v, d), the rate at which they will transmit HIV, per short-term partnership with a partner in risk group j , is

$$\begin{aligned}
 & n_{g,0}(x)Y(a,s,d)\beta_{g,0}I_s^*(a)\Theta_{g,i,0,j}\left(1-\left[1-(1-\gamma_{g,0}(x,t))G(v,a)\right]E\right) \\
 & = n_{g,0}(x)Y(a,s,d)\beta_{g,0}I_s^*(a)\Theta_{g,i,0,j}\left\{\left(1-\gamma_{g,0}(x,t)\right)G(v,a)E+(1-E)\right\}
 \end{aligned}$$

where $n_{g,0}(x)$ is the average number of sex acts per short-term relationship, $\gamma_{g,0}(x,t)$ is the probability of condom use by HIV-negative individuals (as defined in section 2.9), and E is the condom efficacy parameter. From this we can calculate the probability of HIV transmission per short-term partnership:

$$1 - \exp\left(-n_{g,0}(x)Y(a,s,d)\beta_{g,0}I_s^*(a)\Theta_{g,i,0,j}\left\{\left(1-\gamma_{g,0}(x,t)\right)G(v,a)E+(1-E)\right\}\right).$$

The average rate at which individuals transmit HIV, per short-term partnership with a partner in risk group j , is defined as

$$T_{g,i,l,k}^{0,r}(j,x) = \sum_{a,s,v,d} X_{g,i,l,k}^r(x,a,s,v,d) n_{g,0}(x) Y(a,s,d) \beta_{g,0} I_s^*(a) \Theta_{g,i,0,j} \\ \times \left\{ (1 - \gamma_{g,0}(x,t)) G(v,a) E + (1 - E) \right\}$$

For the sake of simplicity, we consider here only the case where the susceptible partner is uncircumcised and is not receiving PrEP or microbicides, but we note that allowing for these factors involves only a multiplicative adjustment to the $T_{g,i,l,k}^{0,r}(j,x)$ variable. It is also worth noting here that although we have expressed these equations in terms of rates of transmission per short-term partnership, the approach is the same for long-term partnerships (replacing 0 with 1 in the above equations), except that $n_{g,1}(x)$ is defined as the number of sex acts *per month*, and hence $T_{g,i,l,k}^{1,r}(j,x)$ represents the average transmission rate per month rather than per partnership. The same approach is also followed in interactions between sex workers and their clients (replacing 0 with 2 in the above equations), except that these interactions are assumed to comprise a single act, meaning that the $n_{g,l}(x)$ factor is 1 and $T_{g,i,l,k}^{2,r}(j,x)$ represents the average transmission probability per sex act. Finally, it should be noted that the relationship type in the superscript is not necessarily the same as the marital status indicator (l) in the subscript, as some married individuals may engage in extramarital or commercial sex activity. Similarly, the risk group of the long-term partner (k) is not necessarily the same as the risk group of the partner under consideration (j).

The average probability of transmission per short-term relationship is calculated as

$$1 - \exp\left(-T_{g,i,l,k}^{0,r}(j,x)\right),$$

and the average probability that an individual aged x , of sex g and risk group i , transmits HIV to a short-term partner in risk group j is

$$U_{g,i}^0(j,x) = 1 - \frac{\sum_{r,l,k} N_{g,i,l,k}^r(x) c_{g,i,l}(x) \exp\left(-T_{g,i,l,k}^{0,r}(j,x)\right)}{\sum_{r,l,k} N_{g,i,l,k}^r(x) c_{g,i,l}(x)},$$

where $c_{g,i,l}(x)$ is the annual rate at which new non-spousal relationships are formed. Similarly, the average monthly probability that an individual aged x , of sex g and risk group i , transmits HIV to a long-term partner in risk group j is

$$U_{g,i}^1(j,x) = 1 - \frac{\sum_r N_{g,i,l,j}^r(x) \exp\left(-T_{g,i,l,j}^{1,r}(j,x)\right)}{\sum_r N_{g,i,l,j}^r(x)},$$

and the average probability that a client transmits HIV to a sex worker is

$$U_{1,1}^2 = \frac{\sum_{r,l,k,x} N_{1,1,l,k}^r(x) w_l(x) T_{1,1,l,k}^{2,r}(1)}{\sum_{r,l,k,x} N_{1,1,l,k}^r(x) w_l(x)},$$

where $w_l(x)$ is the annual rate at which high risk men visit sex workers if they are aged x and of marital status l .

Now consider a sexually experienced HIV-*negative* individual of sex g in risk group i , aged x and with marital status l . The probability that this individual acquires HIV from a short-term partner in the next month is

$$P_{g,i,l}^0(x) = 1 - \exp\left(-\frac{c_{g,i,l}(x)}{12} Z_g(x) \sum_{y=10}^{90} f_{g,0}(y|x) \times [\rho_{g,i,0}(1,t) U_{3-g,1}^0(i,y) + \rho_{g,i,0}(2,t) U_{3-g,2}^0(i,y)]\right)$$

where $f_{g,0}(y|x)$ is the proportion of short-term partners who are aged y (as defined in section 2.6), $\rho_{g,i,0}(j,t)$ is the proportion of partners who are in risk group j (as defined in Appendix A), and $(3-g)$ is the sex opposite to g .

If the individual is married to an individual in risk group j , the probability that they acquire HIV from their marital partner in the next month is

$$P_{g,i,l,j}^1(x) = 1 - \exp\left(-Z_g(x) \sum_{y=10}^{90} f_{g,1}(y|x) U_{3-g,j}^1(i,y)\right).$$

If the individual is a high-risk male, then the probability that they acquire HIV from a sex worker in the next month is

$$P_{1,1,l}^2(x) = 1 - \exp\left(-\frac{w_l(x)}{12} Z_1(x) \sum_{y=10}^{90} N_{2,1,2}^0(y) T_{2,1,2}^{2,0}(1,y) / \sum_{y=10}^{90} N_{2,1,2}^0(y)\right),$$

and if the individual is a female sex worker her probability of HIV acquisition in the next month is

$$P_{2,1,2}^2(x) = 1 - \exp\left(-\frac{C}{12} Z_2(x) U_{1,1}^2\right),$$

where C is the average annual number of clients a sex worker has.

It is worth noting that in the previous ASSA AIDS and Demographic model, the HIV transmission probability was calculated on the assumption of a fixed number of sex acts per partnership, while the approach described here allows for random variation in the number of sex acts per partnership or per period, implicitly assuming the number of sex acts to be Poisson-distributed. Although this makes little difference when HIV transmission probabilities are low, the impact of the Poisson assumption can be material at higher HIV transmission probabilities.

5. Modelling paediatric HIV

The model of paediatric HIV is the same as that described previously (Johnson *et al.* 2012a; Johnson *et al.* 2012d), although several changes have been made in incorporating this paediatric HIV model into the adult model, and several parameters have been updated in light of recent data. The sections that follow briefly describe the model and the changes that have been made. Parameter values have been set at the posterior means of the distributions estimated previously, rather than at the prior means, as we do not intend to refit the model to the paediatric HIV prevalence data at this stage.

5.1 Changes to demographic assumptions

The following changes have been made to the demographic component of the paediatric HIV model:

- The paediatric HIV model has been integrated into the adult HIV model, so that the numbers of births is determined by the adult model, rather than being an independent input into the model.
- The previous paediatric HIV model relied mainly on the ASSA2003 model for the demographic parameters (non-HIV mortality rates and initial population size). The new model relies on the ASSA2008 model and more recent estimates of fertility.
- The new model allows for migration into the population of children below the age of 15, which was not allowed for in the previous paediatric HIV model.

5.2 Changes to vertical transmission assumptions

The model allows for two types of mother-to-child transmission (MTCT): perinatal transmission (at or before the time of birth, i.e. intrapartum or intrauterine) and postnatal transmission (transmission occurring due to breastfeeding). In the case of perinatal transmission, the probability of HIV transmission is assumed to depend on the mother's HIV disease stage (highest when the mother is in the acute and CD4 <200 stages) and the type of antiretroviral prophylaxis that is received (AZT, single-dose nevirapine (sd NVP), AZT + sd NVP, or triple-drug antiretroviral regimens). In the case of postnatal transmission, the monthly probability of transmission through breastfeeding is assumed to depend on the type of feeding (higher for mixed feeding than for exclusive breastfeeding), the mother's HIV disease stage and the type of antiretroviral prophylaxis (extended NVP prophylaxis or maternal triple-drug regimens). Assumptions about maternal choices regarding type of infant feeding and duration of feeding are based on South African studies.

A limitation of the previous model was that it assumed a fixed CD4 distribution in HIV-positive mothers, with no allowance for the change in CD4 distribution (and associated MTCT rate) that might be expected over time, as the epidemic matures and as relatively more women enter the advanced stages of disease. The model also did not allow for the possibility that many of the pregnant HIV-positive women might already have been on ART at the time of their first antenatal visit (i.e. having started ART prior to conception). The new model dynamically determines the number of births to women in different CD4 stages as well as the

number of births to women who were already on ART prior to conception, overcoming both problems. HIV incidence rates in pregnant women are estimated based on the numbers of women in the acute stage of HIV infection.

The following changes have been made to the model of vertical transmission:

- Since the publication of our previous paediatric HIV model, the District Health Barometer (DHB) has reported the proportion of pregnant women tested for HIV to be 100% over the period April 2010-March 2011 (Day *et al.* 2012) and 98% over the period from April 2011 to March 2012 (Massyn *et al.* 2013). This is consistent with the proportion of 97.4% measured in a national survey conducted in June-November 2010 (Goga *et al.* 2012). These estimates are higher than our previously-assumed proportion of 92%. We have increased the assumed proportions of women receiving HIV testing from 91% and 92% in 2009 and 2010 respectively, to 93% and 97% respectively. The assumed ultimate proportion that applies after 2010 has also been increased from 92% to 98%, consistent with the 2011/12 DHB.
- Based on the 2010 national PMTCT survey, it is estimated that the proportion of HIV-positive mothers who received no ARV prophylaxis was 8%, the proportion who received HAART was 33%, the proportion who received sd NVP as well as AZT was 41%, the proportion who received short-course AZT but no sd NVP was 13%, and the proportion who received only sd NVP was 5% (Kate Kerber, personal communication). Using these data, we estimate that of women diagnosed with HIV who do not start HAART, the proportion who receive sd NVP is $(0.05 + 0.41)/(0.974 - 0.33) = 71\%$ (this proportion was previously set at 75%). Of those women who receive sd NVP, the proportion who also receive AZT is $0.41/(0.41 + 0.05) = 89\%$ in the year 2010, which is consistent with the assumptions we made previously. Of those women who are diagnosed positive but do not start HAART or receive nevirapine, the proportion who receive AZT is $0.13/(0.974 - 0.33 - 0.41 - 0.05) = 71\%$, which is 79% of the AZT proportion in women who did receive nevirapine. This is substantially higher than the ratio of 40% assumed previously, based on unpublished cord blood data from the Western Cape and Free State. AZT has a relatively short half life in plasma (Stinson *et al.* 2012), which may explain why the detection of AZT was relatively low in women not receiving intrapartum prophylaxis. We have therefore changed the assumed ratio to 79%.
- Previously it was assumed that there was no repeat testing of HIV in late pregnancy prior to 2010. Recent studies suggest that the proportion of women testing negative who get tested again in late pregnancy has been steadily increasing over time. For example, Orié *et al.* (2009) estimated this proportion to be only 6.1% in a Pietermaritzburg hospital in 2007, while Grimwood *et al.* (2012) estimated that in 58 clinics situated across three provinces, the proportion increased from 25.6% in 2009 to 46.2% in 2011. Based on these data, we assume that the percentage of women offered retesting in late pregnancy increases from 5% in 2007 to 45% in 2011 and then levels off at 50% in subsequent years.
- The model has been updated to take into account the effect of the adoption of WHO option B for PMTCT (announced at the end of November 2012). It is assumed that from the start of 2013 onwards, pregnant HIV-positive women with CD4 counts $\geq 350/\mu\text{l}$ have the same probability of starting ART during pregnancy as pregnant HIV-positive women with CD4 counts $< 350/\mu\text{l}$.
- Previously it was assumed that all women who initiated HAART prior to delivery had the same probability of transmitting HIV to their infants at or before birth. However,

the evidence summarized in Table 5.1 suggests that there is substantial variation in transmission rates between women who start HAART with a CD4 count <200 (standard treatment protocols) and women who start ART at higher CD4 counts (in line with WHO option B). In addition, women who started HAART prior to conception appear to have a very low vertical transmission rates. Based on these data we have set the average MTCT rates at or before birth to 0.6% if HAART was initiated prior to conception, 1.5% if HAART was initiated during pregnancy with a CD4 count of 200 or higher, and 3.1% if HAART was initiated during pregnancy with a CD4 count of <200.

Table 5.1: Rates of perinatal transmission in women initiating HAART

Timing of ART initiation	Study	Location	n	MTCT rate
Prior to conception	Homsy <i>et al</i> (2009)	Uganda	118	0.0%
	Bera <i>et al</i> (2010)	South Africa	172	1.2%
	Hoffman <i>et al</i> (2010)	South Africa	143	0.7%
	Average			0.6%
During pregnancy, no CD4 restriction on ART initiation*	Peltier <i>et al</i> (2009)	Rwanda	532	1.1%
	Palombi <i>et al</i> (2007)	Multicentre study	809	0.8%
		Mozambique	341	1.2%
	Shapiro <i>et al</i> (2010)	Botswana	270	0.4%
	Geddes <i>et al</i> (2011)	South Africa	373	2.1%
	Kesho Bora Study Group (2011)	Multicentre study	375	3.3%
Average			1.5%	
During pregnancy, after meeting standard ART eligibility criteria	Tonwe-Gold <i>et al</i> (2007)	Côte d'Ivoire	107	1.0%
	Bera <i>et al</i> (2010)	South Africa	495	2.8%
	Hoffman <i>et al</i> (2010)	South Africa	730	5.8%
	Shapiro <i>et al</i> (2010)	Botswana	156	0.6%
	Fitzgerald <i>et al</i> (2010)	South Africa	217	5.1%
Average			3.1%	

* In most studies, no restrictions were placed on which women initiated ART, although the results presented for the study of Shapiro *et al* relate only to women with CD4 counts of 200-500, and the study of Geddes *et al* excluded some women with high CD4 counts and low viral loads.

The model has also been updated to allow for the phasing out of free formula milk, which started in 2011 (National Breastfeeding Consultative Group 2011). The proportion of HIV-diagnosed mothers who choose not to breastfeed is assumed to decline from 50% in mid-2011 to 20% by mid-2013.

5.3 Changes to paediatric HIV survival assumptions

The model of paediatric HIV survival specifies HIV survival assumptions that apply to all children under the age of 10. HIV-positive children who are not on ART are classified as being in either an early or a late HIV disease stage (late disease is defined as having met the immunological or clinical criteria that were previously used to determine ART eligibility under the 2006 WHO paediatric ART guidelines (World Health Organization 2007)). Children who are on ART are similarly classified as having started ART either in the early or late disease stage. This model of HIV survival is summarized in Figure 5.1. Although the

model allows for ART discontinuation, we have temporarily set the assumed rates of discontinuation to zero (as in the adult model) pending a more detailed investigation into rates of ART discontinuation in South Africa.

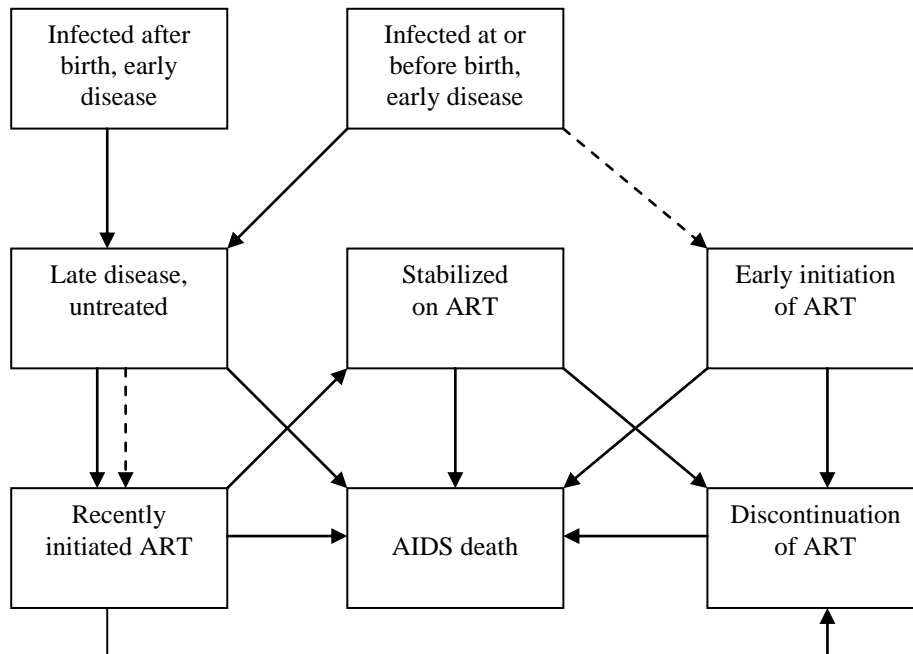


Figure 5.1: Multi-state model of HIV survival in HIV-positive children

All children are assumed to experience non-AIDS mortality rates that vary by age and sex (not shown). Dashed arrows represent ART initiation at 2 months of age, following PCR screening at 6 weeks.

On reaching age 10, children who are in the late HIV stage and ART-naïve get moved into the CD4 <200/ μ l category (since this is the threshold for ART eligibility that was recommended for older children in the 2006 WHO guidelines, and since the modelled mortality rates in untreated 9-year olds with late disease are similar to the modelled mortality rates in untreated 10-year olds with CD4 <200/ μ l). Children who are ART-naïve and in early disease on reaching age 10 are divided equally between the CD4 500+, 350-499 and 200-349 categories. As we do not model HIV diagnosis in children under the age of 10, all of these ART-naïve children are assumed to be undiagnosed at age 10. Children who are on ART, who started ART in late disease, are assumed on reaching age 10 to move into the category of individuals who started ART with a CD4 count <200. Children who are on ART, who started ART in early disease, are also assumed on reaching age 10 to move into the category of individuals who started ART with a CD4 count of <200 (this is to be consistent with the assumption that the benefits to starting ART early in infants are limited mainly to the very young ages). HIV survival in 10-14-year olds is modelled according to the disease progression and mortality assumptions specified for adults, although the model of ART initiation in 10-14-year olds remains consistent with that in children under the age of 10.

The model of ART initiation in children has changed in several respects:

- The assumed proportion of HIV-exposed infants who are tested for HIV at 6 weeks, in the 2009-2010 period, has changed to be consistent with recent statistics from the

NHLS (Sherman and Lilian 2011). Over this period, approximately 93 000 PCR tests were performed in infants under the age of 2 months, in 8 of South Africa's provinces (KwaZulu-Natal was excluded). The number of births to HIV-positive mothers in these 8 provinces, over the same period, is estimated by the ASSA2008 model to be approximately 171 000. If 10% of these births were outside of the public sector, this would imply that approximately 60% of HIV-exposed infants got tested for HIV around 6 weeks in 2009-10 ($93/(0.9 \times 171)$). It is further assumed, as before, that only two thirds of these PCR test results are received (Rollins *et al.* 2009), so that the proportion of HIV- infected infants who actually got diagnosed at 6 weeks is assumed to be only 40% in 2009-10. In subsequent periods, the 60% proportion is assumed to increase to 80%, so that the ultimate proportion diagnosed at 6 weeks is 53% ($80\% \times 66\%$), in line with previous assumptions (Johnson *et al.* 2012a). More recently-published estimates of PCR numbers (Barron *et al.* 2013) are consistent with these assumed trends, and the 2011/12 DHB data suggest that about 82% of HIV-diagnosed mothers bring their infants for testing around 6 weeks of age (Massyn *et al.* 2013), although the data may be somewhat inflated due to the inclusion of PCRs in older infants. Self-reported data from the Western Cape suggest an even higher uptake of PCR testing and collection of test results (le Roux *et al.* 2013).

- In the previous model, it was assumed that all infants who were diagnosed at 6 weeks started ART immediately after diagnosis. Although we do not have local data to support this assumption, data from other African countries suggest that this assumption may be too optimistic, with a recent review finding that in African settings the proportion of infants starting ART following early diagnosis was consistently less than two thirds (Ciaranello *et al.* 2011). We have changed the assumed proportion of infants starting ART immediately after 6-week diagnosis to be consistent with the assumed proportions of symptomatic adults and pregnant women who start ART soon after diagnosis – this proportion rises from 65% in 2010 (when early infant diagnosis was introduced) to 80% by 2012. Although this may appear optimistic when compared with the review of Ciaranello *et al.*, it is in fact conservative when compared with data from the Western Cape, which show that in 2010, 71% of newly-diagnosed infants subsequently had viral load tests performed (indicating that they had started on ART) (Hsiao *et al.* 2013). (This 71% may be an under-estimate, since the denominator includes some children who tested positive but whose caregivers did not receive their test results, although in the Western Cape it appears that almost all test results do get collected (le Roux *et al.* 2013).) If it is assumed that only 66% of positive test results are received and that 80% of those testing positive start ART, the implied ratio of ART initiations to positive PCR results is 53%, consistent with the ratio of 54.4% reported in the 2011/12 DHB and 52.7% reported in the 2010/11 DHB (Massyn *et al.* 2013).
- The numbers of children starting ART in each period have been updated with data up to mid-2011 (Johnson 2012) and data from the 2011/12 year (Department of Health 2012). In the period from mid-2009 to mid-2012, the rate of ART initiation between the ages of 2 months and 15 years is calculated by subtracting the estimated number of children starting ART after early diagnosis from the estimated total number of children starting ART. In the period that follows mid-2012, we have no data on ART enrolment in children, and we therefore set the assumed rates of ART initiation between the ages of 2 months and 15 years with reference to an assumed average delay to starting ART, in children who have late disease. This average delay has been set at 24 months, longer than the assumed delay of 6 months in HIV-diagnosed adults

because we are not modelling the distinction between diagnosed and undiagnosed in children. The assumption of an average treatment delay differs from the approach adopted previously, which relied on an assumed ratio of the number of children starting ART to the number of children becoming eligible for ART.

Survival after ART initiation is modelled in the same way as before. The only change made to the previous model is that we have set the rates of ART discontinuation to zero, to be consistent with the modelling of adult survival after ART initiation. Attempts to estimate rates of ART interruption in children will be incorporated into future versions of the model.

6 Modelling HIV prevention programmes

This chapter describes the modelling of prevention programmes not covered in previous chapters: HIV testing and counselling, male circumcision, microbicides and pre-exposure prophylaxis. The modelling of behaviour change programmes and condom promotion has previously been described in section 2.9 and the modelling of prevention of mother-to-child transmission has been described in section 5.2.

6.1 HIV testing and counselling

6.1.1 Uptake of HIV testing and counselling

Voluntary counselling and testing (VCT) has traditionally taken the form of a stand-alone service provided by health facilities to individuals who independently seek HIV testing. Self-initiated HIV testing has been more frequent in women than in men. For example, Snow *et al* (2010) found that in Mpumalanga province, after excluding individuals who had either been referred for HIV testing by a health worker or tested as part of antenatal screening, the numbers of women tested were more than double the numbers of men tested. It was also found that the age distribution of men seeking testing was older than the age distribution of women seeking testing, mirroring the sex difference in the age pattern of HIV prevalence. A similarly large sex difference was found by Venkatesh *et al* (2011) in a 2007 household survey in Soweto, although this study did not exclude antenatal testing. In the 2009 National Communication Survey, the proportion of women who had been tested was more than double the proportion of men who had been tested below age 25, but at ages 45 and older the proportions were similar in males and females (Johnson *et al.* 2010). April *et al* (2009) also found that in the community of Masiphumelele, there were more women tested for HIV than men (even after excluding testing performed as part of antenatal screening). However, in the 2002 HSRC national household survey, conducted prior to the rollout of the PMTCT programme, the proportion of respondents who reported having ever been HIV-tested was the same in men and women (21.4%), and only in the more recent household surveys did the female proportion start to exceed the male proportion (Shisana *et al.* 2009; Peltzer *et al.* 2009). In a study conducted in Khayelitsha township during 2003-2004, the proportion of women who reported having ever tested for HIV was almost double the proportion of men who reported testing, but almost all of this difference could be attributed to testing as part of the PMTCT programme (Boulle *et al.* 2008b). In other South African studies conducted prior to the widespread rollout of PMTCT, proportions of respondents who reported having ever tested were similar in males and females (Hutchinson and Mahlalela 2006; Pettifor *et al.* 2010).

Self-initiated HIV testing is likely to be determined largely by the individual's perception of their own risk of infection. In the household survey conducted by Venkatesh *et al* (2011), virgins were significantly less likely to report previous HIV testing than youth who were sexually experienced, even after controlling for age and other factors. However, among youth who were sexually experienced, the lifetime number of sexual partners was not a significant determinant of the individual's previous testing, either in men or women. Most other South African studies have also not found significant associations between HIV testing history and

numbers of partners (Hutchinson and Mahlalela 2006; Mfundisi *et al.* 2005; Mitchell *et al.* 2010). However, there are exceptions. For example, in the 2005 national household survey conducted by the HSRC, it was found that the probability of having ever been tested for HIV was significantly associated with the number of sexual partners in the last year, after controlling for age and other factors (Peltzer *et al.* 2009). In a survey of women at high risk of HIV in Pretoria, it was also found that recent engagement in commercial sex and recent STI symptoms were both significantly associated with acceptance of the offer of HIV testing (Luseno and Wechsberg 2009). In other African countries, associations between sexual behaviour and history of HIV testing are inconsistent, although strong associations are often seen between condom use at last sex and history of past HIV testing in men (Cremin *et al.* 2012).

There has been much speculation as to whether the rollout of ART may be causing increased uptake of VCT, due to reduced fear of the consequences of an HIV diagnosis. Several studies have shown increases in VCT uptake concomitant with ART rollout (Snow *et al.* 2010; April *et al.* 2009), and some studies have shown previous HIV testing to be associated with either having heard of ART (Venkatesh *et al.* 2011; Mitchell *et al.* 2010; Cremin *et al.* 2012) or knowing someone on ART (Mfundisi *et al.* 2005; Boulle *et al.* 2008b). However, these studies do not establish a direct causal link between ART availability and VCT uptake.

Independently of whether individuals self-initiate HIV testing, individuals with HIV-related symptoms are likely to be tested for HIV if clinicians suspect that they are HIV-positive. However, South African studies have suggested that only a minority of patients with symptoms associated with HIV actually receive HIV testing. For example, in a trial of TB patients in Port Elizabeth, conducted in 2005, only 26 out of 402 controls (6.5%) received HIV testing (Pope *et al.* 2008) but this proportion was higher (20.2%) in the intervention clinics, where providers were encouraged to offer HIV testing. The authors noted that at the time of the trial, provider-initiated testing and counselling (PITC) was still a relatively new concept and somewhat controversial. In another study of patients referred for HIV testing in a semi-private hospital in Durban in 2004, 137 out of 435 patients (32%) went for HIV testing (Bassett *et al.* 2007). This proportion may be higher than in the Port Elizabeth study because the denominator is patients who were referred for HIV testing (rather than the number of patients who were clinically suspected of having HIV), or because of the semi-private nature of the health facility. In 2007, provider-initiated HIV testing for all TB patients became accepted policy in South Africa, but there remained a substantial proportion of TB patients who did not get tested. For example, the proportion of TB patients in Free State province who were tested for HIV increased to only 43% in 2007 and 46% in 2008 (Kigozi *et al.* 2011). WHO reports quote corresponding proportions of 39% and 49% in 2007 and 2008 respectively, up from less than 10% in 2004 (World Health Organization 2009; Wood *et al.* 2011). In contrast, the proportion of TB patients tested for HIV in Cape Town in 2009 was 87% (Wood *et al.* 2011).

6.1.2 Modelling of the uptake of HIV testing

The rate at which sexually-experienced individuals get tested, if they are in HIV stage s at time t , if they are aged x and of sex g , and if they have HIV testing history i , is assumed to be

$$\tau_{g,i,s}(x,t) = b(t) \times A_g(x,t) \times r_i \times Y_s + \Omega_s d(t) \Psi + F_{g,s}(x,t) v(t) \quad (6.1)$$

where

$b(t)$ = the ‘base’ rate of HIV testing in year t , in individuals who do not have any HIV symptoms and are not pregnant;

$A_g(x, t)$ = an adjustment factor to take into account differences in the rate of voluntary uptake of HIV testing by age (x) and sex (g);

r_i = an adjustment factor to take into account the effect of testing history (never been tested ($i = 0$), previously tested negative ($i = 1$), or previously tested positive ($i = 2$));

Y_s = an adjustment factor to take into account the effect of HIV status on the rate of HIV testing;

Ω_s = the annual incidence of opportunistic infections in CD4 stage s ;

$d(t)$ = the reported fraction of TB cases that are tested for HIV in year t ;

Ψ = bias adjustment factor for rate of HIV testing in patients with opportunistic infections;

$F_{g,s}(x, t)$ = the fertility rate in sexually experienced individuals of sex g and age x , in HIV stage s , during year t (this is set to zero for males);

$\nu(t)$ = the proportion of pregnant women who receive HIV testing in year t .

The $A_g(x, t)$ function is assumed to be of the form

$$A_g(x, t) = B_g(t) \exp(-a_g(x - 25)^2 + \beta_g(x - 25)), \quad (6.2)$$

where $B_g(t)$ is a time-dependent sex adjustment factor, and a_g and β_g are coefficients for the effect of age on the rate of HCT uptake. $B_g(t)$ is set to 1 for females ($g = 1$), while for males the ratio is assumed to change over time. This time dependency is modelled by specifying the parameters $B_0(2002)$ and $B_0(2010)$, and calculating the ratios for the remaining years using the function

$$B_0(t) = \begin{cases} B_0(2002) & t \leq 2002 \\ B_0(2002) + (B_0(2010) - B_0(2002))(t - 2002)/8 & 2002 < t \leq 2010 \\ B_0(2010) & t > 2010 \end{cases}$$

In the absence of reliable information regarding trends in the ratio of male testing to female testing, we have assigned the same distribution to represent the uncertainty regarding the $B_0(2002)$ and $B_0(2010)$ parameters. This prior distribution is a gamma distribution with a mean of 0.8 and a standard deviation of 0.1, chosen based on the odds ratio of 0.79 estimated by Kincaid *et al* (2008) when comparing male and female reports of HIV testing in the last 12 months in the 2006 National Communication Survey. The a_g and β_g parameters have been estimated based on data from a survey of HIV testing facilities in Mpumalanga province in 2006 (Snow *et al.* 2010). Quadratic functions of the form in equation 6.2 were fitted to the age- and sex-specific rates of HIV testing, and the male estimates of a_g and β_g were 0.00224 and 0.0388 respectively, while the female estimates were 0.00190 and 0.0027. Using the formula for the axis of symmetry of a quadratic function, the corresponding estimates of the age at which HCT uptake peaks ($25 + 0.5\beta_g/a_g$) were 33.7 and 25.7 years in males and females respectively. Given the similarity of the a_g estimates in males and females, we assigned the same prior to represent the uncertainty regarding the a_g parameters in males and females (a gamma distribution with a mean of 0.002 and a standard deviation of 0.0005). Rather than specify priors on the β_g parameters directly, we specify priors on the age at which HCT uptake peaks (modal age ζ_g), and calculate β_g from the modal age using the formula

$$\beta_g = 2a_g (\zeta_g - 25).$$

The prior distributions assigned to the ζ_0 and ζ_1 parameters are gamma distributions with means of 34 years and 26 years respectively (based on the estimates derived from the Mpumalanga data) and standard deviations of 3 years.

The $b(t)$ function is estimated from the annual numbers of people who receive HIV testing in the public sector, as reported in various published and unpublished sources (Pillay *et al.* 2012; World Health Organization 2011a; Republic of South Africa 2008; Department of Health 2012). These numbers are summarized in Table 6.1. We assume that the totals include HIV tests performed antenatally, although this is not clear from the published statistics. We have therefore estimated numbers of women receiving antenatal HIV testing (based on previously documented assumptions regarding PMTCT rollout (Johnson *et al.* 2012d) and based on ASSA2008 estimates of the number of births in each year (Actuarial Society of South Africa 2011)) and have deducted these from the reported totals to obtain tests performed outside of antenatal settings. If Θ_t is the reported number of HIV tests performed in individuals aged 15 and older in year t , after excluding antenatal HIV tests, then if we ignore the complications around HIV testing in HIV-positive individuals,

$$\Theta_t \approx \sum_g \sum_x N_g(x,t) \hat{b}(t) A_g(x,t),$$

where $N_g(x,t)$ is the population of sex g , aged x , in year t . This equation can be used to solve for $\hat{b}(t)$, using the ASSA2008 estimates of the $N_g(x,t)$ parameters and estimating the $A_g(x)$ function using the 0.8 male adjustment factor and mean age adjustment factors assumed in the previous paragraph. The resulting estimates are included in Table 6.1. This method may lead to the true value of $b(t)$ being under-estimated, as we are not including HIV tests performed outside the public health sector, and we may be including in the denominator individuals who have previously been diagnosed HIV-positive (who would presumably not get retested). However, it is also possible that $b(t)$ may be over-estimated if a high proportion of the population has been tested previously (since $b(t)$ applies to previously-untested individuals, but previously-tested individuals have a higher testing rate if not diagnosed positive). The first source of bias is likely to be most significant in the period prior to 2002, when the private sector and NGOs accounted for a lot of HIV testing; for example, in the 2002 HSRC household survey, 38% of HIV-negative individuals and 15% of HIV-positive individuals, who reported having tested for HIV previously, said that they had been tested due to an external request (from employers, banks or insurers) (Human Sciences Research Council 2002). The second source of bias is likely to be relatively more significant in recent years, following the dramatic increases in proportions of individuals tested for HIV previously. We therefore include in Table 6.1 an adjusted set of estimates if it is assumed that the ratio of the true rate of HIV testing to that derived from the public sector totals is 2 in 2002/3 and decreases linearly to 1.2 in 2010/11.

Table 6.1: Estimated rates of HIV testing in asymptomatic individuals

	2002/3	2004/5	2006/7	2009/10	2010/11	2011/12
Total HIV tests performed	691 000	1 300 000	1 611 000	6 770 000	11 670 000	9 700 000
excluding antenatal tests (Θ_t)	513 000	833 000	835 000	5 802 000	10 694 000	8 725 000
HIV testing rate in HIV-negative non-pregnant women aged 25	0.024	0.039	0.038	0.254	0.463	0.373
Adjusted HIV testing rate*	0.049	0.069	0.060	0.330	0.555	0.448

* Assuming the ratio of the true testing rate to the rate derived from the public health sector statistics drops linearly from 2 in 2002/3 to 1.2 in 2010/11.

Based on the adjusted estimates in Table 6.1, the $b(t)$ function is assumed to increase linearly, from 0 in 1990 to 0.05 in 2002/3, to 0.06 in 2006/7, to 0.33 in 2009/10 and to 0.56 in 2010/11. To reflect the uncertainty around these rates, we assign gamma priors to each parameter, with means equal to the rates quoted and standard deviations that are 15% of the corresponding means. In the interests of simplicity, we set the rate of HCT uptake in 2011/12 to be 80% of that in 2010/11.

The parameter r_0 has been set to 1, so that $b(t)$ is the rate that applies to previously untested individuals. The parameter r_1 has been set to 2, based on a cross-sectional study in Gauteng (Pettifor *et al.* 2010), which found that seeking VCT was strongly associated with having previously tested for HIV (OR 1.97, 95% CI: 1.00-3.87). It is also supported by a study of patients offered HIV testing in health facilities, which found a higher uptake of HIV testing in those who had been tested for HIV previously (aOR 1.70, 95% CI: 0.98-2.94). The r_2 parameter has been set to 0, meaning that individuals who have previously been diagnosed HIV-positive are assumed not to be retested.

The parameter Y_s has been included to allow for the possibility that HIV-infected individuals may – independently of their HIV symptoms and pregnancy risk – be more or less likely to get tested for HIV than HIV-negative individuals. We set $Y_0 = 1$ for HIV-negative individuals, and set $Y_s = Y^*$ for all $s > 0$ (HIV-positive individuals). Evidence of an association between sexual risk behaviour and HIV testing (discussed in section 6.1.1) suggests the possibility that HIV-infected individuals may be more likely to get tested for HIV ($Y^* > 1$). Individuals who do not test for HIV often cite as their reason for not testing that they do not perceive themselves to be at risk of HIV (Mall *et al.* 2013; Kigozi *et al.* 2011), which also suggests that HIV-negative individuals may be less likely to get tested. However, fear of a positive result is also frequently cited as a reason for not testing (Mall *et al.* 2013; Kigozi *et al.* 2011; Kharsany *et al.* 2010), which may be relatively more of a barrier in individuals who suspect that they might be infected. Maughan-Brown and Nyblade (2013) found that in youth in the Cape Town area, having tested for HIV was strongly associated with low self-perceived risk of HIV infection and (in men) higher educational attainment. Other studies have also shown a strong association between educational attainment and HIV test uptake (Venkatesh *et al.* 2011; Peltzer *et al.* 2009; Hutchinson and Mahlalela 2006; Cremin *et al.* 2012). Given the association between lower educational attainment and HIV risk that has emerged in the more advanced stages of the HIV epidemic (Hargreaves *et al.* 2008; Johnson *et al.* 2009a), it is possible that HIV-infected individuals may be less likely to have been tested on account of their lower educational attainment and/or socioeconomic status ($Y^* < 1$). The evidence reviewed here is therefore unclear as to whether HIV-positive individuals are more or less likely to have been tested for HIV; different HIV risk factors influence the rate of HIV testing in different directions. To represent this uncertainty, we

have assigned a gamma prior to the Y^* parameter, with a mean of 1 and a standard deviation of 0.5.

The assumed Ω_s parameters have been specified previously (Table 3.2 of section 3.2). The assumed values of $d(t)$ are shown in Table 6.2, together with the sources on which the assumptions are based. All sources are studies quoting proportions of TB patients who received HIV testing. It is assumed that there was minimal HIV testing in TB patients prior to the start of the ART rollout in 2004; in all years pre-2004, the assumed proportion tested is 5%. After 2011, the proportion tested is assumed to increase by 5% per annum, until a maximum of 90% is reached in 2017, in line with recent estimates of proportions of TB patients tested for HIV in Cape Town (Wood *et al.* 2011) and in line with the ultimate target of 90% in the 2012-16 National Strategic Plan (South African National AIDS Council 2011). Very few studies have estimated the rate of HIV testing in cases of opportunistic infections other than TB, but it is likely that the average rate of HIV testing for other OIs is lower than that for TB. For example, South African guidelines recommend testing all pneumonia patients for HIV, but only after the patient has recovered from pneumonia (Feldman *et al.* 2007), which may lead to a substantial fraction of HIV cases being missed. TB is well recognized as being related to HIV in the South African setting, and the rate of HIV testing in TB patients is a key performance indicator, which may lead to HIV testing being performed more routinely in TB patients than in patients with other HIV symptoms. It is also possible that there may be some degree of over-reporting in published estimates of proportions of TB patients who receive HIV testing. For these reasons we apply a bias adjustment factor, Ψ , to the $d(t)$ estimates. Given the uncertainty regarding the likely magnitude of this bias, we assign a uniform (0, 1) prior distribution to represent the range of possible values of Ψ .

The assumptions regarding rates of fertility and VCT uptake through PMTCT programmes are described in sections 7.2 and 5.2 respectively.

Table 6.2: Assumed proportions of TB cases leading to HIV diagnosis

Year	% tested	Source
Pre-2004	5%	
2004	8%	World Health Organization (2009)
2005	20%	World Health Organization (2010)
2006	31%	World Health Organization (2010)
2007	40%	World Health Organization (2010), Kigozi <i>et al</i> (2011)
2008	45%	World Health Organization (2010), Kigozi <i>et al</i> (2011)
2009	50%	World Health Organization (2010)
2010	55%	World Health Organization (2011b)
2011	60%	
2012	65%	
2013	70%	
2014	75%	
2015	80%	
2016	85%	
Post-2016	90%	South African National AIDS Council (2011)

The model assumes that individuals who previously tested positive would be as likely to get tested again if they are offered HIV testing through antenatal services or through provider-initiated testing, because in these situations it is the provider who initiates the HIV test, and

the provider often requires confirmation of HIV status, even if the patient voluntarily discloses that they are HIV-positive.

It is important to note that we do not explicitly model antibody HIV testing in children (under the age of 10) and youth who are not yet sexually experienced. For this reason, the model is likely to under-estimate the total number of HIV tests that are performed. However, the model does allow for the effect of PCR testing in infants at 6-week immunization, as described previously (Johnson *et al.* 2012a).

In modelling the potential future effect of home-based HCT or mobile HCT, we replace the first term on the right hand side of equation (6.1) with a single value representing the frequency of testing (for example, a value of 0.5 implies that household/mobile testing reaches the whole population on average once every 2 years). The implicit assumption is that any age and sex differences in the frequency of HIV testing would become negligible when screening is conducted on such a large scale.

6.1.3 Effectiveness of HIV testing and counselling

The model assumptions regarding the effect of HIV testing on sexual behaviour is described in section 2.11, together with a discussion of the evidence on which the model assumptions are based.

6.2 Male circumcision

6.2.1 Uptake of male circumcision prior to the promotion of male circumcision as an HIV prevention strategy

South African studies conducted prior to the promotion of male circumcision as an HIV prevention strategy have produced inconsistent estimates of the median age at which circumcision is performed. In a national household survey conducted in 2002, the median age at circumcision in men who were aged 15 or older was 18 in black South Africans, but lower in other race groups (Connolly *et al.* 2008). A slightly higher median age at circumcision, 20, was reported in a sample of 100 circumcised men in the Khutsong township (Rain-Taljaard *et al.* 2003). In a survey conducted in the Westonaria district in Gauteng province, the median age at circumcision in 143 men aged 24-29 was 16 (Lagarde *et al.* 2003). The age at which male circumcision occurs varies substantially between ethnic groups. In Xhosa-speaking men, male circumcision tends to occur slightly later. For example, both Boulle *et al.* (2008b) and Mark *et al.* (2012) found the median age at circumcision among Xhosa-speaking men in the Western Cape to be 21 years, and Rain-Taljaard *et al.* (2003) found the median age to be higher among Xhosa men (23 years) than in Sotho and Tswana men (18 years) and men of other ethnic groups (16.5 years). These estimates of the median age at circumcision derived from cross-sectional surveys may under-estimate the true median age if the sample includes a significant proportion of young men (aged <25) who are uncircumcised but likely to become circumcised at an older age.

Self-reports of circumcision status appear to conflict substantially with assessments by clinicians based on physical examination. This may be due to genuine ignorance on the part of respondents, social desirability bias in cultures that promote male circumcision as a rite of

passage into manhood, or possibly even error on the part of clinicians (Weiss *et al.* 2008b). Table 6.3 summarizes evidence from six studies conducted in southern and eastern Africa. For each study, the accuracy of self-reported circumcision status is expressed in terms of sensitivity and specificity, relative to clinician assessment of circumcision status. In some of these studies, clinicians classified men as ‘partially circumcised’; for the purpose of calculating the sensitivity and specificity parameters, these men are considered uncircumcised, since there is little evidence to suggest that partial circumcision provides protection against HIV (Maughan-Brown *et al.* 2011) or that men who incorrectly report themselves to be circumcised are at a reduced risk of HIV when compared to other uncircumcised men (Lissouba *et al.* 2011). The median sensitivity and specificity rates are 96.4% and 88.4% respectively, with substantial variation in levels of accuracy between studies. This indicates that in African populations, almost all men who are truly circumcised report themselves to be circumcised, but a substantial proportion of men who are not circumcised or only partially circumcised report themselves to be circumcised. Surveys that estimate the proportion of the male population that is circumcised, based on self-report, are therefore likely to over-estimate the true proportion of men who are completely circumcised.

Table 6.3: African studies assessing the accuracy of male self-reporting of circumcision status

Study	Location	Population	n	Sensi- tivity	Speci- ficity
Lissouba <i>et al</i> (2011)	Orange Farm, South Africa	Men in households	608	99.2%	78.0%
Lagarde <i>et al</i> (2003)	Westonaria, South Africa	Men in households	473	72.0%	85.1%
Weiss <i>et al</i> (2008b)	Mwanza, Tanzania	Adolescent boys	5083	95.8%	97.2%
Lavreys <i>et al</i> (1999)	Mombasa, Kenya	Trucking company employees	746	100.0%*	98.9%*
Thomas <i>et al</i> (2011)	Lesotho	Military recruits	239	97.0%	91.8%
Urassa <i>et al</i> (1997)	Mwanza, Tanzania	Male factory workers	202	93.2%	67.2%
Median				96.4%	88.4%

* Although it was reported that there was only one case of inconsistency between self-report and clinician assessment, it was not stated whether this involved a man reporting that he was circumcised or uncircumcised. The former has been assumed for the purpose of the calculations, although it would not change the median sensitivity and specificity if the latter were assumed instead.

National estimates of the fraction of the South African male population that is circumcised have been obtained from two sources: the 2002 HSRC household survey (Connolly *et al.* 2008) and the 2003 Demographic and Health Survey (Department of Health 2004). Table 6.4 summarizes the estimates of the age-specific prevalence of male circumcision estimated in both surveys. At all ages, the reported prevalence of male circumcision was found to be higher in the DHS than in the HSRC survey. The weighted average prevalence, across both surveys, is lowest in the 15-19 age group and rises steadily in subsequent age groups, before stabilizing at around 45% prevalence in men aged 30 and older. Because the prevalence estimates from both surveys are based on self-report, it is necessary to adjust the self-reported prevalence estimates in age group x , $p_r(x)$, by the sensitivity (Se) and specificity (Sp) of self-reporting, relative to ‘true’ circumcision status. If $p_t(x)$ is the true prevalence of male circumcision at age x , then we would expect the reported prevalence to be

$$p_r(x) = p_t(x)Se + (1 - p_t(x))(1 - Sp),$$

from which it follows that the true prevalence of male circumcision can be estimated by

$$\hat{p}_t(x) = \frac{p_r(x) + Sp - 1}{Se + Sp - 1}. \quad (6.3)$$

Substituting into equation (6.3) the median sensitivity and specificity parameters from Table 6.3, together with the weighted average prevalence levels based on self-report, yields adjusted prevalence estimated shown in the fifth column of Table 6.4. This adjustment makes a relatively greater difference to prevalence estimates at the young ages than at the older ages.

Table 6.4: Prevalence of male circumcision by age: observed and modelled

Age	2002 HSRC survey	2003 DHS	Weighted survey average	Adjusted prevalence	Model estimate*
15-19	23.7%	25.5%	24.6%	15.4%	19.2%
20-24	39.4%	42.4%	41.0%	34.7%	30.3%
25-29	38.3%	43.5%	41.6%	35.4%	39.1%
30-34	38.0%	51.7%	46.2%	40.8%	41.8%
35-39	36.0%	55.0%	47.5%	42.3%	42.0%
40-44	43.2%	53.1%	49.2%	44.4%	42.0%
45-49	36.3%	52.6%	45.0%	39.4%	42.0%
50-54	42.0%	56.2%	49.6%	44.8%	42.0%
55-59	34.5%	48.9%	43.2%	37.3%	42.0%

* Model estimate is calculated as the average of the proportions for the five ages in the age range.

In modelling the prevalence of male circumcision prior to the promotion of male circumcision as an HIV prevention strategy, we use a cumulative Weibull distribution to represent the age-related changes in the prevalence of male circumcision. We assume that the prevalence of male circumcision at age x is determined by the function

$$p_t(x) = a + (b - a) \left(1 - 0.5 \left(\frac{x}{m_1} \right)^\phi \right),$$

where a is the proportion of males who are circumcised soon after birth, b is the level at which circumcision prevalence ‘stabilizes’ in older men, m_1 is the median age at circumcision in men who get circumcised after birth, and ϕ is the shape parameter that determines the concentration of the distribution of circumcision ages (post-birth) around the median. Since surveys usually report the median age at circumcision for all men (not excluding those who are circumcised soon after birth), it is useful to parameterize the model in terms of this overall median circumcision age, m_2 , noting that

$$m_1 = m_2 \left(\frac{\ln(b/(2(b-a)))}{\ln(0.5)} \right)^{-1/\phi} \quad \text{for } \frac{b}{2} > a.$$

Parameter b is set at 0.42, the average of the adjusted male circumcision prevalence estimates at ages 30 and older (Table 6.4). Parameter a is set at 25% of b (0.105), where the 25% has been chosen to be marginally lower than the reported fraction of circumcisions occurring below age 13 (31.4%) in the 2002 HSRC survey (Connolly *et al.* 2008). The median age at circumcision, m_2 , is set at 18, the median age at circumcision reported by Africans in the 2002 HSRC survey. Although a lower median might be justified on the basis that circumcision tends to occur at younger ages in other race groups, it has been noted previously that cross-sectional surveys will tend to under-estimate the true median age at circumcision. The shape parameter ϕ is set at 4.5, after varying the shape parameter to identify the values that yield model estimates most consistent with the $\hat{p}_t(x)$ values (see last two columns of Table 6.4). This value of ϕ also yields model estimates of the proportions of circumcisions occurring in the <13, 13-16 and 17+ age groups consistent with those reported in the 2002 HSRC survey (31.7%, 13.5% and 54.8% respectively in the model, compared to 31.4%, 15.4% and 53.2% in the survey).

6.2.2 Uptake of medical male circumcision

A study conducted in Soweto found that out of 113 uncircumcised men enrolled in a vaccine trial, 38 (33.6%) became circumcised when they were informed of the health benefits of medical male circumcision and were offered free medical male circumcision, with the proportion being significantly higher in older men and men who reported higher levels of exposure to HIV and other STIs (de Bruyn *et al.* 2009). A higher proportion of men (58.8%) got circumcised when it was offered to them in the Orange Farm community, during the course of a household survey (Lissouba *et al.* 2011), with the acceptability of circumcision being particularly high among younger men and Sotho-speaking men. Acceptability of medical male circumcision may be lower in populations in which a high proportion of men are circumcised as part of a traditional rite of passage. For example, Maughan-Brown *et al.* (2011) found that among Xhosa men in Cape Town, only 2.2% believed that male circumcision should be performed in a health facility, and the balance almost all believed that it was better for male circumcision to be performed as part of the traditional ritual. Similarly, Mark *et al.* (2012) found that 82% of Xhosa-speaking men felt it would be better for their sons to be circumcised traditionally rather than in a health facility. Most studies in other African countries have shown that younger men are more willing to get circumcised than older men, although it is not clear whether this refers specifically to medical circumcision (Westercamp and Bailey 2007). Unpublished data from the 2012 National Communication Survey also indicate a much greater willingness to get circumcised in young men than in older men.

A recent WHO report has summarized the numbers of medical male circumcisions performed in South Africa as part of the drive to promote male circumcisions: these numbers were 5 190 in 2008, 9 168 in 2009 and 131 117 in 2010 (World Health Organization 2011a). These numbers are likely to be under-estimates of the actual number of circumcisions, as they relate mainly to PEPFAR-supported programmes, and it is not clear how many medical male circumcisions are being performed outside of PEPFAR-supported programmes (Dickson *et al.* 2011). Nevertheless, we have based our model assumptions about the scale up of MMC up to 2010 on these numbers; no promotion of MMC is assumed to have occurred prior to 2007. More recently, the Department of Health reported that 347 973 male circumcisions were performed in the 2011-12 financial year. Suppose that in year t , the reported number of medical male circumcisions performed as part of the MMC promotion drive is $\Lambda(t)$. We wish

to use this number to estimate $\eta_i(x)$, the annual probability that uncircumcised, HIV-negative men aged x in risk group i get medically circumcised through MMC campaigns. This is distinct from the annual probability that uncircumcised men aged x would get circumcised in the absence of MMC campaigns, which we denote $\psi(x)$. The probability $\psi(x)$ is calculated from the $p_t(x)$ values defined previously using the equation

$$\psi(x) = 1 - \frac{1 - p_t(x+1)}{1 - p_t(x)}.$$

We assume that the annual probability of getting circumcised as a result of MMC campaigns is proportional to the individual's probability of acquiring a new short-term partner in the next 12 months. The rationale for this assumption is that it means that younger men and men who are more sexually active are more likely to get medically circumcised, consistent with the empirical evidence summarized previously. Mathematically, we assume that if $c_i(x)$ is the annual rate at which men aged x in risk group i acquire short-term partners, then

$$\eta_i(x) = R(t)[1 - \exp(-c_i(x))],$$

where $R(t)$ is the constant of proportionality in year t (we can also think of it as the annual probability of medical male circumcision in individuals who have a high rate of partner acquisition, since the term in square brackets will be very close to 1 in these individuals). If we define $N_i(x)$ to be the number of uncircumcised HIV-negative men aged x who are in risk group i , then we obtain

$$\Lambda(t) = \sum_i \sum_x N_i(x) \times \eta_i(x) (1 - 0.5 \times \psi(x)),$$

from which it follows that

$$R(t) = \frac{\Lambda(t)}{\sum_i \sum_x N_i(x) [1 - \exp(-c_i(x))] (1 - 0.5 \times \psi(x))}.$$

It is implicitly assumed here that all of the men who are reported to be circumcised ($\Lambda(t)$) were HIV-negative at the time of circumcision. This is because it is generally recommended that MMC be coupled with provision of HIV testing and counselling (World Health Organization 2008), and men who test HIV-positive would generally have less incentive to get circumcised. However, it is likely that there are some HIV-positive men who do get circumcised, either because they refuse the offer of HIV testing, or because they are interested in MMC for reasons other than HIV risk reduction. Our approach may therefore overestimate the number of HIV-negative men getting circumcised.

Another limitation of this approach to modelling male circumcision is that it assumes that for any uncircumcised male, the probability of circumcision through an MMC campaign ($\eta_i(x)$) is independent of the probability that they would get circumcised in the absence of MMC campaigns ($\psi(x)$). In reality, men from cultural groups that traditionally practise male circumcision as a rite of passage may be more resistant to MMC than men in other cultural groups. By assuming that the men who are not circumcised through MMC campaigns are as

likely to get circumcised traditionally as the other men (supposing they had not received MMC), we are probably under-estimating the effect of MMC campaigns. It is also possible that MMC campaigns may have the effect of increasing the number of men who seek traditional male circumcision – an effect that we are not measuring because we are focusing only on the reported numbers of MMCs performed as part of MMC campaigns. Our approach to quantifying the impact of MMC is therefore relatively conservative, but in the absence of good data regarding the change in the prevalence of male circumcision over time, a more detailed modelling approach would be difficult to justify.

After the year 2011, we assume that the proportion $R(t)$ increases linearly from the rate estimated in 2011 to some ultimate rate. We have provisionally set this ultimate proportion to 5% and have assumed that this ultimate proportion is reached in 2016 (after which the annual probability of receiving MMC through MMC campaigns is assumed to remain constant).

The model does not currently allow for changes over time in the proportion of infants who are circumcised neonatally, but this may be revisited in future versions of the model. It has been argued that current South African law does not permit male circumcision below age 16 except in special circumstances (McQuoid-Mason 2013).

6.2.3 Effect of male circumcision on HIV transmission probabilities

There is substantial evidence from cross-sectional studies showing that after controlling for age and other confounding factors, men who are circumcised are at a significantly lower risk of HIV than men who are uncircumcised (Weiss *et al.* 2000). This has been demonstrated conclusively in three randomized controlled trials, all of which found that men who were randomly assigned to get circumcised had a significantly lower risk of acquiring HIV than men who were not (Auvert *et al.* 2005; Bailey *et al.* 2007; Gray *et al.* 2007). In a meta-analysis of the data collected in these three trials, the average percentage reduction in male HIV acquisition risk, following circumcision, was 58% (95% CI: 43-69%) in the ‘intention-to-treat’ analysis and 65% (95% CI: 46-76%) in the ‘as-treated’ analysis (Weiss *et al.* 2008a). Weiss *et al.* argue that the results from the as-treated analysis are probably a better reflection of the biological effect of male circumcision, as they are not biased by cross-over between study arms. Similar levels of efficacy have been estimated following the promotion of MMC outside of trial conditions (Auvert *et al.* 2013) and at longer durations of follow-up (Gray *et al.* 2012).

Although there is consensus that male circumcision reduces men’s risk of acquiring HIV, there is less clarity regarding the effect of male circumcision on male-to-female transmission of HIV. Only one randomized controlled trial has investigated this question, and has shown no protective effect of male circumcision on male-to-female transmission (RR 1.49, 95% CI: 0.62-3.57) (Wawer *et al.* 2009). In a recent large multicentre study, infected circumcised men were found to have a lower risk of transmitting HIV to their female partners when compared to infected uncircumcised men, although this difference was not quite statistically significant (RR 0.53, 95% CI: 0.26-1.07) (Baeten *et al.* 2010). A meta-analysis, which combined the data from the RCT with observational data from longitudinal studies, also found no significant protective effect (RR 0.80, 95% CI: 0.54-1.19) (Weiss *et al.* 2009).

Based on the evidence reviewed, it is assumed that circumcised men are 60% less likely to acquire HIV than uncircumcised men, but that male circumcision has no effect on the risk of male-to-female transmission.

6.2.4 Risk compensation

Although some evidence of risk compensation was found in the randomized trial conducted in Orange Farm (Auvert *et al.* 2005), risk compensation was not observed in the other randomized trials conducted in Kenya and Uganda (Bailey *et al.* 2007; Gray *et al.* 2007). Perhaps more significantly, following the end of the trial in Uganda, when trial participants were informed of the efficacy of male circumcision and were offered free circumcision, there was no evidence of any difference in behaviour when comparing those who chose to get circumcised and those who elected to remain uncircumcised (Gray *et al.* 2012). Similarly, in the South African trial setting, there was no evidence of risk compensation in circumcised men following the promotion of MMC as an HIV prevention strategy (Auvert *et al.* 2013), and in the Kenyan trial setting there was also no evidence of disinhibition in the post-trial period (Kong *et al.* 2012). In our model we have therefore assumed that there is no change in sexual behaviour following male circumcision. However, a recent study conducted in KwaZulu-Natal found that male condom use at last sex declined from 65.6% prior to circumcision to 52.1% 12 months after circumcision, suggesting that some risk compensation may be occurring (Phili 2013).

6.3 Microbicides

6.3.1 Microbicide acceptability

Microbicide acceptability studies have generally found high levels of acceptability. In the CAPRISA 004 trial, which involved the administration of tenofovir gel both before and after sex, 98% of the study subjects reported that they would use the gel if it was found to be effective (Abdool Karim *et al.* 2010). In a study of women in Burkina Faso, Zambia and Tanzania, who were provided with microbicides in different forms, the proportion of women who said they would ‘definitely’ use the product was consistently above 80% for all product forms (Nel *et al.* 2011).

Microbicide acceptability may be related to the form of administration. Van der Straten *et al.* (2012a) found that in Zimbabwean women there was a slight preference for pre-coital microbicide use over daily microbicide use, although the difference was not statistically significant. Different delivery methods have been examined: in the CAPRISA 004 trial, the microbicide was in the form of a gel that was applied with the use of an applicator device (Abdool Karim *et al.* 2010); a microbicide could also be applied vaginally in the form of a film, a soft-gel capsule or a tablet, all of which dissolve after insertion (Nel *et al.* 2011). In the latter study the film was found to be the most liked method overall, but the authors noted that different delivery methods were preferred by different women. In another study of sexually active women in South Africa and Tanzania, the idea of using a vaginal ring to deliver the microbicide product was highly acceptable, with only 6% of women initially indicating any reluctance to use the ring (van der Straten *et al.* 2012b). At the end of the study, after having actually used the vaginal ring, all women said they would be willing to use the ring if it was effective in preventing HIV.

6.3.2 Microbicide adherence

Some studies have found very high levels of adherence to gel use. For example, a Zimbabwean study of married women found that regardless of whether women were assigned to apply the gel daily or precoitally, about 90% reported using the gel at every sex act (van der Straten *et al.* 2012a). However, in another study of Zimbabwean women, most of whom were married and monogamous, the proportion who reported using the gel the last time they had sex was 80%, and only 56% of women assigned to the use of the gel reported using it every time they had sex in the least 3 months (van der Straten *et al.* 2008). In the CAPRISA 004 trial, conducted in South African women, adherence was estimated to be even lower, with gel being applied at only 72% of sex acts (Abdool Karim *et al.* 2010). In the VOICE trial, adherence was 90% when estimated based on self-report, but testing for the presence of tenofovir in vaginal fluids suggested adherence of only 22% (Marrazzo *et al.* 2013).

Adherence is likely to be related to the administration of the product. If the microbicide were delivered through a vaginal ring, it would not be necessary to remove and insert the ring on a daily basis and adherence would therefore be high. In a study of ring users in South Africa and Tanzania, for example, 99% of women used the ring on at least 80% of the study days, and over each four-week study interval 97% of women were perfectly adherent (Montgomery *et al.* 2012). Half of women reported never checking that the ring was in place (apart from at the four-weekly study visits) and only 15-20% of women reported checking the placement of the ring on a daily basis (van der Straten *et al.* 2012b).

6.3.3 Microbicide efficacy

To date only one randomized controlled trial has found a statistically significant reduction in HIV risk in women receiving antiretroviral-based microbicides. The CAPRISA 004 study, conducted in KwaZulu-Natal, found that the risk of HIV acquisition was reduced by 39% in women who were randomly assigned to use a tenofovir gel before and after sex, and efficacy increased to 54% in women whose adherence levels exceeded 80% (Abdool Karim *et al.* 2010). A more recent randomized trial of the tenofovir gel, which was also conducted predominantly in South Africa, found only a 15% reduction in HIV incidence, which was not statistically significant (Marrazzo *et al.* 2013).

6.3.4 Risk compensation

In a study of women in South Africa and Tanzania, it was found that although overall acceptability of microbicides was high, women were resistant to the idea of using both condoms and microbicides simultaneously (van der Straten *et al.* 2012b). This suggests that women who choose to use microbicides might be less likely to use condoms. However, in the CAPRISA 004 trial, participants were not found to reduce condom use over the course of trial (Abdool Karim *et al.* 2010).

6.3.5 Discontinuation

Few studies have assessed the likely rates at which women would discontinue microbicide use in field settings. Madden and Blumenthal (2007) review evidence suggesting that between 17 and 32% of women using vaginal rings for contraceptive purposes discontinue

their use of the vaginal ring in the short term. However, these studies do not provide information on longer-term rates of discontinuation. It is also unclear whether women using vaginal rings or vaginal microbicides for the purpose of HIV prevention would have rates of discontinuation comparable to those in women using the products for contraceptive purposes.

6.3.6 Model assumptions

In our model, the average microbicide efficacy is assumed to be 25%, based on the average of the efficacies of antiretroviral-based microbicides in the two trials that have been published to date. Although the assumption of 25% may appear low relative to the efficacy of 54% estimated in highly adherent women, our model assumption makes implicit allowance for suboptimal adherence. The average duration of microbicide use is assumed to be 5 years, and women who use microbicides are assumed to be 10% less likely to use condoms than women of the same age who are not using microbicides. The model is used to consider the effect of various strategies for targeted provision of microbicides to high risk groups such as sex workers, pregnant women, adolescent girls, females aged 15-24, etc. If microbicides are promoted to a particular group, the default assumption is that the annual rate of microbicide uptake in that group is 30%. It is further assumed that all women who received microbicides would be regularly tested for HIV, and that any breakthrough infections that occur would be detected shortly after seroconversion.

6.4 Pre-exposure prophylaxis (PrEP)

6.4.1 PrEP acceptability

In a survey of young South African women and men who have sex with men (MSM), around 60-70% indicated that they would 'definitely' be willing to use PrEP if it was available to them (Eisingerich *et al.* 2012). In a study of Kenyan MSM and sex workers who were assigned to use PrEP daily, 80% reported at the end of the study that they would use the product if it was found to be effective against HIV (Mutua *et al.* 2012). In HIV-negative Kenyan individuals with HIV-positive partners, the proportion reporting that they would be willing to use PrEP if it was effective against HIV was even higher, at 94% in men and 86% in women (Heffron *et al.* 2012). Although these studies suggest high levels of acceptability, it has been noted that self-reported acceptability may be a poor predictor of actual use (Mensch *et al.* 2012).

6.4.2 PrEP adherence

Levels of adherence vary between populations. In Kenyan MSM and female sex workers assigned to daily PrEP, the median daily adherence rate was estimated to be 92% (Mutua *et al.* 2012). Similarly high levels of adherence were observed in a randomized controlled trial of PrEP in serodiscordant couples in Kenya and Uganda: 97% of dispensed tablets were estimated to have been taken and 82% of HIV-negative participants had study drug detectable in their blood (Baeten *et al.* 2012). Rates of adherence were similar, at 84%, in another randomized controlled trial of PrEP conducted in men and women in Botswana, and the study drug was detected in the blood plasma of 80% of the HIV-negative subjects (Thigpen *et al.* 2012). In another study of women receiving PrEP in Kenya, South Africa and Tanzania (the FEM-PrEP trial), pill-count data suggested an adherence rate of 88%, but levels of study drug

detected in blood plasma suggested much lower adherence: it was estimated that only about 36% of HIV-negative women and 25% of women who seroconverted had taken the study drug in the last 48 hours (Van Damme *et al.* 2012). Similar levels of study drug detection (28-29%) were found in the VOICE trial (Marrazzo *et al.* 2013). In another study of PrEP use in Ghanaian women recruited from sex work venues, self-reported adherence data suggested a daily adherence rate of around 83%, but when adherence was estimated based on pill counts adherence reduced to only 68%, as the latter measure included periods when women did not come to the clinic for refills (Guest *et al.* 2010).

6.4.3 PrEP efficacy

Trials have produced conflicting findings regarding the efficacy of PrEP, and these discrepancies appear to be largely due to differences in adherence. In the study conducted among men and women in Botswana, PrEP efficacy was estimated to be 61.7% in the per-protocol analysis and 77.9% in the as-treated analysis (Thigpen *et al.* 2012). Similarly high levels of efficacy were observed in the trial conducted in serodiscordant couples in Kenya and Uganda: 67% when PrEP consisted of tenofovir and 75% when PrEP consisted of truvada (Baeten *et al.* 2012). This study estimated the efficacy to be even higher in patients who had detectable levels of study drug in their blood plasma: 86% in the case of tenofovir and 90% in the case of truvada. A similarly high efficacy (95%) in individuals with detectable study drug in their blood plasma was estimated in the iPrEx trial, although overall efficacy was lower (44%) due to poor overall adherence (Grant *et al.* 2010). In contrast, the efficacy of PrEP estimated in the FEM-PrEP trial was only 6%, with no significant difference in HIV incidence between the placebo group and women randomized to receive PrEP (Van Damme *et al.* 2012). The latter result is consistent with the very low levels of study drug detected in the blood plasma of women enrolled in this trial. In addition, the VOICE trial found HIV incidence in women receiving truvada and tenofovir as PrEP to be no lower than that in women receiving placebo (Marrazzo *et al.* 2013). This lack of effect can be explained by the low frequency of study drug detected in blood plasma: 28% in the case of tenofovir and 29% in the case of truvada.

6.4.4 Risk compensation

Data from randomized trials generally do not show evidence of risk compensation in trial participants. Thigpen *et al.* (2012), for example, found that levels of condom use in trial participants remained stable over the course of the trial, while the number of sex partners declined. Van Damme *et al.* (2002) also found that reported numbers of partners declined over the course of their trial, and consistent with Baeten *et al.* (2012) reported reductions in the frequency of unprotected sex. However, it is difficult to extrapolate from the data collected in these randomized trials, as trial participants would have been counselled on the uncertainty regarding the efficacy of the products that were being evaluated, and even if they believed the study products to be effective, would not have known whether they were receiving the study drug or the placebo. In a recent analysis of changes in behaviour after the unblinding of the Partners trial data, a slight increase was noted in unprotected extramarital sex, amongst individuals who were receiving open-label PrEP (Mugwanya *et al.* 2013). This suggests that some risk compensation could occur.

6.4.5 Model assumptions

In our model, the average PrEP efficacy is assumed to be 40%, based on the average of the efficacies in the trials that have to date been conducted in heterosexual populations (this assumption therefore makes implicit allowance for the poor adherence levels that have been observed in some trials). The average duration of microbicide use is assumed to be 5 years, the same as the average assumed for microbicides. As with microbicides, we assume that individuals using PrEP are 10% less likely to use condoms than individuals of the same age who are not using PrEP. The model is used to consider the effect of various strategies for targeted provision of PrEP to high risk groups such as sex workers, pregnant women, adolescents, youth aged 15-24, etc. If PrEP is promoted to a particular group, the default assumption is that the annual rate of PrEP uptake in that group is 30% (and that 80% of pregnant women would start using PrEP prior to delivery). It is further assumed that all individuals who receive PrEP would be regularly tested for HIV, and that any breakthrough infections that occur would be detected shortly after seroconversion.

7. Demographic assumptions

Most of the current demographic assumptions are the same as those in the ASSA2008 AIDS and Demographic model (Actuarial Society of South Africa 2011), although a adjustments have been made. It is likely that these demographic assumptions will be more extensively revised in the near future, once the unit record data from the 2011 census have been released.

7.1 Base population

The projection of the South African population starts in the middle of 1985. The assumed initial numbers of males and females at each age, from 0 to 89 and the open interval 90+, at the middle of 1985, are the same as those assumed in the ASSA2008 model. These population numbers were derived from a reconciliation of a forward projection of the population from the 1970 Census population and a backward projection of the 1996 and 2001 census populations.

7.2 Fertility

Assumptions regarding average fertility rates, for each age from 15 to 49, and for each year from 1985 to 2010, are obtained by adjusting the ASSA2008 model assumptions in proportion to the total fertility rates estimated from a back-projection of the number of surviving South African-born children in the 2011 census (Dorrington 2013). These average fertility rates are adjusted to take into account differences in fertility rates between women in different stages of HIV disease and between virgins and women who are sexually experienced. The process by which these adjustments are made is described below.

Fertility rates in different stages of HIV disease are assumed to be related to frequencies of sex by HIV stage. In women who are HIV-positive and untreated, with CD4 count in category s and current age x , the fertility rate in year t is assumed to be

$$F(x,t)\Gamma(s)^q,$$

where $F(x,t)$ is the fertility rate in sexually-experienced HIV-negative women aged x in year t , $\Gamma(s)$ is the coital reduction factor that applies to CD4 stage s , and q is an adjustment factor. The coital reduction factors in CD4 stages ≥ 500 , 350-499, 200-349 and < 200 are 1, 0.92, 0.76 and 0.55 respectively (the same as the assumed relative frequencies of sex in different stages, as discussed in section 2.10). However, previous studies have suggested that in countries in which contraceptive usage is high and fertility is low, the impact of HIV on fertility may be relatively modest (Lewis *et al.* 2004; Gregson *et al.* 2002). Thus the assumption of a reduction in fertility proportional to the reduction in coital frequency may be overly conservative, and we have therefore set the q parameter to 0.5, which brings the reduction factors closer to 1.

In women who initiated ART d years previously, at a CD4 count of s , the current fertility rate is assumed to be

$$F(x, t) \sum_{s'=2}^5 \psi_d(s' | s) \Gamma(s')^q$$

where $\psi_d(s' | s)$ is the proportion of ART patients with current CD4 count in category s' , in the cohort of patients who started ART with a CD4 count of s and who have been on ART for d years (as defined in Appendix C). Fertility in women receiving ART is thus assumed to be related to their frequency of sex, which is in turn assumed to be related to the current CD4 count rather than the baseline CD4 count. According to this model, HIV-positive fertility rates in treated women can be expected to increase after ART initiation, as a result of the increases in CD4 counts. This is consistent with what has been observed in a number of studies of the incidence of pregnancy in Africa (Myer *et al.* 2010; Tweya *et al.* 2013; Homsy *et al.* 2009; Makumbi *et al.* 2011). Although a case could be made for further adjusting fertility rates in HIV-positive women to take into account likely differences in condom use between diagnosed and undiagnosed women, studies conducted in Africa have generally found little or no significant evidence of a difference in fertility rates between women who report using condoms for contraceptive purposes and those who do not (Ngure *et al.* 2012; Halpern *et al.* 2011; Reid *et al.* 2010; Schwartz *et al.* 2012). We have also found when attempting to allow for an effect of condom usage on fertility in our model that the resulting trends in HIV prevalence in pregnant women are too inconsistent with observed trends to be plausible, and we have therefore not made any allowance for an effect of condom use on fertility in the results that are presented here.

For the purpose of calculating the HIV-negative fertility rate, $F(x, t)$, we define $N_{a,s,d}^i(x, t)$ to be the total number of women aged x with sexual experience indicator i (0 for virgins, 1 for sexually-experienced women), ART status a (0 for ART-naïve, 1 for treated), CD4 stage s (0 corresponding to HIV-negative women), and ART duration d years (0 if untreated). The average fertility rate is then

$$\bar{F}(x, t) = \frac{F(x, t) \left[N_{0,0,0}^1(x, t) + \sum_{s=1}^5 N_{0,s,0}^1(x, t) \Gamma(s)^q + \sum_{s,d} N_{1,s,d}^1(x, t) \sum_{s'=2}^5 \psi_d(s' | s) \Gamma(s')^q \right]}{\sum_{i,a,s,d} N_{a,s,d}^i(x, t)}$$

and this equation is then used to solve for $F(x, t)$, given the $\bar{F}(x, t)$ value. It is worth noting in passing that this equation can also be used to determine the HIV prevalence in pregnant women aged x , for the purpose of model calibration (see section 8.2.1):

$$H_{x,t} = 1 - \frac{F(x, t) N_{0,0,0}^1(x, t)}{\bar{F}(x, t) \sum_{i,a,s,d} N_{a,s,d}^i(x, t)}.$$

In the years that follow 2010, we have projected the HIV-negative fertility rates forward on the assumption of a steady decline in HIV-negative mortality, converging toward an ultimate set of fertility rates. These assumptions about declining future non-HIV mortality are the same as in the ASSA2008 ‘lite’ model.

The assumed proportion of births that are male is 0.5039, again based on the ASSA2008 model.

7.3 Non-HIV mortality

In the years from 1985 to 2007, non-HIV mortality rates are specified separately for each age, sex and year, using the same assumptions as in the ASSA2008 model. In the years following 2007, we have followed the same approach as ASSA2008, projecting continued declines in non-HIV mortality rates, converging towards an assumed ultimate set of non-HIV mortality rates.

It is worth noting that the term ‘non-HIV mortality’ is used here to refer to the mortality rate in HIV-negative individuals. The same rates are assumed to apply to HIV-positive individuals, representing the mortality rates that would be expected in HIV-positive individuals if they were not HIV-infected. The ratio of assumed non-HIV mortality to assumed HIV-related mortality in HIV-positive individuals is not necessarily the same as the actual ratio of non-AIDS deaths to AIDS-related deaths, as HIV may increase the risk of many causes of death that are not considered AIDS-defining. Our model estimate of ‘AIDS deaths’ (deaths in excess of those that would be expected if HIV-positive individuals experienced only HIV-negative mortality rates) therefore represents a greater fraction of deaths than those that might be estimated based only on AIDS-related causes. Independent of the effect of HIV on non-HIV mortality, there may also be a positive association between HIV infection and non-HIV mortality due to overlap in risk factors such as smoking and alcohol use, which increase the risk of HIV (Furber *et al.* 2007; Fisher *et al.* 2007) as well as the risk of non-HIV mortality. These effects are not considered in the present study, but they are unlikely to alter substantially the estimates of all-cause mortality.

7.4 Migration

For each year from 1985 to 2015, we specify a number of net in-migrants (immigrants less emigrants) for each age and sex. These numbers have been obtained by replacing the ASSA2008 net numbers of migrants for the periods 1996-2000, 2001-2005 and 2006-2010 by the average annual numbers estimated from the change in stock of foreign-born people identified by the censuses and the 2007 Community Survey as well as the estimated number of White emigrants used to produce the official mid-year estimates (Dorrington 2013). In addition, the annual numbers for the period 2011-2015 were set the same as those for the preceding period, and the ASSA2008 estimates of net outmigration up to 1996, of children born between 1985 and 1995, were all but eliminated (Rob Dorrington, personal communication).

For each age, sex and year, we calculate a migration adjustment factor, which is one plus the number of net in-migrants divided by the number of individuals of the relevant age and sex at the end of the relevant projection year. This migration adjustment factor is applied multiplicatively to all sexual behaviour and HIV disease sub-strata within the relevant age-sex stratum. The implicit assumption that is made in applying this adjustment factor is that migrants (whether they are coming into South Africa or leaving South Africa) have the same sexual behaviour and HIV disease profile, on average, as the remainder of the South African population.

8. Model fitting and uncertainty analysis

The model fitting and uncertainty analysis follows a two-part process. The first part involves setting the model assumptions about HCT uptake based on fitting the model to self-reported HIV testing data. The second part involves setting the sexual behaviour, HIV survival and HIV transmission parameters based on fitting the model to HIV prevalence data and mortality data. The reason for this separation is that it is not practical to consider all sources of uncertainty simultaneously; the larger the number of free parameters in the uncertainty analysis, the slower the convergence of the model fitting procedure. The model fit to the self-reported HIV testing data is relatively insensitive to the assumptions about sexual behaviour, HIV transmission and HIV survival, while the model fit to the HIV prevalence data is to some extent dependent on the HCT parameters. It therefore makes sense to first estimate the HCT uptake parameters before estimating the remaining model parameters.

For both phases of the two-part process, we adopt a Bayesian approach to model fitting and uncertainty analysis. This follows a standard three-step procedure. In the first step, prior distributions are specified to represent the ranges of uncertainty around the parameters of interest. These distributions represent the prior beliefs about the model parameters *before* fitting the model to the data, and are therefore based mainly on previously-published literature. In the second step, a likelihood function is specified to represent how well the model fits the available data, for a given choice of parameter values. The final step in the Bayesian procedure is the calculation of the posterior distribution, which represents the uncertainty around the model parameters *after* having integrated the prior uncertainty and the data to which the model is fitted. For the purpose of the second uncertainty analysis, the HCT uptake parameters are fixed at the posterior means estimated in the first uncertainty analysis.

8.1 Prior distributions

Most of the prior distributions have been specified in previous sections, but are repeated here for ease of comparison. Table 8.1 summarizes the prior distributions for the HCT uptake parameters that are considered in the first uncertainty analysis, and Table 8.2 summarizes the prior distributions that have been assumed for the parameters in the second uncertainty analysis. The only prior distributions in these tables that have not been explained previously are those for the reduction in the log of the excess mortality rate per unit increase in the ART initiation rate (explained in Appendix B), and the initial HIV prevalence in the high risk group, V_0 . Early South African prevalence surveys, conducted between 1985 and 1987, generally found no evidence of HIV in the heterosexual population, except amongst Malawian migrant workers (Dusheiko *et al.* 1989; Schoub *et al.* 1987; Hoosen *et al.* 1989; O'Farrell *et al.* 1989; Abdool Karim and Abdool Karim 1992). 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 women aged 15-49 in 1985 would have been more than 0.04% (0.0076×1.8^{-5}), since antenatal HIV prevalence tends to exceed prevalence in the general female population. Since we assume that 25% of women are in the high risk group, this suggests an upper limit of 0.16% on the initial HIV prevalence in the high risk group ($0.0004/0.25$). The initial HIV prevalence in 15-49 year old females in the high risk group has therefore been assigned a

uniform (0, 0.002) prior. The initial ratio of male prevalence to female prevalence, as well as the initial age distribution of HIV, is set to be consistent with patterns of infection observed in the early stages of the epidemic in KwaZulu-Natal in 1991 (Williams *et al.* 2000b).

Table 8.1: Prior distributions for HCT uptake parameters

Parameter	Symbol	Prior distribution	Prior mean, std deviation
Ratio of male HIV testing rate to female rate (at age 25)			
2002	$B_0(2002)$	Beta(12, 3)	0.80, 0.10
2010	$B_0(2010)$	Beta(12, 3)	0.80, 0.10
Age at which HCT uptake peaks in HIV-negative men	ζ_0	Gamma(128, 3.78)	34.0, 3.00
Age at which HCT uptake peaks in HIV-negative women	ζ_1	Gamma(75.1, 2.89)	26.0, 3.00
Effect of age ² on rate of HCT uptake in men	a_0	Gamma(16.0, 8000)	0.002, 0.0005
Effect of age ² on rate of HCT uptake in women	a_1	Gamma(16.0, 8000)	0.002, 0.0005
Annual rate of testing in HIV-negative women aged 25			
2002	$b(2002)$	Gamma(44.4, 889)	0.05, 0.0075
2006	$b(2006)$	Gamma(44.4, 741)	0.06, 0.0090
2009	$b(2009)$	Gamma(44.4, 135)	0.33, 0.0495
2012	$b(2012)$	Gamma(44.4, 79.4)	0.56, 0.0840
Ratio of HIV testing rate in HIV-positive asymptomatic individuals to rate in HIV-negative individuals	Y^*	Gamma(4, 4)	1.0, 0.5
Bias adjustment factor for rate of HIV testing in patients with HIV symptoms	Ψ	Uniform(0, 1)	0.50, 0.29

Table 8.2: Prior distributions for sexual behaviour, HIV survival and HIV transmission

Parameter	Symbol	Prior distribution	Prior mean, std deviation
Sexual behaviour parameters			
Mean of non-spousal sex age adjustment function	α/λ	Gamma(49, 1.4)	35, 5
Std deviation of non-spousal sex age adjustment function	$\alpha^{0.5}/\lambda$	Gamma(18.8, 1.44)	13, 3
Relative rate of partner acquisition in low-risk men	L_1	Uniform(0, 1)	0.50, 0.29
Relative rate of partner acquisition in low-risk women	L_2	Uniform(0, 1)	0.50, 0.29
Reduction in unprotected sex after HIV diagnosis	δ	Beta(5.90, 2.77)	0.68, 0.15
HIV survival parameters			
Mean adult HIV survival time in absence of ART (years)	π	Gamma(144, 12)	12.0, 1.0
Increase in CD4 decline/HIV mortality per 10-year increase in age, in the absence of ART	k	Gamma(4, 10)	0.40, 0.20
Reduction in log of excess HIV mortality per unit increase in annual ART initiation rate	m	Gamma(4, 0.8)	5.0, 2.5
HIV transmission parameters			
Female-to-male transmission probability in short-term/non-spousal partnerships	$\beta_{2,0}$	Gamma(5.68, 468)	0.012, 0.005
Male-to-female transmission probability in short-term/non-spousal partnerships	$\beta_{1,0}$	Gamma(5.68, 468)	0.012, 0.005
Female-to-male transmission probability in long-term/spousal partnerships	$\beta_{2,1}$	Gamma(7.09, 3540)	0.002, 0.00075
Male-to-female transmission probability in long-term/spousal partnerships	$\beta_{1,1}$	Gamma(7.09, 3540)	0.002, 0.00075
Initial HIV prevalence in high risk group, ages 15-49	V_0	Uniform(0, 0.002)	0.001, 0.00058

8.2 Likelihood function

The likelihood function represents the ‘goodness of fit’ to South African HIV data sources, for a given set of model assumptions. The likelihood function is calculated separately for

each of the data sources, and the sections that follow describe the process of calculating the likelihood for the different data sets.

8.2.1 Antenatal HIV prevalence data

The model is fitted to antenatal HIV prevalence data from national surveys that have been conducted every year from 1991 to 2011 (although there was also a survey conducted in 1990, we do not include it for the purpose of calibration as it did not include a number of the former ‘homeland’ states and it did not report HIV prevalence by age (Küstner *et al.* 1994)). We include HIV prevalence estimates for 5 age groups (15-19, 20-24, 25-29, 30-34 and 35-39), but do not include the estimates for the 40+ age group due to the small numbers of pregnant women in this age group and inconsistencies in the reporting of HIV prevalence in this age group (in some years, prevalence is reported for the 40-44 and 45+ age groups separately, while in other years prevalence is reported only for women aged 40+).

Suppose that $H_{x,t}(\boldsymbol{\phi})$ is the model estimate of HIV prevalence in pregnant women aged x to $x + 4$, in year t , where the vector $\boldsymbol{\phi}$ represents the values of the model input parameters. The corresponding prevalence of HIV actually measured in the antenatal survey is represented by $y_{x,t}$. It is assumed that if $\boldsymbol{\phi}$ is the true set of parameter values, then the difference between the logit-transformed model estimate and the logit-transformed observed prevalence is normally distributed. The mean of this normal distribution represents the extent of antenatal bias, which could arise due to the exclusion of women receiving private antenatal care from the sample. 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. More formally, it is assumed that

$$\log\left(\frac{y_{x,t}}{1-y_{x,t}}\right) = \log\left(\frac{H_{x,t}(\boldsymbol{\phi})}{1-H_{x,t}(\boldsymbol{\phi})}\right) + b_t + m_{x,t} + \varepsilon_{x,t},$$

where b_t is the antenatal bias parameter in year t , $m_{x,t} \sim N(0, \sigma_m^2)$ and $\varepsilon_{x,t} \sim N(0, \sigma_{x,t}^2)$. 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 that the model error terms are roughly independent of the level of HIV prevalence. For a given parameter combination $\boldsymbol{\phi}$, the antenatal bias parameter in 1997 and subsequent years is estimated using the formula

$$\hat{b}_{1997} = \frac{1}{75} \sum_x \sum_{t=1997}^{2011} \left(\log\left(\frac{y_{x,t}}{1-y_{x,t}}\right) - \log\left(\frac{H_{x,t}(\boldsymbol{\phi})}{1-H_{x,t}(\boldsymbol{\phi})}\right) \right).$$

It is assumed that the antenatal bias is the same in all years from 1997 to 2011, although it is possible that there was some change in bias following the introduction of a new survey protocol in 2006, which led to a substantially expanded sample of clinics (Dorrington and Bourne 2008). Prior to the introduction of a formal survey protocol in 1997 (Abdool Karim *et al.* 1997), it is likely that a different antenatal bias applied, as the early antenatal surveys were based on convenience samples that were biased towards urban areas (Webb 1994), where HIV prevalence was substantially higher (Cronje *et al.* 1994; Department of National Health

and Population Development 1994). However, it appears that the urban-rural differences in HIV prevalence diminished over time, and by 2003 the urban-to-rural prevalence ratio was only 1.2 (Reproductive Health Research Unit 2004). We have therefore assumed that the antenatal bias declined linearly over the period from 1991 to 1997, i.e. for $t < 1997$

$$b_t = \frac{1}{6} [b_{1991}(1997 - t) + b_{1997}(t - 1991)].$$

It can be shown that the maximum likelihood estimate of b_{1991} , given \hat{b}_{1997} , is

$$\hat{b}_{1991} = \frac{2}{35} \left\{ \sum_x \sum_{t=1991}^{1996} \left(\log \left(\frac{y_{x,t}}{1 - y_{x,t}} \right) - \log \left(\frac{H_{x,t}(\boldsymbol{\varphi})}{1 - H_{x,t}(\boldsymbol{\varphi})} \right) \right) - \frac{25}{2} \hat{b}_{1997} \right\}.$$

For $t \geq 1998$, the $\sigma_{x,t}^2$ values are estimated from the 95% confidence intervals that have been published for the various survey estimates. However, for the surveys conducted prior to 1998, the published confidence intervals are incorrectly calculated, as they do not take into account clustering in the survey design. We have therefore multiplied the published standard error estimates by a factor of 1.24, which is the average ratio of the correct standard error to the standard error that would be estimated in the absence of clustering, over the period from 1998-2005. Once these $\sigma_{x,t}^2$ values have been obtained, the σ_m^2 parameter is estimated using the formula

$$\hat{\sigma}_m^2 = \frac{1}{105} \sum_x \sum_t \left(\log \left(\frac{y_{x,t}}{1 - y_{x,t}} \right) - \log \left(\frac{H_{x,t}(\boldsymbol{\varphi})}{1 - H_{x,t}(\boldsymbol{\varphi})} \right) - \hat{b}_t \right)^2 - \sigma_{x,t}^2.$$

The likelihood in respect of the antenatal data is then calculated based on the assumption that the error terms are normally distributed:

$$L_1(\mathbf{y}_1 | \boldsymbol{\varphi}) = \prod_x \prod_t (2\pi(\hat{\sigma}_m^2 + \sigma_{x,t}^2))^{-0.5} \exp \left[-\frac{(\text{logit}(y_{x,t}) - \text{logit}(H_{x,t}(\boldsymbol{\varphi})) - \hat{b}_t)^2}{2(\hat{\sigma}_m^2 + \sigma_{x,t}^2)} \right],$$

where \mathbf{y}_1 represents the matrix of $y_{x,t}$ values, across age bands 15-19 to 35-39, and across calendar years 1991 to 2011.

8.2.2 Household HIV prevalence data

The model is calibrated to HIV prevalence data from three nationally-representative household surveys conducted by the Human Sciences Research Council (HSRC) in 2005 (Shisana *et al.* 2005), 2008 (Shisana *et al.* 2009) and 2012 (Shisana *et al.* 2013).³ HIV

³ Although the final results of the 2012 survey have been used in calculating the likelihood, the final results have not yet been published, and we therefore show only the preliminary survey results when presenting the model calibration.

prevalence levels in each survey are estimated by 5-year age group (from 15-19 up to 55-59) and by sex. We have not included the data from two household surveys conducted in 2002 (Human Sciences Research Council 2002) and 2003 (Pettifor *et al.* 2005b), because although both surveys were nationally representative, they relied on a single saliva-based test for the purpose of determining the presence of HIV infection, with no confirmatory testing. In addition, response rates were low in the 2002 survey.

The approach adopted in defining the likelihood function in respect of the HSRC HIV prevalence data is the same as that for the antenatal data, except that the bias term (b) and model error term (m) are both omitted. 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; Alkema *et al.* 2008), in which it is assumed that household prevalence data provide an unbiased estimate of HIV prevalence in the general population. However, this assumption is potentially controversial, as several recent studies have suggested that household prevalence surveys could under-estimate HIV prevalence if a substantial fraction of the HIV-positive population is diagnosed and HIV-diagnosed individuals are less likely to consent to HIV testing (Bärnighausen *et al.* 2012b; Reniers and Eaton 2009; Floyd *et al.* 2013; Nyirenda *et al.* 2010; Hogan *et al.* 2012). If this were true, we would expect survey estimates of the fraction of adults on ART to be less than the corresponding model estimates (since individuals on ART have all been diagnosed positive). However, this was not the case in the 2008 survey (Johnson 2012), and the preliminary results from the 2012 survey suggest ART numbers only slightly less than our model estimates (Shisana *et al.* 2013). This suggests that if there is a non-response bias due to knowledge of HIV-positive status, it is likely to be fairly small in the South African context. Further work is required to quantify the magnitude of this bias.

The model error term is omitted because the 95% confidence intervals around the household HIV prevalence estimates are very wide, relative to the confidence intervals around the antenatal survey estimates. Introducing a model error term was found to yield a better fit to the antenatal prevalence data at the expense of the fit to the household prevalence data, which was considered inappropriate. The likelihood is represented by $L_2(\mathbf{y}_2 | \boldsymbol{\phi})$, where \mathbf{y}_2 represents the matrix of HIV prevalence measurements in household prevalence surveys.

8.2.3 Proportions of individuals tested for HIV

The model is calibrated to data from three national household surveys conducted by the Human Sciences Research Council, in 2005, 2008 and 2012. In each survey, respondents were asked whether they had ever tested for HIV. In calibrating the model to these data, we define $B_{g,x,s}(t)$ to be the model estimate of the proportion of the population ever tested, in individuals of sex g and HIV status s , in age group x , at time t . The corresponding survey estimate is denoted by $\zeta_{g,x,s}(t)$. For the purpose of calibration, the data are grouped into five age categories: 15-24, 25-34, 35-44, 45-59 and 60+. The likelihood is calculated on the assumption that the differences between the logit-transformed survey estimates and the logit-transformed model estimates are normally distributed with mean U . In mathematical terms, we assume

$$\log\left(\frac{\zeta_{g,x,s}(t)}{1-\zeta_{g,x,s}(t)}\right) = \log\left(\frac{B_{g,x,s}(t)}{1-B_{g,x,s}(t)}\right) + U + m_{g,x,s}(t) + \varepsilon_{g,x,s}(t)$$

where U is a reporting bias parameter, $m_{g,x,s}(t)$ is a model error term and $\varepsilon_{g,x,s}(t)$ is the survey error term, which is assumed to follow a $N(0, \sigma_{g,x,s}^2(t))$ distribution. The reporting bias parameter U has been included to allow for the possibility that individuals may be inclined to over-report past HIV testing in face-to-face interviews. In a meta-analysis of studies that evaluated the accuracy of self-reported cancer screening, Rauscher *et al* (2008) found that for almost all cancer screening tests, individual reporting of previous cancer screening was more common than was suggested by their medical records. They further noted that self-reporting appeared to exaggerate actual screening most substantially when self-reporting was through face-to-face interviews, and speculated that the exaggeration may be due to social desirability bias. Similar biases may occur when individuals report whether they have been screened for other conditions. For example, Klein *et al* (1999) found that when US adolescents were questioned by telephone, they consistently reported higher rates of testing for common conditions (pregnancy, high cholesterol, HIV, TB, gonorrhoea and chlamydia) at recent preventive care visits than their medical records suggested. The U parameter is estimated using the standard maximum likelihood formula,

$$\hat{U} = \frac{1}{60} \sum_g \sum_x \sum_s \sum_t \log \left(\frac{\zeta_{g,x,s}(t)}{1 - \zeta_{g,x,s}(t)} \right) - \log \left(\frac{B_{g,x,s}(t)}{1 - B_{g,x,s}(t)} \right), \quad (8.1)$$

and the $\sigma_{g,x,s}^2(t)$ parameter is estimated from the 95% confidence interval widths. The standard deviation of the model error is estimated using the same approach as described in section 8.2.1, i.e. as the average of the difference between the squared error and the $\sigma_{g,x,s}^2(t)$ estimate.

8.2.4 Adult mortality data

To calculate the likelihood in respect of the reported death data, we restrict this analysis to deaths occurring over the period from the start of 1997 to the end of 2010 (Statistics South Africa 2013). Although more recent data are available through the Department of Home Affairs National Population Register (Bradshaw *et al.* 2012), these numbers relate only to those South Africans who have ID numbers, and are therefore not directly comparable to the numbers published by Statistics South Africa. Because cause of death information is seldom captured accurately, and reported AIDS deaths are likely to be only a fraction of the actual AIDS deaths (Groenewald *et al.* 2005), we compare model estimates of all-cause mortality with reported levels of all-cause mortality. This comparison is only likely to be meaningful in those age groups in which a substantial proportion of deaths are AIDS-related, and this analysis is therefore restricted to deaths occurring from ages 20 to 59. As with the HIV prevalence data, the mortality data are grouped in 5-year age bands for calibration purposes, and estimates are considered separately for males and females.

In order to specify a likelihood function for the reported death data, it must be assumed that in year t a certain proportion of adult deaths, c_t , is reported. This proportion is assumed to be constant with respect to age and sex. Suppose that $D_{g,x,t}(\boldsymbol{\phi})$ represents the model estimate of the number of deaths in individuals of sex g , between ages x and $x + 4$, in year t , where the vector $\boldsymbol{\phi}$ represents the values of the model input parameters. Further suppose that $R_{g,x,t}$

represents the reported number of deaths in individuals of sex g , between ages x and $x + 4$, in year t . It is assumed that if $\boldsymbol{\phi}$ is the true set of parameter values, then the difference between the log-transformed model estimate of the number of reported deaths ($D_{g,x,t}(\boldsymbol{\phi})c_t$) and the log-transformed actual number of reported deaths is normally distributed with zero mean. More formally, the likelihood is calculated on the assumption that

$$\log(R_{g,x,t}) = \log(D_{g,x,t}(\boldsymbol{\phi})c_t) + \varepsilon_{g,x,t},$$

where $\varepsilon_{g,x,t} \sim N(0, \sigma_d^2)$. The parameter $\varepsilon_{g,x,t}$ can be regarded as comprising both a ‘model error’ and ‘random binomial error’ component, but because the population numbers are very large, the random binomial component of the error is relatively small on the log scale. It is therefore reasonable to assume that the variance of the error term is independent of the population size in the relevant sex and age group.

The c_t parameters have been estimated from a variety of sources. Over the period from October 1996 to October 2001, Dorrington *et al* (2004) estimate that the fraction of adult deaths recorded was 84%, based on comparing the recorded numbers of adult deaths to the changes in the population sizes in each age cohort over the inter-census period. The authors also estimate that the annual increase in the proportion of deaths recorded, over this 5-year period, was 1.7% in men and 2.1% in women, based on an assumption of stable mortality rates at ages 65 and older (where AIDS would be expected to have relatively little impact on mortality). Based on these estimates, we assume that c_t increased linearly from 80.2% in 1997 to 87.8% in 2001 (an increase of 1.9% per annum, with 84% completeness in 1999). For 2002 and subsequent years, we rely on two studies of patients on ART in South Africa, who had ID numbers and whose vital status was therefore recorded on the National Population Register (Boulle *et al.* 2010; Fox *et al.* 2010). In both studies, a subset of patients were known to have died, based on their clinical records, and of these patients whose deaths were known to healthcare providers before checking against the vital registration system, 90% were found to have been recorded on the population register. Based on these studies, we have set c_t to 90% for years 2002 and later. Further research is currently being conducted to verify that this proportion is stable over the period post-2002.

The maximum likelihood estimate of the parameter σ_d^2 is calculated as

$$\hat{\sigma}_d^2 = \frac{1}{224} \sum_g \sum_x \sum_{t=1997}^{2010} \left[\log(R_{g,x,t}) - \log(D_{g,x,t}(\boldsymbol{\phi})c_t) \right]^2.$$

The likelihood in respect of the reported death data is then calculated based on the assumed normality of the error terms:

$$L_3(\mathbf{R} | \boldsymbol{\phi}) = \prod_g \prod_x \prod_{t=1997}^{2010} (2\pi\hat{\sigma}_d^2)^{-0.5} \exp\left(-\frac{(\log(R_{g,x,t}) - \log(D_{g,x,t}(\boldsymbol{\phi})c_t))^2}{2\hat{\sigma}_d^2}\right),$$

where \mathbf{R} represents the matrix of reported death data.

8.3 Posterior analysis

The description that follows relates only to the posterior analysis of the HIV prevalence data and recorded death data. However, it is worth noting that a similar process applies when we consider the posterior analysis of the self-reported HIV testing history data, for which a different set of prior distributions and likelihood functions apply.

The posterior distribution, $p(\boldsymbol{\phi} | \mathbf{y}_1, \mathbf{y}_2, \mathbf{R})$, represents the synthesis of the prior beliefs regarding the parameters in the vector $\boldsymbol{\phi}$ (i.e. the prior distribution discussed in section 8.1, which we represent by $p(\boldsymbol{\phi})$), and the likelihood functions for the antenatal prevalence data ($L_1(\mathbf{y}_1 | \boldsymbol{\phi})$), HSRC household prevalence data ($L_2(\mathbf{y}_2 | \boldsymbol{\phi})$), and recorded death data ($L_3(\mathbf{R} | \boldsymbol{\phi})$). By Bayes' theorem, the posterior distribution is calculated as

$$p(\boldsymbol{\phi} | \mathbf{y}_1, \mathbf{y}_2, \mathbf{R}) = k \times p(\boldsymbol{\phi}) \times L_1(\mathbf{y}_1 | \boldsymbol{\phi}) \times L_2(\mathbf{y}_2 | \boldsymbol{\phi}) \times L_3(\mathbf{R} | \boldsymbol{\phi}), \quad (8.2)$$

where k is a constant, calculated in such a way that the integral of the posterior distribution is 1. Because the calculation of the likelihood function requires us to run a complex mathematical model, there is no closed-form analytical solution to equation (8.2), i.e. there is no simple formula for calculating $p(\boldsymbol{\phi} | \mathbf{y}_1, \mathbf{y}_2, \mathbf{R})$ for given values of \mathbf{y}_1 , \mathbf{y}_2 , \mathbf{R} and $\boldsymbol{\phi}$. It is therefore necessary to use numerical methods to approximate $p(\boldsymbol{\phi} | \mathbf{y}_1, \mathbf{y}_2, \mathbf{R})$.

The numerical method used in this analysis is Incremental Mixture Importance Sampling (IMIS) (Raftery and Bao 2010). The method we use to generate a posterior sample of parameter combinations follows these steps:

1. Randomly sample 10 000 parameter combinations from the prior distribution $p(\boldsymbol{\phi})$.
2. For each parameter combination sampled, $\boldsymbol{\phi}_i$, run the model and calculate the likelihood functions $L_1(\mathbf{y}_1 | \boldsymbol{\phi}_i)$, $L_2(\mathbf{y}_2 | \boldsymbol{\phi}_i)$ and $L_3(\mathbf{R} | \boldsymbol{\phi}_i)$.
3. Calculate weights for each of the 10 000 parameter combinations, where the weight for the i^{th} parameter combination is $W_i = \frac{L_1(\mathbf{y}_1 | \boldsymbol{\phi}_i) L_2(\mathbf{y}_2 | \boldsymbol{\phi}_i) L_3(\mathbf{R} | \boldsymbol{\phi}_i)}{\sum_j L_1(\mathbf{y}_1 | \boldsymbol{\phi}_j) L_2(\mathbf{y}_2 | \boldsymbol{\phi}_j) L_3(\mathbf{R} | \boldsymbol{\phi}_j)}$.
4. Form a new multivariate normal sampling distribution, using the parameter combination with maximum weight from the previous step as the mean and calculating the weighted covariance matrix from the 1 000 parameter combinations that are closest to the parameter combination with maximum weight.
5. Randomly sample 1 000 parameter combinations from this new multivariate normal distribution and calculate the likelihood weights in the same way as before, but adjust the weights by the ratio of the prior density to the updated sampling density.
6. Form a new multivariate normal sampling distribution based on the weights in the previous step, repeating steps 4 and 5 until such time as there is an acceptable degree of heterogeneity in the sample weights.
7. Draw a sample of 1 000 parameter combinations (with replacement) from the sets of parameter combinations generated in all previous steps, using the weights calculated in the last step as the sample weights. If the heterogeneity in the weights is adequate,

the fraction of unique parameter combinations in the sample should be greater than $1 - \exp(-1) = 0.63$.

The set of 1 000 parameter combinations is effectively a sample from the posterior distribution, since sampling from the prior distribution and then resampling from this distribution using the likelihood values as sample weights is equivalent to sampling from the product of the prior distribution and likelihood function. A more detailed description of the method is provided by Raftery and Bao (2010). The distributions of model estimates shown in subsequent sections are the distributions of results obtained when the model is run for all 1 000 parameter combinations, with the 95% confidence intervals representing the 2.5 and 97.5 percentiles of these distributions. However, in the case of the model estimates of HIV incidence, HIV prevalence and AIDS mortality, the confidence intervals calculated from the 2.5 and 97.5 percentiles of these distributions may give a misleading sense of precision, as they do not reflect the uncertainty regarding the extent of the model errors referred to in sections 8.2.1 and 8.2.4. The confidence intervals are therefore adjusted to reflect the model error variances estimated previously. A more detailed explanation of this adjustment is provided in Appendix D.

9. Projections and programming

The model projects the change in HIV disease profile and population profile at monthly time steps, starting from the middle of 1985. Stock variables such as population size and HIV prevalence are reported at the middle of each year, while flow variables such as the HIV incidence rate and number of AIDS deaths are reported over projection years that run from mid-year to mid-year (for example, the number of new infections in the 2000 projection year is the number of new infections occurring between mid-2000 and mid-2001).

Two versions of the model have been programmed: one in Excel and Visual Basic for Applications (VBA), the other in C++. The two models have been reconciled to ensure that they produce identical results. It is anticipated that the Excel version of the model will be made freely available in the near future, as a tool for individuals needing HIV and demographic estimates for South Africa. The C++ version of the model can be run using the freely-available Visual Studio Express 2013 for Windows Desktop. However, this C++ version of the model currently lacks a user-friendly interface, and it is therefore not yet clear if this version will be made publicly available.

The Excel/VBA model is slow to run, taking about 30 minutes to perform a projection from 1985 to 2010. The C++ version of the model has been developed primarily for the purpose of the uncertainty analysis, as it is substantially faster than the Excel/VBA version of the model, taking around 5 seconds to perform the same projection. However, even at 5 seconds per simulation, it can take a long time to perform an uncertainty analysis involving hundreds of thousands of simulations. To further reduce the run times in the C++ model, some of the calculations that are updated on a monthly basis have been changed so that they are instead performed on an annual basis. This makes hardly any difference to the results, as the calculations in question relate to variables that change very little over the course of a single projection year. The switching of these calculations from monthly to annual leads to an almost 50% reduction in the run times.

In the C++ model, the following calculations are performed on a monthly basis:

- Fertility rates
- Numbers of births and new infections in children
- Initiation or discontinuation of PrEP and microbicides
- Rates of ART initiation
- Changes in paediatric HIV stage and AIDS mortality in children
- Heterosexual HIV transmission probabilities
- New infections in adults, changes in HIV stage and AIDS mortality in adults
- Entry into sex work and retirement from sex work

The following calculations are performed on an annual basis (those calculations marked with an asterisk are performed on a monthly basis in the Excel/VBA version of the model, and those marked with an obelisk are performed at the end of the year, after the monthly projections have been completed):

- Non-AIDS and AIDS mortality rates
- Female preferences regarding age of male partners*

- Rates of short-term partnership formation in men, male preferences regarding female partner ages*
- Rates of mixing between high and low risk groups*
- Rates of condom use*
- Rates of HIV testing*
- Male circumcision†
- Migration†
- Marriage, divorce and widowhood†
- Age changes and non-HIV mortality†
- Entry of virgins into the sexually active population†

In most instances, the results presented are the mean from the posterior sample and the 95% confidence intervals. However, in some instances it is useful to consider a single simulation (for example, when running the Excel/VBA model it is not practical to run the model for all the parameter combinations in the posterior sample). The single parameter combination that is chosen to best represent the model is the parameter combination with the largest weight in the generation of the posterior sample (as explained in section 8.3, this weight is the likelihood multiplied by the prior density and divided by the sampling density).

Two libraries were copied into the C++ version of the model for the purpose of the uncertainty analysis. 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.

10. Results

10.1 Comparison of prior and posterior distributions for model parameters

Table 10.1 summarizes the posterior estimates for the HCT uptake parameters and compares these with the corresponding prior parameters. In most cases the posterior distributions do not depart substantially from the prior distributions. However, the effect of male sex on the rate of HCT uptake appears to be much more significant in 2010 than in 2002, which suggests that HCT uptake has increased more substantially in women than in men over the last decade. The growth in HCT uptake in recent years has also been more modest than that assumed *a priori*. The posterior analysis also suggests that HIV-positive individuals who are undiagnosed and asymptomatic are significantly less likely to get tested than their HIV-negative peers. The posterior estimate of the HCT reporting bias parameter (parameter U in equation 8.1) is 0.49 (95% CI: 0.27-0.69), which is equivalent to an odds ratio of 1.64 (95% CI: 1.31-2.00) comparing reported HIV testing to actual HIV testing.

Table 10.1: Comparison of prior and posterior distributions for HCT parameters

Parameter	Prior distribution (mean, 95% CI)	Posterior distribution (mean, 95% CI)
Ratio of male HIV testing rate to female testing rate (at age 25)		
2002	0.80 (0.57-0.95)	0.85 (0.71-1.02)
2010	0.80 (0.57-0.95)	0.59 (0.45-0.72)
Age at which HCT uptake peaks in HIV-negative men	34.0 (28.4-40.1)	31.5 (28.3-34.1)
Age at which HCT uptake peaks in HIV-negative women	26.0 (20.5-32.2)	23.6 (20.2-27.4)
Effect of age ² on rate of HCT uptake in men	0.002 (0.0011-0.0031)	0.0017 (0.0012-0.0022)
Effect of age ² on rate of HCT uptake in women	0.002 (0.0011-0.0031)	0.0016 (0.0011-0.0021)
Annual rate of testing in HIV-negative women aged 25		
2002	0.05 (0.036-0.066)	0.051 (0.041-0.062)
2006	0.06 (0.044-0.079)	0.066 (0.049-0.084)
2009	0.33 (0.240-0.434)	0.274 (0.214-0.350)
2012	0.56 (0.408-0.736)	0.370 (0.277-0.486)
Ratio of HIV testing rate in HIV-positive asymptomatic individuals to HIV testing rate in HIV-negative individuals	1.00 (0.27-2.19)	0.72 (0.52-0.93)
Bias adjustment factor for rate of HIV testing in patients with HIV symptoms	0.50 (0.025-0.975)	0.38 (0.10-0.78)

Table 10.2 compares the prior and posterior means for the 13 parameters that are allowed to vary when fitting the model to the HIV prevalence data and mortality data. For most of these parameters, the prior and posterior distributions overlap substantially, though the posterior 95% confidence intervals are substantially narrower, reflecting the increased precision due to the HIV prevalence data and mortality data. However, in some cases the posterior mean lies outside the range between the 2.5 and 97.5 percentiles of the prior distribution, or close to the limits. This is particularly true for the standard deviation of the age distribution of sexual activity, suggesting that rates of non-spousal partnership formation are less concentrated at young ages than assumed *a priori*. The reduction in unprotected sex after HIV diagnosis is more modest than studies from the literature suggest. The male-to-female HIV transmission probability in short-term partnerships is also estimated to be substantially higher in the posterior analysis than empirical data suggest.

Table 10.2: Comparison of prior and posterior distributions for sexual behaviour, HIV survival and HIV transmission parameters

Parameter	Prior distribution (mean, 95% CI)	Posterior distribution (mean, 95% CI)
Sexual behaviour parameters		
Mean of non-spousal sex age adjustment function	35.0 (25.9-45.5)	40.7 (39.9-41.5)
Std deviation of non-spousal sex age adjustment function	13.0 (7.8, 19.5)	21.2 (20.4-22.0)
Relative rate of partner acquisition in low-risk men	0.50 (0.025-0.975)	0.44 (0.31-0.56)
Relative rate of partner acquisition in low-risk women	0.50 (0.025-0.975)	0.13 (0.12-0.14)
Reduction in unprotected sex after HIV diagnosis	0.68 (0.36-0.93)	0.37 (0.31-0.43)
HIV disease progression and mortality parameters		
Mean adult HIV survival time in absence of ART (years)	12.0 (10.1-14.0)	11.2 (10.9-11.4)
Increase in CD4 decline/HIV mortality per 10-year increase in age, in the absence of ART	0.40 (0.11-0.88)	0.27 (0.25-0.29)
Reduction in log of excess HIV mortality per unit increase in annual ART initiation rate	5.0 (1.4-11.0)	5.3 (4.5-6.4)
HIV transmission parameters		
Female-to-male transmission probability in short-term/ non-spousal partnerships	0.0120 (0.0043-0.0236)	0.0059 (0.0057-0.0062)
Male-to-female transmission probability in short-term/ non-spousal partnerships	0.0120 (0.0043-0.0236)	0.0283 (0.0251-0.0313)
Female-to-male transmission probability in long-term/ spousal partnerships	0.0020 (0.0008-0.0037)	0.0019 (0.0017-0.0022)
Male-to-female transmission probability in long-term/ spousal partnerships	0.002 (0.0008-0.0037)	0.0020 (0.0017-0.0026)
Initial HIV prevalence in high risk group, ages 15-49	0.001 (0.00005- 0.00195)	0.00154 (0.00142- 0.00164)

10.2 Calibration to self-reported HIV testing data

Figure 10.1 compares the proportions of men reporting having ever been tested for HIV with the corresponding model estimates (after adjustment for reporting bias). Most of the model estimates lie within the 95% confidence intervals around the household survey data, though these confidence intervals are particularly wide for HIV-positive men due to the relatively small sample sizes. The model appears to slightly under-estimate reported rates of testing in men in 2008, although the same pattern is not seen when the model results are compared with survey results from 2009 (Figure 10.3a) and 2012 (results not shown). The 2009 survey results (Johnson *et al.* 2010) have not been included in the specification of the likelihood function, and are therefore presented here as a validation of the model.

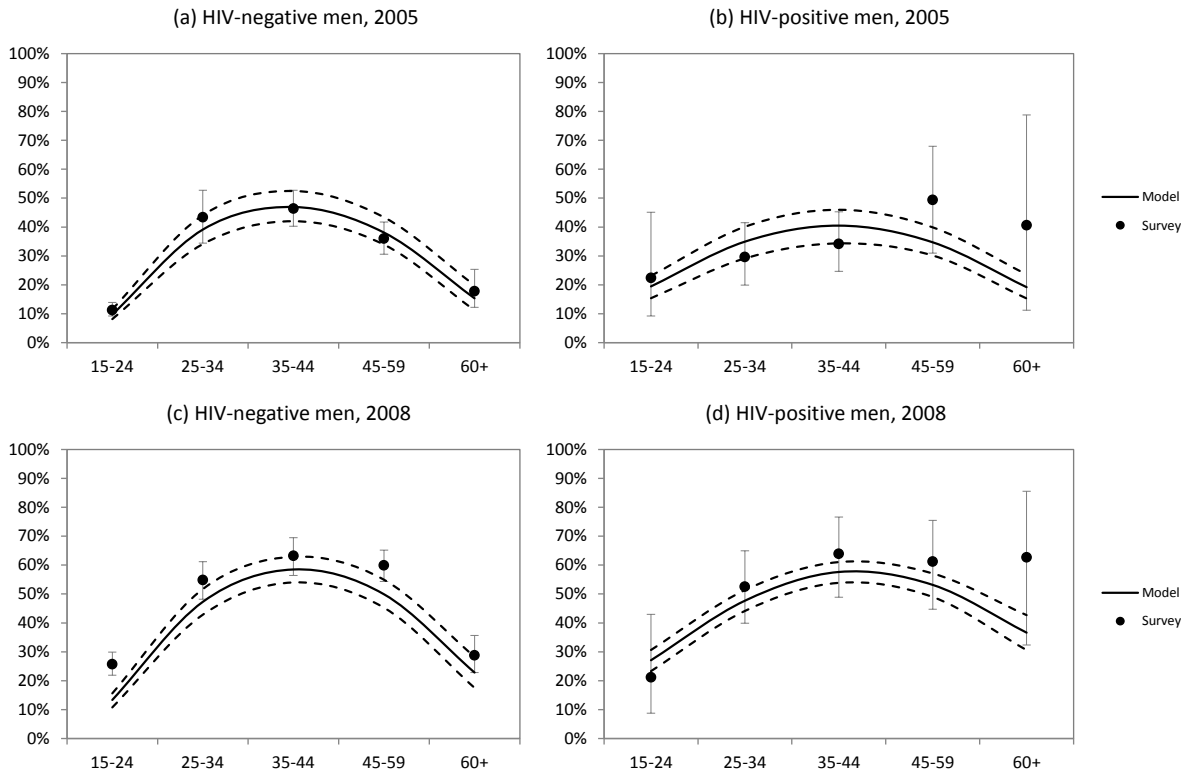


Figure 10.1: Proportion of men who have ever been tested for HIV, by age and HIV status
 Model estimates (solid lines) are calculated as posterior averages, after adjusting model estimates for reporting bias. Dashed lines represent 95% confidence intervals around model estimates. Survey results for 2012 are not shown, as these have not yet been published.

Figure 10.2 shows the calibration for women. Here it is apparent that the model is slightly over-estimating rates of HIV testing in 2005, while in 2008 the model under-estimates the rates of HIV testing in women aged 15-24. Model results also tend to under-estimate reported rates at young ages in 2009 (Figure 10.3b) but are more consistent with survey results in 2012 (results not shown).

Model estimates of total numbers of HIV tests performed in South Africa are roughly consistent with reported totals, although the model estimates are significantly higher than the public sector totals reported in 2002, 2004 and 2006 (Figure 10.4). This is consistent with a relatively high proportion of HIV tests being performed in the private and NGO sectors, in the years prior to the government-initiated HCT campaigns.

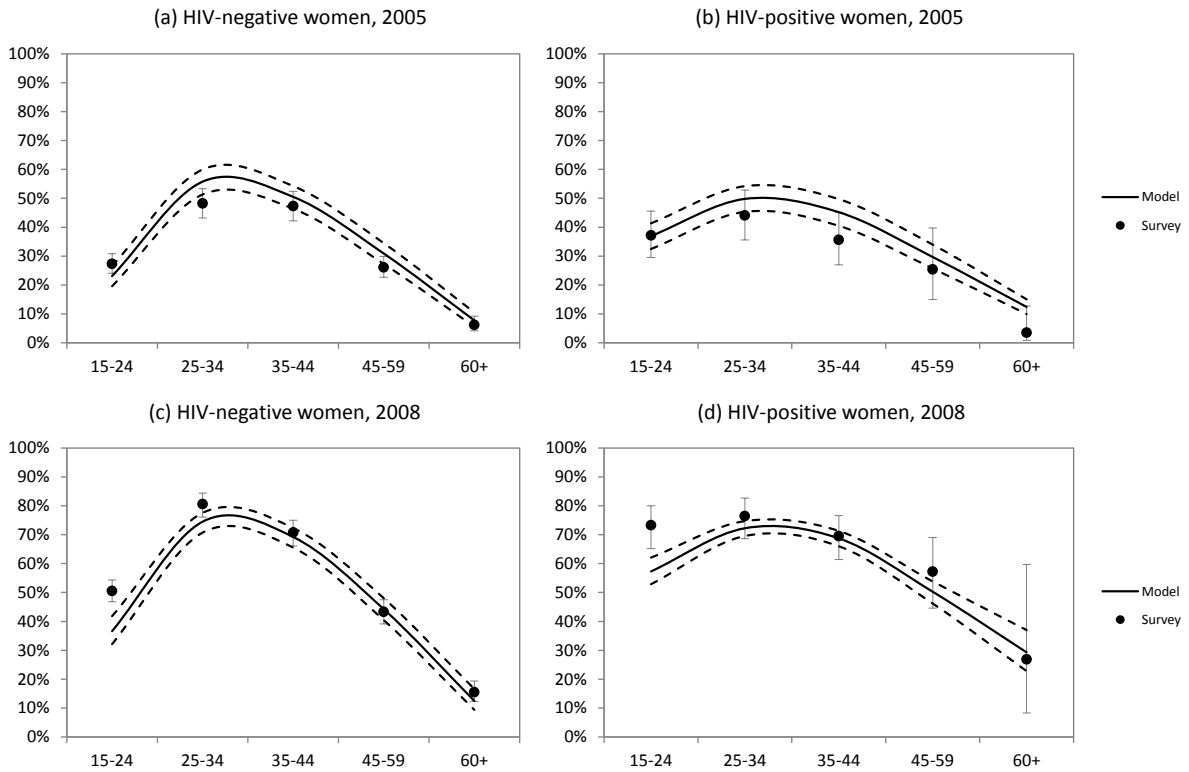


Figure 10.2: Proportion of women who have ever been HIV-tested, by age and HIV status
 Model estimates (solid lines) are calculated as posterior averages, after adjusting model estimates for reporting bias. Dashed lines represent 95% confidence intervals around model estimates. Survey results for 2012 are not shown, as these have not yet been published.

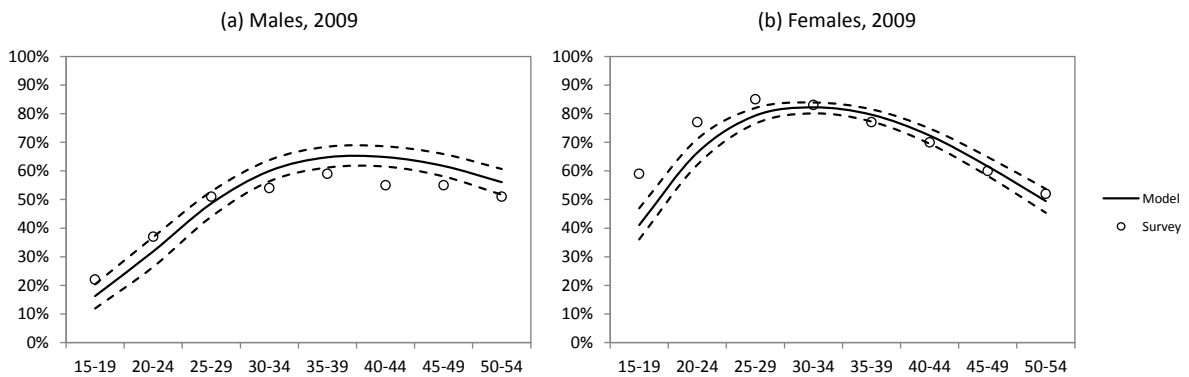


Figure 10.3: Proportions of sexually-experienced adults who have ever been tested for HIV in 2009
 Model estimates (solid lines) are calculated as posterior averages, after adjusting model estimates for reporting bias. Dashed lines represent 95% confidence intervals around model estimates. Survey results have not been included in the calculation of the likelihood and are therefore represented by open circles.

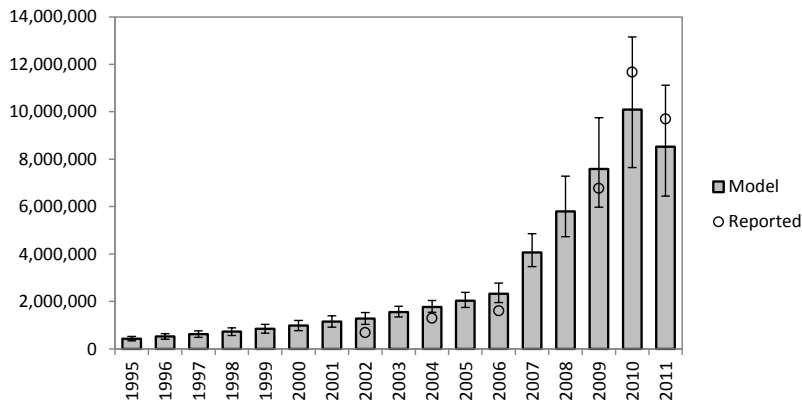


Figure 10.4: Annual numbers of HIV tests performed in South Africa

Grey bars represent posterior averages (with error bars representing 95% confidence intervals). Open circles represent totals reported by Department of Health (excluding private sector, and with data missing for several years).

10.3 Calibration to HIV prevalence data

The calibration of the model to the antenatal HIV prevalence data is shown in Figure 10.5, after adjusting the model estimates of prevalence in pregnant women to account for antenatal survey bias. (The estimated antenatal bias parameter is 0.48 (95% CI: 0.41-0.56) for 1991 and 0.43 (95% CI: 0.39-0.46) for the period after 1996). Overall, the model provides a reasonable fit to the prevalence data, but slightly over-estimates antenatal prevalence after 2005, possibly reflecting a change in the survey bias after the expansion of the survey sample size in 2006. The model fit to the HIV prevalence data in the 20-24 age group is poor, although the model estimates of HIV prevalence in women aged 20-24 correspond very closely with those measured in the HSRC household surveys (Figure 10.6).

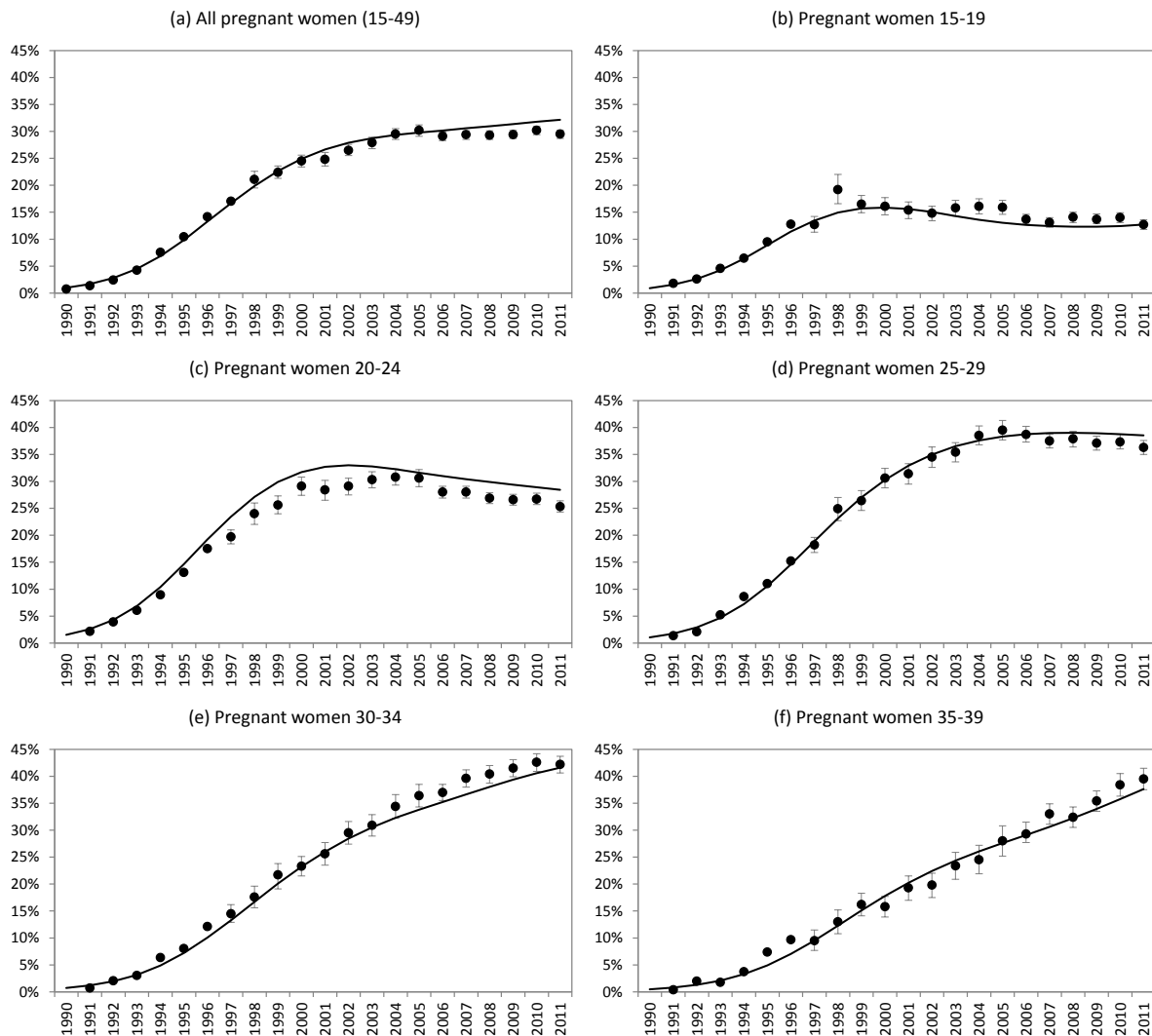


Figure 10.5: HIV prevalence levels in pregnant women attending public antenatal clinics. Dots represent HIV prevalence levels reported in surveys conducted from 1991-2011 (the 1998 data were adjusted to correct an error in the provincial weights in that year). 95% confidence intervals for survey estimates prior to 1998 are not shown, as the reported confidence intervals did not account for design effects. Solid lines represent the posterior mean model estimates of HIV prevalence in pregnant women, after adjusting for antenatal bias.

The calibration of the model to the HSRC prevalence data is shown in Figure 10.6. In general there is good agreement between the model estimates and the survey estimates, although the model under-estimates HIV prevalence in 15-19-year old males and females in 2005, and to a lesser extent in 2008. Although there are other instances of model estimates lying outside of the survey confidence intervals, these are isolated to individual years, and do not appear to indicate any consistent shortcoming of the model across multiple years.

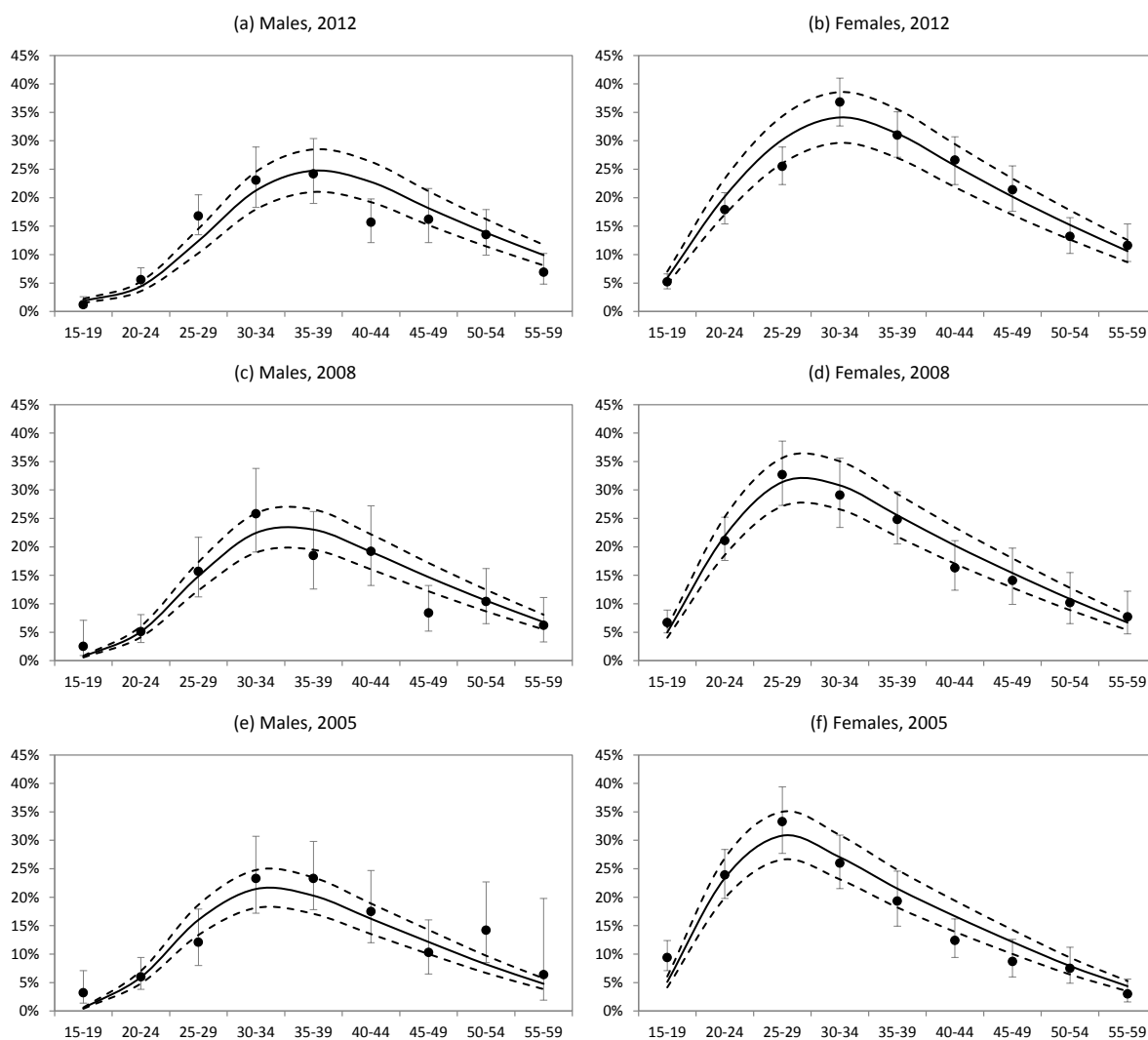


Figure 10.6: HIV prevalence levels in the general population

Dots represent HSRC survey prevalence estimates, together with 95% confidence intervals (results from the 2012 survey are provisional (Shisana *et al.* 2013)). Solid lines represent the posterior mean model estimates of HIV prevalence, and dashed lines represent the 95% confidence intervals around these estimates, after adjusting for model error (see Appendix D).

10.4 Calibration to mortality data

Figure 10.7 shows the model calibration to the age-specific recorded death data, and Figure 10.8 shows the calibration to the data when ages 20-59 are aggregated. Overall, the model fits the data well, though the model may be slightly over-estimating male deaths in 2010. The model also consistently over-estimates male mortality in the 20-29 and 50-59 age groups, possibly as a result of inaccuracies in the non-AIDS mortality assumptions. In the 20-24 age group, the model estimates a different trend in female mortality from that reported, at first overstating the recorded number of deaths but then falling short of the recorded numbers of deaths after 2003.

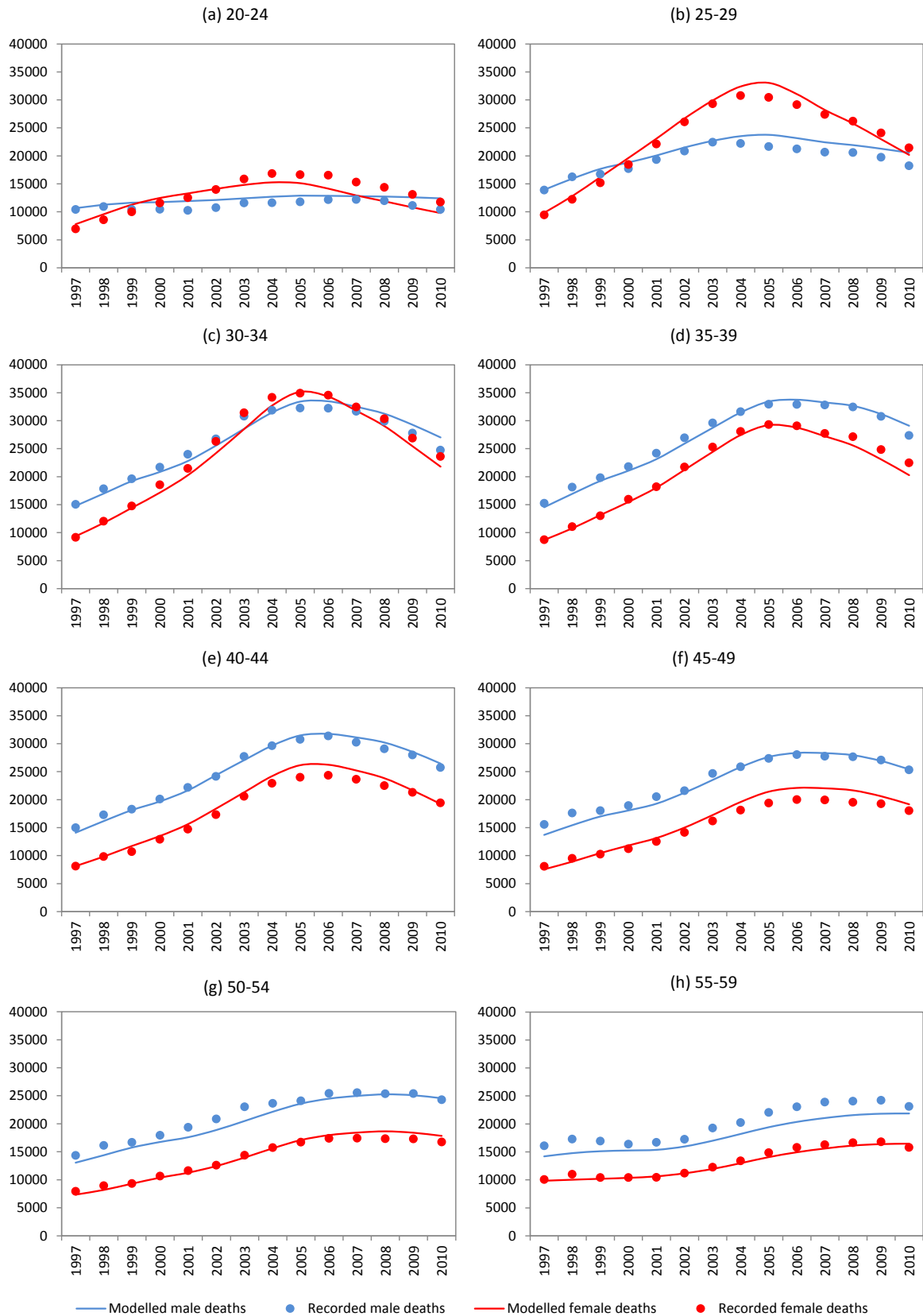


Figure 10.7: Trends in recorded numbers of deaths in South Africa, by age
 Solid lines represent posterior means. Dots represent recorded death estimates, after adjustment for incomplete vital registration.

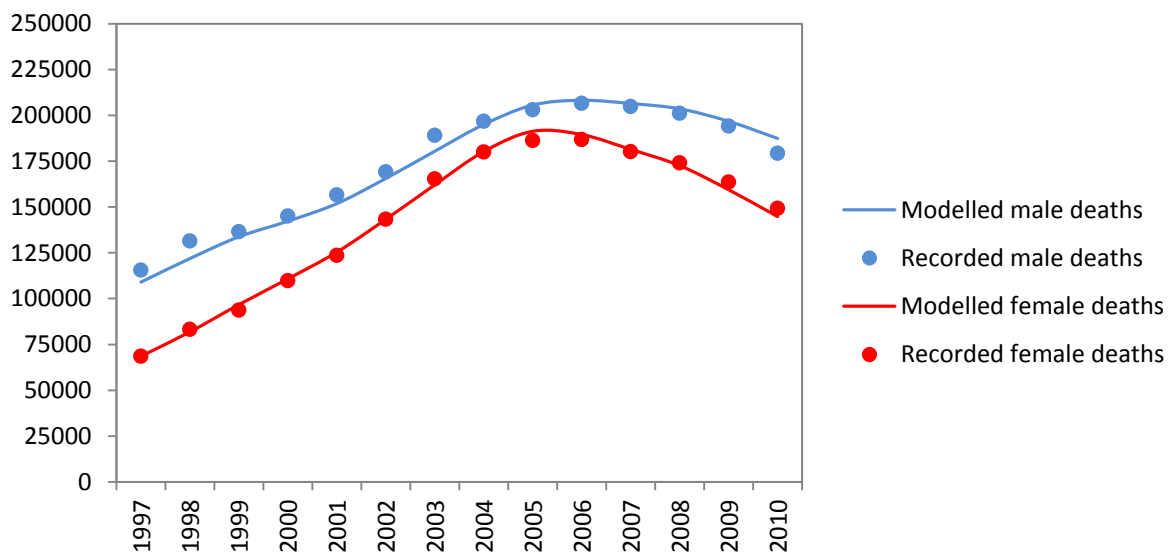


Figure 10.8: Trends in recorded numbers of deaths in South Africa, ages 20-59
 Solid lines represent posterior means. Dots represent recorded death estimates, after adjustment for incomplete vital registration.

10.5 HIV incidence outputs

Table 10.3 summarizes the model estimates of HIV incidence over the period from 1990 through to 2011. The annual HIV incidence rate in 15-49-year olds increased from 0.28% in 1990 to 2.33% in 1998 before beginning a gradual decline, reaching 1.47% (95% CI: 1.23-1.72) over the period from mid-2011 to mid-2012. HIV incidence rates in 15-49-year old females have consistently been around 50% greater than those in males of the same age, and HIV incidence rates have declined more substantially in males than in females over the last decade. Annual numbers of new HIV infections in children peaked in 2002, accounting for 15% of all HIV transmission, but declined more rapidly than new HIV infections in adults, accounting for only 8% of all new infections by 2011. The perinatal transmission rate (transmission from HIV-positive mothers at or before birth) dropped from 21.2% in 2000 to 4.2% in 2011, reflecting the success of the PMTCT programme.

Table 10.3: New HIV infections

Year†	New HIV infections ('000)	New HIV in children ('000)*	15-49 incidence	15-49 incidence in males	15-49 incidence in females	Perinatal transmission rate (6 weeks)*
1990	55 (50-61)	5	0.28% (0.24-0.32)	0.19% (0.16-0.23)	0.36% (0.29-0.43)	20.2%
1991	94 (85-104)	9	0.46% (0.39-0.53)	0.32% (0.26-0.39)	0.59% (0.48-0.71)	20.2%
1992	154 (139-170)	15	0.73% (0.63-0.83)	0.52% (0.42-0.61)	0.93% (0.76-1.11)	20.1%
1993	237 (213-260)	23	1.09% (0.93-1.24)	0.78% (0.64-0.92)	1.38% (1.12-1.64)	20.0%
1994	334 (302-367)	33	1.49% (1.28-1.70)	1.09% (0.89-1.29)	1.87% (1.52-2.23)	19.9%
1995	431 (389-472)	45	1.86% (1.59-2.13)	1.40% (1.14-1.66)	2.31% (1.86-2.77)	19.8%
1996	508 (457-559)	56	2.14% (1.82-2.46)	1.64% (1.32-1.96)	2.62% (2.08-3.16)	19.8%
1997	553 (494-612)	64	2.29% (1.92-2.65)	1.80% (1.43-2.17)	2.77% (2.16-3.38)	19.8%
1998	573 (506-639)	70	2.33% (1.94-2.73)	1.86% (1.45-2.28)	2.80% (2.14-3.46)	20.0%
1999	577 (505-649)	75	2.31% (1.89-2.72)	1.87% (1.43-2.30)	2.75% (2.06-3.43)	20.2%
2000	574 (498-649)	80	2.24% (1.82-2.66)	1.83% (1.39-2.28)	2.66% (1.96-3.35)	20.5%
2001	565 (488-642)	82	2.17% (1.75-2.59)	1.79% (1.34-2.24)	2.56% (1.88-3.25)	20.5%
2002	555 (478-632)	80	2.11% (1.70-2.52)	1.75% (1.30-2.19)	2.48% (1.82-3.15)	20.4%
2003	549 (473-626)	79	2.07% (1.67-2.46)	1.71% (1.28-2.14)	2.43% (1.79-3.07)	19.8%
2004	546 (471-621)	79	2.03% (1.65-2.40)	1.68% (1.27-2.09)	2.39% (1.78-3.00)	19.0%
2005	541 (469-613)	80	1.98% (1.62-2.34)	1.63% (1.24-2.02)	2.35% (1.77-2.92)	17.7%
2006	530 (460-600)	75	1.93% (1.60-2.27)	1.58% (1.21-1.94)	2.31% (1.76-2.85)	16.0%
2007	520 (453-587)	71	1.88% (1.56-2.19)	1.52% (1.17-1.86)	2.26% (1.75-2.77)	14.3%
2008	500 (435-564)	64	1.79% (1.49-2.09)	1.43% (1.11-1.75)	2.19% (1.70-2.67)	12.1%
2009	470 (408-532)	52	1.69% (1.41-1.97)	1.33% (1.03-1.63)	2.09% (1.64-2.54)	8.5%
2010	434 (375-493)	40	1.58% (1.31-1.84)	1.21% (0.93-1.49)	1.98% (1.55-2.40)	5.5%
2011	408 (352-464)	33	1.47% (1.23-1.72)	1.10% (0.84-1.36)	1.88% (1.48-2.28)	4.2%

95% confidence intervals have been adjusted to reflect model error (see Appendix D). * 95% confidence intervals are not shown for paediatric outputs, as the uncertainty analysis does not include any of the mother-to-child transmission or paediatric survival parameters. † All HIV incidence statistics relate to the period from the middle of the year indicated to the middle of the following year (i.e. last row corresponds to period from mid-2011 to mid-2012).

10.6 HIV prevalence outputs

Table 10.4 summarizes the model estimates of HIV prevalence. The total number of HIV infections in South Africa is estimated to have increased steadily over the last two decades, reaching a total of 6.40 million by the middle of 2012 (95% CI: 6.14-6.67 million). There has been a corresponding steady increase in overall HIV prevalence, reaching 12.5% (95% CI: 12.0-13.1%) by 2012. However, the change in HIV prevalence has not been uniform across age groups: HIV prevalence in children (aged <15) rose to 4.0% in 2009 before declining, while prevalence in the 15-49 age group has increased throughout the period. Amongst youth (ages 15-24), HIV prevalence peaked at 9.2% in 2001 before slowly declining.

Table 10.4: HIV prevalence

Year	Total HIV infections ('000)	HIV prevalence (all ages)	HIV prevalence (15-49)	HIV prevalence (15-24)	HIV prevalence (<15)*
1990	72 (67-76)	0.20% (0.18-0.21)	0.37% (0.34-0.40)	0.38% (0.33-0.43)	0.04%
1991	125 (117-134)	0.34% (0.32-0.36)	0.62% (0.57-0.67)	0.65% (0.57-0.74)	0.07%
1992	218 (203-233)	0.57% (0.53-0.61)	1.04% (0.96-1.13)	1.11% (0.97-1.25)	0.12%
1993	370 (344-395)	0.95% (0.88-1.01)	1.70% (1.56-1.85)	1.82% (1.59-2.06)	0.20%
1994	602 (561-643)	1.50% (1.40-1.60)	2.67% (2.45-2.90)	2.85% (2.48-3.21)	0.33%
1995	927 (867-988)	2.26% (2.11-2.41)	3.97% (3.66-4.29)	4.13% (3.62-4.64)	0.50%
1996	1341 (1260-1423)	3.19% (3.00-3.39)	5.54% (5.12-5.96)	5.54% (4.88-6.19)	0.74%
1997	1804 (1703-1904)	4.22% (3.99-4.46)	7.24% (6.72-7.75)	6.83% (6.06-7.60)	1.02%
1998	2289 (2172-2406)	5.28% (5.01-5.55)	8.92% (8.33-9.52)	7.87% (7.02-8.72)	1.33%
1999	2767 (2635-2899)	6.30% (6.00-6.60)	10.5% (9.83-11.2)	8.59% (7.69-9.50)	1.66%
2000	3217 (3072-3362)	7.24% (6.91-7.57)	11.9% (11.2-12.6)	9.01% (8.08-9.94)	2.00%
2001	3628 (3471-3785)	8.07% (7.72-8.42)	13.0% (12.3-13.8)	9.19% (8.25-10.13)	2.34%
2002	3992 (3824-4160)	8.79% (8.42-9.16)	14.0% (13.2-14.8)	9.18% (8.25-10.12)	2.67%
2003	4309 (4131-4487)	9.40% (9.02-9.79)	14.8% (13.9-15.6)	9.06% (8.14-9.98)	2.98%
2004	4582 (4395-4770)	9.92% (9.52-10.3)	15.4% (14.5-16.3)	8.88% (7.97-9.78)	3.26%
2005	4818 (4621-5014)	10.3% (9.93-10.8)	15.9% (15.0-16.8)	8.67% (7.79-9.56)	3.50%
2006	5033 (4828-5239)	10.7% (10.3-11.1)	16.3% (15.4-17.2)	8.48% (7.61-9.34)	3.71%
2007	5267 (5051-5483)	11.1% (10.6-11.5)	16.7% (15.8-17.6)	8.31% (7.47-9.16)	3.86%
2008	5500 (5273-5726)	11.4% (10.9-11.9)	17.1% (16.1-18.0)	8.18% (7.35-9.02)	3.96%
2009	5727 (5489-5965)	11.7% (11.2-12.2)	17.4% (16.5-18.4)	8.10% (7.27-8.92)	3.99%
2010	5955 (5707-6203)	12.0% (11.5-12.5)	17.8% (16.8-18.8)	8.05% (7.23-8.88)	3.95%
2011	6175 (5917-6433)	12.3% (11.8-12.8)	18.1% (17.1-19.2)	8.06% (7.23-8.89)	3.85%
2012	6402 (6135-6670)	12.5% (12.0-13.1)	18.5% (17.4-19.5)	8.12% (7.28-8.95)	3.71%

95% confidence intervals have been adjusted to reflect model error (see Appendix D). * 95% confidence intervals are not shown for paediatric outputs, as the uncertainty analysis does not include any of the mother-to-child transmission or paediatric survival parameters.

10.7 AIDS mortality outputs

The model estimates of trends in AIDS mortality are summarized in Table 10.5. Annual numbers of AIDS deaths peaked in 2005 at 303 000 and dropped to 169 000 (95% CI: 158 000-180 000) over the period from mid-2011 to mid-2012. Although AIDS deaths in adult females were around 25% greater than those in adult males in 2005, the decline in AIDS deaths since 2005 has been more rapid in females than in males, and by 2011 the number of AIDS deaths in adult females was almost equal to the number of AIDS deaths in adult males. In the 20-59 age group, the fraction of deaths attributable to AIDS rose to 53.8% and 72.6% in males and females respectively, by 2005. Thereafter the fraction of deaths attributable to AIDS declined steadily, reflecting the impact of the ART programme. Over the 2005-2011 period, annual numbers of AIDS deaths in children were halved, as a result of both the impact of the PMTCT programme and the impact of ART.

Table 10.5: AIDS mortality

Year †	Total AIDS deaths (‘000)	AIDS deaths in children (‘000)*	AIDS deaths in adults 15+ (‘000)		% of deaths (20-59) attributable to AIDS	
			Males	Females	Males	Females
1990	1.9 (1.1-2.6)	0.8	0.5 (0.1-0.9)	0.5 (0.2-0.9)	0.7% (0.2-1.3)	1.3% (0.6-2.1)
1991	3.3 (2.3-4.3)	1.4	0.9 (0.4-1.4)	1.0 (0.5-1.4)	1.2% (0.5-1.9)	2.3% (1.3-3.4)
1992	5.6 (4.3-7.0)	2.4	1.5 (0.8-2.3)	1.7 (1.1-2.4)	2.0% (1.0-2.9)	4.0% (2.6-5.3)
1993	9.6 (7.8-11.4)	3.9	2.7 (1.7-3.7)	3.1 (2.2-3.9)	3.2% (2.0-4.4)	6.5% (4.8-8.3)
1994	16.0 (13.6-18.4)	6.1	4.6 (3.3-5.9)	5.3 (4.1-6.5)	5.2% (3.6-6.7)	10.5% (8.3-12.6)
1995	25.7 (22.6-28.9)	9.0	7.7 (6.0-9.5)	9.0 (7.4-10.6)	8.1% (6.2-10.0)	16.0% (13.3-18.7)
1996	39.8 (35.8-43.9)	12.5	13 (10-15)	15 (13-17)	12.0% (9.7-14.4)	23.1% (19.9-26.4)
1997	58.7 (53.6-63.9)	16.3	19 (16-23)	23 (20-26)	16.6% (13.8-19.4)	29.9% (26.2-33.6)
1998	83.1 (76.7-89.6)	20.2	29 (25-33)	34 (30-38)	22.0% (18.8-25.2)	37.7% (33.5-41.8)
1999	113 (105-121)	24.3	40 (36-45)	49 (44-53)	28.6% (24.9-32.3)	45.4% (40.9-50.0)
2000	149 (140-158)	28.7	54 (49-60)	66 (60-72)	36.6% (32.4-40.8)	55.3% (50.3-60.3)
2001	185 (174-195)	32.9	68 (61-75)	84 (77-91)	42.2% (37.7-46.7)	61.4% (56.2-66.7)
2002	220 (208-232)	36.2	82 (74-89)	102 (95-110)	46.4% (41.7-51.1)	65.9% (60.5-71.4)
2003	256 (243-270)	39.2	96 (87-104)	121 (112-130)	49.9% (45.0-54.8)	69.5% (63.9-75.0)
2004	290 (276-305)	42.1	109 (100-118)	139 (129-149)	52.8% (47.8-57.8)	72.0% (66.4-77.7)
2005	303 (288-318)	44.4	115 (106-125)	144 (133-154)	53.8% (48.8-58.8)	72.6% (66.8-78.3)
2006	293 (278-308)	44.8	113 (104-122)	135 (125-145)	52.9% (47.9-57.9)	71.2% (65.3-77.0)
2007	282 (266-297)	44.0	110 (101-120)	127 (117-137)	51.8% (46.8-56.8)	69.7% (63.8-75.6)
2008	266 (251-280)	42.0	106 (97-115)	118 (108-127)	50.4% (45.4-55.3)	67.8% (61.9-73.6)
2009	234 (220-247)	37.0	95 (87-104)	101 (93-110)	47.3% (42.4-52.1)	64.1% (58.5-69.7)
2010	204 (192-216)	30.0	85 (77-93)	89 (81-96)	44.1% (39.3-48.8)	60.6% (55.1-66.2)
2011	169 (158-180)	23.8	71 (64-78)	74 (68-81)	38.9% (34.4-43.4)	55.8% (50.6-61.0)

95% confidence intervals have been adjusted to reflect model error (see Appendix D). * 95% confidence intervals are not shown for paediatric outputs, as the uncertainty analysis does not include any of the mother-to-child transmission or paediatric survival parameters. † All death statistics relate to the period from the middle of the year indicated to the middle of the following year (i.e. last row corresponds to period from mid-2011 to mid-2012).

10.8 CD4 distributions and access to antiretroviral treatment

Table 10.6 summarizes estimates of total numbers of patients on ART and measures of ART coverage. Coverage is defined as the proportion of people eligible to receive ART who are actually on ART, where eligibility is defined according to the South African guidelines currently in place (in adults, this includes all individuals with CD4 counts <350 cells/μl, and in children this includes all HIV-infected children below the age of 5 years, regardless of their CD4 count). The total number of patients receiving ART is estimated to have increased to 2.32 million by the middle of 2012, representing 57% of all South Africans in need of ART. Coverage was higher in adult females (62.7%) compared to adult males (51.5%). Coverage was substantially lower in children (44.7%), reflecting the recent shift in guidelines and the greater number of children meeting the ART eligibility criteria in the absence of CD4 restrictions below the age of 5 years.

Table 10.6 Total numbers on ART and ART coverage

Year	Numbers receiving ART ('000)				ART coverage			
	Total	Males 15+	Females 15+	Children	Total	Males 15+	Females 15+	Children
2001	6	2	3	0	0.4%	0.5%	0.5%	0.2%
2002	14	5	7	1	0.9%	1.1%	0.9%	0.3%
2003	23	9	12	2	1.3%	1.6%	1.4%	0.5%
2004	43	15	23	4	2.1%	2.4%	2.3%	1.2%
2005	101	33	58	10	4.4%	4.5%	5.0%	2.6%
2006	215	66	126	23	8.6%	8.3%	9.9%	5.3%
2007	354	106	212	36	13.0%	12.2%	15.0%	8.2%
2008	553	165	335	54	18.7%	17.3%	21.5%	11.8%
2009	869	259	532	78	27.0%	24.8%	31.1%	16.9%
2010	1247	369	763	115	35.7%	32.4%	40.4%	24.9%
2011	1735	524	1060	151	46.0%	42.1%	51.1%	33.5%
2012	2322	699	1426	197	57.0%	51.5%	62.7%	44.7%

95% confidence intervals are not shown, as the uncertainty analysis does not include any of the HIV disease progression, ART uptake and ART survival parameters.

Table 10.7 shows the model estimates of the numbers on individuals starting ART in each year and the corresponding ART enrolment ratios. The ART enrolment ratio is defined as the number of individuals starting ART in a given year, divided by the number of individuals reaching the ART eligibility threshold in that year (for adults, the denominator is the number whose CD4 count falls below 350 cells/ μ l, and for children the denominator is the number of new paediatric HIV infections). The 2007-2011 National Strategic Plan target of an 80% ART enrolment ratio was exceeded over the 2009-2010 period, and there has been a steady increase in the ART enrolment ratio over each subsequent year, with the ratio reaching 1.42 over the 2011-2012 period. The ART enrolment ratio in males has in most periods been roughly 25% less than that in females. In children the ratio has historically been lower than in adults, but over the 2011-2012 period the ratio in children exceeded that in adults, as a result of the dramatic declines in mother-to-child transmission rates (i.e. a declining denominator).

Table 10.7 Total numbers initiating ART and ART enrolment ratios

Year	Numbers initiating ART ('000)				ART enrolment ratio			
	Total	Males 15+	Females 15+	Children	Total	Males 15+	Females 15+	Children
2000/01	6.7	2.7	3.5	0.5	0.02	0.02	0.02	0.01
2001/02	10.4	4.3	5.5	0.7	0.02	0.03	0.02	0.01
2002/03	12.2	4.9	6.5	0.8	0.02	0.03	0.03	0.01
2003/04	24.7	8.4	13.7	2.6	0.05	0.05	0.05	0.03
2004/05	71.2	22.4	42.6	6.2	0.14	0.12	0.16	0.08
2005/06	139.9	43.1	84.0	12.9	0.26	0.23	0.31	0.16
2006/07	171.4	52.3	104.2	15	0.32	0.27	0.39	0.2
2007/08	242.2	74.5	148.1	19.5	0.45	0.38	0.55	0.28
2008/09	380.2	118.0	233.7	28.4	0.72	0.61	0.86	0.44
2009/10	453.1	137.5	272.2	43.5	0.88	0.72	1.01	0.84
2010/11	582.9	190.6	346.0	46.4	1.18	1.01	1.29	1.17
2011/12	681.4	207.5	413.8	60.1	1.42	1.13	1.57	1.81

95% confidence intervals are not shown, as the uncertainty analysis does not include any of the HIV disease progression, ART uptake and ART survival parameters. All statistics relate to the period from the middle of the year indicated to the middle of the following year (i.e. last row corresponds to period from mid-2011 to mid-2012).

As a result of the rapid rollout of ART in South Africa, there has been a gradual change in the CD4 distribution of the HIV-positive adult population in South Africa, as shown in Figure 10.9. In the early 1990s, most HIV infections had been recently acquired, and consequently fewer than 30% of HIV-positive adults had CD4 counts below 500 cells/ μ l. However, as the

HIV epidemic matured and HIV incidence rates began to decline, this proportion rose to 65% and higher. Since the rollout of ART, there has been a change in CD4 distributions, particularly at low CD4 levels: the fraction of HIV-positive adults with CD4 counts < 200 cells/ μ l has dropped from 19% in 2007 to 12% in 2011. The figure shows that these model estimates are roughly consistent with the results of studies that have measured CD4 distributions in HIV-positive adults, although these surveys are not nationally representative (Auvert *et al.* 2004; Rehle and Shisana 2005; Connelly *et al.* 2007; Kranzer *et al.* 2013; Malaza *et al.* 2013; van Rooyen *et al.* 2013).

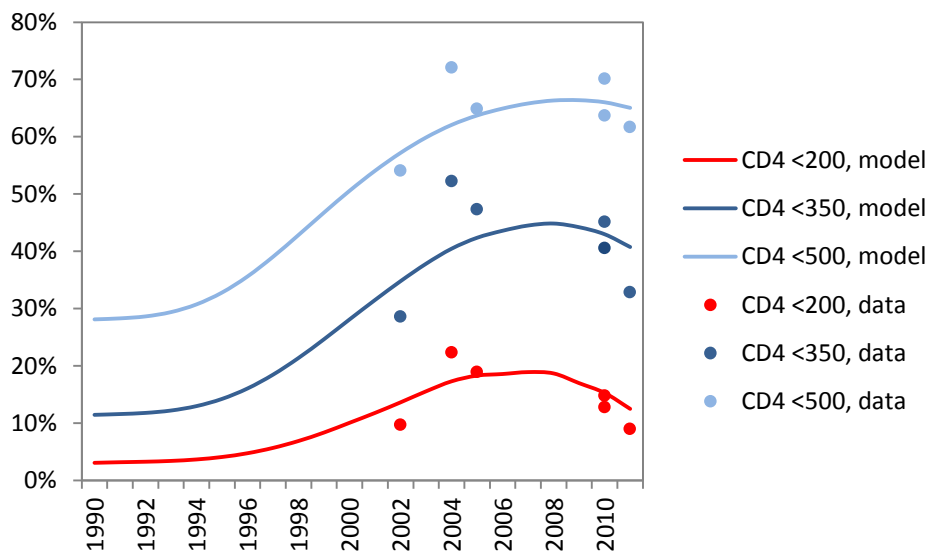


Figure 10.9: CD4 distribution of the HIV-positive South African adult population

10.9 Comparison with ASSA2008 and UNAIDS

Selected outputs of the Spectrum/EPP, ASSA2008 and THEMBISA models are compared in Figure 10.10. The Spectrum/EPP results are those published as part of the 2013 UNAIDS report (UNAIDS 2013). Although the three models produce similar estimates of adult (15-49) HIV prevalence in 2012, there is substantial disagreement between the three models in their estimates of the course of the epidemic up to this time. The Spectrum/EPP model estimates a relatively high HIV prevalence in the early stages of the epidemic, while the THEMBISA model estimates a relatively low peak HIV incidence rate and a more gradual decline in HIV incidence after the late 1990s. The ASSA2008 model estimates a relatively slow start to the epidemic when compared to the other two models. The THEMBISA model estimates a much more dramatic decline in AIDS mortality after 2005 than either of the other two models, although the Spectrum/EPP model does estimate a substantial reduction in AIDS mortality between 2011 and 2012.

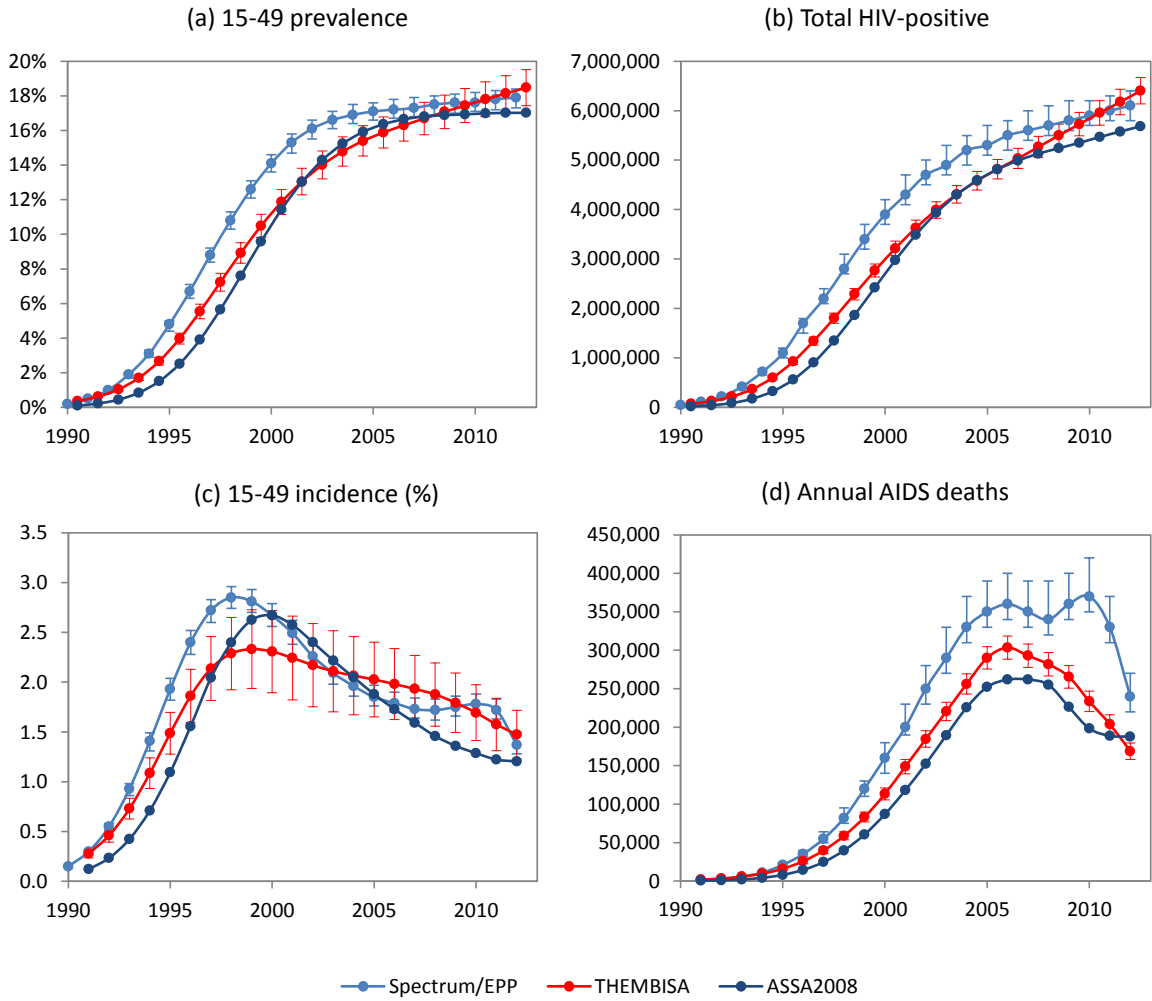


Figure 10.10: Comparison of model estimates of key HIV indicators

11. Discussion

This paper reaffirms the encouraging results from previous analyses, which suggest that HIV incidence in South Africa has declined over the last decade and that AIDS mortality has reduced substantially since the start of the public-sector antiretroviral treatment programme (Actuarial Society of South Africa 2011; Rehle *et al.* 2010; Bradshaw *et al.* 2012). However, these reductions have not been uniform across the population. For example, reductions in adult AIDS mortality have been much more substantial in females than in males, a finding that is consistent with both the higher rate of ART uptake in females (Johnson 2012) and the lower rate of mortality in females following ART initiation (Cornell *et al.* 2012). Reductions in HIV incidence have also been much more dramatic in children than in adults, which is a reflection of the remarkable success of the PMTCT programme (Goga *et al.* 2012).

An innovative feature of this model is that it is calibrated to self-reported HIV testing history data, and the posterior analysis of these data yields a number of important insights. Firstly, the rate of HIV testing in HIV-positive individuals who are undiagnosed and asymptomatic is only 72% of that in HIV-negative individuals of the same age and sex. This may be a reflection of poorer socio-economic status and associated barriers to HIV testing (Cremin *et al.* 2012), or it may reflect a fear of getting tested in individuals who suspect that they might be HIV-positive (Mall *et al.* 2013; Kigozi *et al.* 2011; Kharsany *et al.* 2010). The lower rate of HIV testing in asymptomatic HIV-positive individuals is not immediately obvious from the data alone (Figures 10.1 and 10.2), as the data group together individuals in different stages of HIV disease as well as different ages, but by using a mathematical model that controls for other determinants of HIV test uptake, it is possible to isolate the independent effect of HIV status. Another important insight is that there appears to be substantial over-reporting of past HIV testing, relative to the actual numbers of HIV tests performed in South Africa. This is consistent with studies on the accuracy of self-reported testing histories for other diseases (Rauscher *et al.* 2008; Klein *et al.* 1999), and may be due to social desirability bias in face-to-face interviews. Our results also suggest that the increases in HCT uptake over the last decade have been much more substantial in women than in men (even after excluding testing through antenatal services). This points to the need for HIV testing strategies that will reach greater numbers of men, for example workplace-based programmes and mobile HCT services (van Schaik *et al.* 2010; Maheswaran *et al.* 2012).

Our calibration of the model to the South African HIV prevalence data and mortality data appears acceptable, although there is still substantial room for improvement. It is difficult to simultaneously fit a model to three different data sources (antenatal prevalence data, household survey prevalence data and mortality data) and achieve a good fit to all three data sets. To some extent the lack of fit reflects a degree of tension between the epidemiological patterns suggested by the different data sets. For example, the HSRC data suggest a substantial and steady reduction in HIV prevalence in 15-19-year olds over the 2005-2012 period, but the antenatal data suggest only a very modest decline; our model fits the latter better than it does the former. In other cases, the lack of fit may be due to survey biases that we have not fully accounted for. For example, the model slightly over-estimates antenatal prevalence after 2005, which may reflect a change in the extent of the antenatal bias after the expansion of the antenatal survey sample in 2006 (Dorrington and Bourne 2008).

The uncertainty analysis is limited in that it does not include several key parameters about which there is substantial uncertainty. There is a trade-off between the number of sources of uncertainty included in the posterior analysis and the time taken to perform the uncertainty analysis; even with only 13 parameters in the uncertainty analysis of the HIV prevalence and mortality data, it took 150 IMIS steps (equivalent to 131 hours on a Proline i7 with 16 GB RAM) for the IMIS algorithm to reach convergence. Some of the key parameters that have been fixed despite significant uncertainty regarding their true values include the relative rate of HIV disease progression in females, the reduction in infectiousness following ART initiation, the rate at which men visit sex workers and the effect of HIV on fertility. Uncertainty regarding these parameters needs to be explored in future work. It is also important to explore the uncertainty regarding the mortality rates of patients on ART, which have been fixed at values estimated from IeDEA-SA data (Johnson *et al.* 2013), though the IeDEA-SA data may well be biased. To some extent there is an implicit allowance for bias in the IeDEA data through the assumed reduction in the log of the excess mortality per unit increase in the ART initiation rate (the m parameter described in Appendix B), and this parameter is allowed to vary in the uncertainty analysis. If the IeDEA data were biased towards overstating AIDS mortality, we might expect relatively high values of the m parameter to produce better fits to the mortality data (and conversely if the IeDEA data were biased towards understating mortality). However, the posterior mean of the m parameter is not substantially different from the prior mean, so there is as yet no strong signal of a bias in the IeDEA data.

We have also not explored the uncertainty due to the mother-to-child transmission and paediatric HIV parameters, nor have we included paediatric HIV prevalence data and mortality data in the fitting of the model. For these reasons, the paediatric HIV estimates presented here should be regarded as tentative. We have not attempted to provide confidence intervals for these paediatric outputs, as these confidence intervals would convey a spurious sense of precision if they reflected only the uncertainty in the adult HIV parameters. Nevertheless, our model estimates of HIV prevalence in children are reasonably consistent with HIV prevalence data from the national surveys conducted in 2005 and 2008 (Shisana *et al.* 2010). Our model estimate of the perinatal transmission rate at 6 weeks in 2010, 5.4%, is somewhat higher than the rate of 3.5% estimated in a national survey in the same year (Goga *et al.* 2012), but this could possibly be due to a bias towards reduced PCR sensitivity in recently-infected infants who are receiving nevirapine prophylaxis (Gayle Sherman, personal communication). The empirical data therefore appear roughly consistent with paediatric HIV estimates of the model.

For similar reasons, we have not included confidence intervals when presenting estimates of ART access. The current analysis does not consider uncertainty regarding relative rates of CD4 decline in different disease stages, or uncertainty regarding the accuracy of reported ART totals, and it would therefore be spurious to present confidence intervals. However, it is worth noting that in a previous analysis, which did consider these sources of uncertainty, coefficients of variation for ART totals and ART coverage estimates were around 4-5% (Johnson 2012). If similar coefficients of variation were to apply here, the 95% confidence interval around the 57% coverage estimate in 2012 would be roughly 52-62%. Our current estimates of ART access are slightly lower than those estimated previously, but this is because the previous estimates were derived from the ASSA2008 model incidence rates, which are substantially different from those estimated in THEMBISA.

There is some inconsistency between the outputs of the THEMBISA model and the outputs of the two most widely-used AIDS models in South Africa, Spectrum/EPP and ASSA2008. Many of these differences appear to be due to differences in assumptions about antenatal bias. The ASSA2008 model estimates relatively low HIV numbers in the early stages of the South African epidemic, probably because the ASSA2008 model assumes a substantial degree of bias in the early antenatal surveys relative to the later antenatal surveys. Although the THEMBISA model also allows for a change in the extent of the antenatal bias in the early stages of the HIV epidemic, our posterior estimates suggest only a moderate change in the antenatal bias parameter (from 0.48 in 1991 to 0.43 in 1997); we would therefore struggle to match the early increases in mortality in the late 1990s if we assumed a degree of antenatal bias similar to that in the ASSA2008 model. Although the Spectrum/EPP model estimates an earlier ‘levelling off’ in 15-49 prevalence than the THEMBISA model, this is probably because the former model assumes that 15-49 prevalence is proportional to antenatal HIV prevalence. However, antenatal surveys are heavily biased towards the younger ages in the 15-49 age range, and the age-specific HIV prevalence data suggest an early levelling off in prevalence at young ages while prevalence continues to increase at the older ages. The trend in HIV prevalence across the whole 15-49 age group is therefore not likely to be the same as the trend in antenatal prevalence; we would expect the former to level off at a later stage. Calibration to age-specific prevalence data is therefore important in improving the accuracy of estimated trends in HIV incidence and prevalence. The ASSA2008 model is also calibrated to age-specific prevalence data, and although it also estimates a later levelling off in prevalence than the Spectrum/EPP model, its estimates of prevalence trends remain different from those in the THEMBISA model. This may be because the ASSA2008 model assumes increases in the extent of antenatal bias at ages 30 and older, over time (implying a substantially lower ‘true’ prevalence at the older ages than that observed in the antenatal surveys in recent years). In the THEMBISA model we have adopted a more parsimonious approach, assuming a single antenatal bias parameter for the whole of the 1997-2011 period, which is the same (on the logit scale) for all ages and all calendar years. Although it is possible that there may be variation in the extent of the antenatal bias by age and year, we currently lack strong evidence to support this.

Not all of the differences between the three models are attributable to antenatal bias assumptions. Some of the differences may be due to the data sources used in calibration; for example, the ASSA2008 model relies only on HIV prevalence data and recorded death data published up to 2008. The substantial differences in estimated AIDS mortality over the last decade are probably due mainly to assumptions about ART uptake and ART efficacy. The Spectrum estimates of annual AIDS deaths are surprising, as they suggest little reduction in AIDS mortality until 2012, despite evidence from vital registration of a steady improvement in adult mortality after 2005 (Bradshaw *et al.* 2012). The ASSA2008 model also estimates a more moderate decline in AIDS mortality than the THEMBISA model, but this is likely to be because the ASSA2008 model under-estimates the numbers of patients on ART as well as rates of survival following ART initiation (Actuarial Society of South Africa 2012). The ASSA2008 model also makes no allowance for the changes in ART eligibility criteria that occurred in 2010 and 2011, which partly explains why it estimates a levelling off in AIDS mortality after 2010. Recognizing these problems, the AIDS Committee of ASSA has acknowledged that the recent estimates of AIDS mortality produced by the ASSA2008 model are not realistic (Actuarial Society of South Africa 2012).

When compared with the HIV incidence estimates of the earlier ASSA and STI-HIV Interaction models, THEMBISA estimates a slightly more modest decline in HIV incidence over the last decade. In a recent analysis of the ASSA2003 and STI-HIV Interaction models, the percentage reduction in HIV incidence in 15-49 year olds, over the period from the start of 2000 to the start of 2008, was estimated to be 31% and 27% respectively (Johnson *et al.* 2012c). This compares with a reduction of 19% estimated by THEMBISA. The reasons for this discrepancy are not immediately obvious, but may be related to the revised assumptions regarding trends in condom use, with THEMBISA allowing for some reduction in condom use in recent years. These reductions in condom use could be the result of reduced funding for HIV communication programmes in recent years (Scalway 2010), or they could be the result of risk compensation in the ART era (Shafer *et al.* 2011; Cohen *et al.* 2009; de Walque *et al.* 2012).

A limitation of this model is that the demographic assumptions are somewhat out-of-date. We have relied on the ASSA2008 model (published in early 2011) in setting most of the demographic assumptions, with provisional updates to the fertility and migration assumptions. Since the publication of the ASSA2008 model, the results of the 2011 census have been published (Statistics South Africa 2012), and there have been associated estimates of changes to the population age distribution (Dorrington 2013). It will only be possible to produce a fully updated set of demographic estimates once the unit record data from the 2011 census have been published, but this may take some time. We have therefore not included in this paper our estimates of demographic indicators such as infant mortality and life expectancy, though we recognize that they are critical in assessing South Africa's progress towards meeting development goals. It is anticipated that the Excel version of the model will be made publicly available once the demographic parameters have been finalized.

Further work is also required to apply the THEMBISA model to each of the provinces in South Africa. There is substantial variation in HIV prevalence in South Africa, and it will be important to assess how much of the regional variation is attributable to factors such as male circumcision, age at marriage and the prevalence of concurrency (Williams *et al.* 2006b; Bongaarts 2007; Kenyon 2013). It will also be important to examine how much variation there is in access to key HIV services such as PMTCT and ART, and how patterns of inter-provincial migration may be influenced by these variations in access to HIV services.

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Appendix A: Mathematical approach to modelling sexual behaviour

This appendix provides further mathematical detail regarding the modelling of sexual behaviour. Sections A.1-A.3 describe the calculations performed to ensure that male rates of partnership formation are consistent with female rates of partnership formation. Section A.4 explains the method for calculating female rates of movement into and out of commercial sex. Finally, section A.5 explains the approach to modelling divorce and widowhood. In all sections, the symbol $N_{g,i,l,j}(x,t)$ represents the number of sexually active individuals aged x in year t , who are of sex g and risk group i , in relationship category l (0 for unmarried, 1 for married/cohabiting and 2 for sex workers) with a partner in risk group j (the j subscript is omitted in the case of unmarried individuals, i.e. for $l = 0$ or $l = 2$). Within this group we define $X_{g,i,l,j}(x,a,s,v,d)$ to be the proportion who are in HIV stage s (representing CD4 category in untreated infection), with ART status a (0 if untreated), HIV testing history v and ART duration d .

A.1 Non-spousal relationships

Suppose that $\Phi_{g,i}(x,t)$ is the total number of non-spousal relationships formed by individuals of sex g and age x , in risk group i , during year t . For high-risk women this is calculated as

$$\Phi_{2,1}(x,t) = N_{2,1,0}(x,t)c_{2,1,0}(x) + (N_{2,1,1,1}(x,t) + N_{2,1,1,2}(x,t))c_{2,1,1}(x),$$

where $c_{g,i,l}(x)$ is the annual rate of non-marital partnership formation in individuals aged x , of sex g and marital status l , who are in risk group i , as defined in section 2.3. For low-risk women the number of new partnerships is just

$$\Phi_{2,2}(x,t) = N_{2,2,0}(x,t)c_{2,2,0}(x),$$

since married women in the low risk group are assumed not to have extramarital partners. The total number of new non-spousal partnerships involving men of age y is then calculated as

$$\Phi_{1,\cdot}(y,t) = \sum_{x=10}^{90} (\Phi_{2,1}(x,t) + \Phi_{2,2}(x,t))f_{2,0}(y|x),$$

where $f_{g,l}(y|x)$ is the probability that for an individual of sex g and age x , in a relationship of type l , the partner's age is y (as defined in section 2.7). The rate at which unmarried men in the high risk group form new partnerships in year t is then calculated by observing that

$$\Phi_{1,0}(y,t) = N_{1,1,0}(y,t)c_{1,1,0}(y,t) + N_{1,2,0}(y,t)c_{1,1,0}(y,t)L_1 + (N_{1,1,1,1}(y,t) + N_{1,1,1,2}(y,t))c_{1,1,0}(y,t)R_1,$$

where L_1 and R_1 are the relative rates of non-spousal partnership formation in unmarried low-risk men and married high-risk men respectively (expressed as multiples of the rate in unmarried high-risk men). From this we calculate

$$c_{1,1,0}(y,t) = \frac{\Phi_{1..}(y,t)}{N_{1,1,0}(y,t) + N_{1,2,0}(y,t)L_1 + (N_{1,1,1,1}(y,t) + N_{1,1,1,2}(y,t))R_1}.$$

It is worth noting in passing that the rates at which men form non-spousal relationships are a function of t , while the rates at which women form non-spousal relationships are assumed to be independent of t . This is because male sexual activity is assumed to change over time in response to demographic changes (relative numbers of males and females at different ages and numbers of married and unmarried individuals at different ages). In reality, both male and female sexual behaviour patterns would change and male behaviour would not be dictated entirely by female ‘demand’ for sexual partners, but in the interests of mathematical simplicity, we fix the female sexual behaviour parameters.

For a man who is aged y , starting a new non-spousal relationship in year t , the probability that his partner is between the ages of x and $x + 1$ is

$$f_{1,0}(x|y,t) = \frac{(\Phi_{2,1}(x,t) + \Phi_{2,2}(x,t))f_{2,0}(y|x)}{\Phi_{1..}(y,t)}.$$

A.2 Mixing between risk groups in non-spousal relationships

The total number of non-spousal relationships formed by men in the high risk group in year t is

$$\Phi_{1,1}(.,t) = \sum_{y=10}^{90} N_{1,1,0}(y,t)c_{1,1,0}(y,t) + (N_{1,1,1,1}(y,t) + N_{1,1,1,2}(y,t))c_{1,1,0}(y,t)R_1,$$

and the total number of non-spousal relationships formed by low-risk men is

$$\Phi_{1,2}(.,t) = \sum_{y=10}^{90} N_{1,2,0}(y,t)c_{1,1,0}(y,t)L_1.$$

The total numbers of non-spousal relationships formed by women in the high-risk and low-risk groups ($\Phi_{2,1}(.,t)$ and $\Phi_{2,2}(.,t)$) respectively) are similarly defined. For women who are in risk group i in year t , the probability that their non-spousal partner is in risk group j is

$$\rho_{2,i,0}(j,t) = (1 - \varepsilon) \times I(i = j) + \varepsilon \times \frac{\Phi_{1,j}(.,t)}{\Phi_{1,1}(.,t) + \Phi_{1,2}(.,t)},$$

where ε is the assortativeness parameter described in section 2.6, and $I(i = j)$ is an indicator function (taking on value 1 when $i = j$ and value 0 when $i \neq j$). For men who are in risk group j in year t , the probability that their non-spousal partner is in risk group i is calculated as

$$\rho_{1,i,0}(i,t) = \frac{\Phi_{2,i}(\cdot,t)\rho_{2,i,0}(j,t)}{\Phi_{2,1}(\cdot,t)\rho_{2,1,0}(j,t) + \Phi_{2,2}(\cdot,t)\rho_{2,2,0}(j,t)}.$$

A.3 Partner age and risk group preferences in spousal relationships

We calculate the proportion of married men, aged y in year t , whose partners are aged x as:

$$f_{1,1}(x|y,t) = \frac{(N_{2,1,1,1}(x,t) + N_{2,1,1,2}(x,t) + N_{2,2,1,1}(x,t) + N_{2,2,1,2}(x,t))f_{2,1}(y|x)}{\sum_{v=15}^{90} (N_{2,1,1,1}(v,t) + N_{2,1,1,2}(v,t) + N_{2,2,1,1}(v,t) + N_{2,2,1,2}(v,t))f_{2,1}(y|v)}.$$

It is worth noting here that y represents the *current* partner age, not the age of partners in newly-formed spousal relationships, since there is an implicit allowance for differential rates of survival at different ages in the calculation of $f_{2,1}(y|x)$.

The number of individuals of sex g , in risk group i , who enter spousal relationships in year t is calculated as

$$D_{g,i}(t) = \sum_{y=15}^{90} N_{g,i,0}(y,t) m_{g,i}(y,t),$$

where $m_{g,i}(y,t)$ is the annual probability of forming a new spousal relationship at age y . For women who are in risk group i , entering into a spousal relationship in year t , the probability that their new partner is in risk group j is

$$\rho_{2,i,1}(j,t) = (1 - \varepsilon) \times I(i = j) + \varepsilon \times \frac{D_{1,j}(t)}{D_{1,1}(t) + D_{1,2}(t)}.$$

For men in risk group j who are entering spousal relationships in year t , the probability that their new partner is in risk group i is calculated as

$$\rho_{1,j,1}(i,t) = \frac{D_{2,i}(t)\rho_{2,i,1}(j,t)}{D_{2,1}(t)\rho_{2,1,1}(j,t) + D_{2,2}(t)\rho_{2,2,1}(j,t)}.$$

A.4 Female rates of entry into and exit from sex work

At the end of each month the model updates female movements into and out of sex work based on assumed rates of retirement from sex work and based on male demand for sex work. The total male demand for sex workers at time t is calculated as

$$E(t) = \frac{1}{C} \sum_{x,l,j} \sum_{a,s,v,d} N_{1,1,l,j}(x,t) X_{1,1,l,j}(x,a,s,v,d) w_l(x) Y(a,s,d)$$

where $w_l(x)$ is the rate at which HIV-negative men visit sex workers (as defined in section 2.5), $Y(a, s, d)$ is the adjustment made to the coital frequencies of HIV-positive individuals (as defined in section 4.6), and C is the assumed average annual number of clients per sex worker. As explained in section 2.5, there is assumed to be a constant sex worker age distribution, with $\phi(x)$ representing the fraction of sex workers who are aged x years. The required number of sex workers aged x at time t is therefore $E(t)\phi(x)$.

Suppose that $\tau(a, s, d)$ represents the monthly probability of retirement from commercial sex in sex workers who are in HIV stage s , with ART status a and ART duration d years. Then at age x , the total number of sex workers retiring from sex work in month t is

$$N_{2,1,2}(x, t-1) \sum_{a,s,v,d} X_{2,1,2}(x, a, s, v, d) \tau(a, s, d).$$

(It is worth noting that although the symbol $N_{2,1,2}(x, t-1)$ represents the number of sex workers at time $(t-1)$, the calculation is actually performed *after* HIV disease progression and AIDS mortality in month t have been updated.) In order to meet the male demand for sex workers, the number of women aged x who need to enter sex work during month t is

$$\Delta_c(x, t) = E(t-1)\phi(x) - N_{2,1,2}(x, t-1) \left(1 - \sum_{a,s,v,d} X_{2,1,2}(x, a, s, v, d) \tau(a, s, d) \right).$$

Women enter into sex work from the unmarried high risk group, but it is assumed that women in the advanced stages of HIV disease are less likely to enter sex work than women who are HIV-negative or asymptomatic. The symbol $W(a, s, d)$ represents the relative probability of entry into commercial sex (compared to HIV-negative women) for women who are in HIV stage s , with ART status a and ART duration d years. For sexually experienced HIV-negative women in the high risk unmarried group, who are aged x at time $(t-1)$, the probability of entry into sex work in month t is

$$\frac{\Delta_c(x, t)}{N_{2,1,1}(x, t-1) \sum_{a,s,v,d} X_{2,1,1}(x, a, s, v, d) W(a, s, d)}.$$

For HIV-positive women, the probability of entry into sex worker is obtained by multiplying the above expression by the relevant $W(a, s, d)$ factor.

The variables $\tau(a, s, d)$ and $W(a, s, d)$ have been defined in section 2.10 as a function only of current CD4 count in untreated individuals (s), but for treated individuals the variable s represents the baseline CD4 category. In treated individuals the $\tau(a, s, d)$ and $W(a, s, d)$ variables are therefore calculated based on the expected distribution of current CD4 counts in individuals who started ART in CD4 category s , d years previously. This expected CD4 distribution is defined in Appendix C.

A.5 Divorce and widowhood

Divorce and widowhood are calculated on an annual basis. Consider a married individual of age x and sex g , in risk group i , with married partner in risk group j . The probability that the relationship does not terminate in the current year is calculated as the product of three probabilities:

- a) the probability that the partner does not die from AIDS;
- b) the probability that the partner does not die from non-AIDS causes; and
- c) the probability that the relationship does not end through divorce.

Considering the first probability, we define $q_{g,j,i}^A(y,t)$ to be the probability of AIDS death during the course of year t , for a married individual of age x and risk group j , who is alive at the start of year t . The average probability that the partner does not die from AIDS during year t is

$$1 - \sum_{y=15}^{90} f_{g,1}(y | x, t) q_{3-g,j,i}^A(y, t),$$

where $(3 - g)$ is the sex opposite to g . Similarly, we define $q_g^N(y, t)$ to be the probability of death due to a non-AIDS cause during the course of year t , for a married individual of age x and sex g , who is alive at the start of year t . The average probability that the partner does not die from non-AIDS causes during year t is then

$$1 - \sum_{y=15}^{90} f_{g,1}(y | x, t) q_{3-g}^N(y, t).$$

Finally, we define $\delta_g(x)$ to be the annual rate at which married individuals of age x and sex g divorce, so that the probability that the relationship does not end in divorce is $\exp(-\delta_g(x))$. Combining these three expressions, the probability that an individual of age x , sex g and risk group i , who is married to a partner of risk group j at the start of year t , returns to the single state in the course of year t is

$$1 - \left(1 - \sum_{y=15}^{90} f_{g,1}(y | x, t) q_{3-g,j,i}^A(y, t) \right) \left(1 - \sum_{y=15}^{90} f_{g,1}(y | x, t) q_{3-g}^N(y, t) \right) \exp(-\delta_g(x)).$$

Appendix B: Modelling of changes in CD4 distributions at low CD4 counts

To describe mortality at CD4 counts below 200/ μl , we assume that the untreated HIV mortality rate in individuals with CD4 count x is

$$\mu(x) = a(b^x), \quad (\text{B1})$$

where a is the mortality rate we would expect in an untreated individual with a CD4 count of zero, and b is the factor by which the mortality rate decreases per unit increase in the CD4 count. The b parameter is estimated by fitting regression models of the form given in equation (B1) to average mortality levels reported over different CD4 ranges, in different African studies conducted prior to the availability of ART (Anglaret *et al.* 2012; Mermin *et al.* 2008; van Oosterhout *et al.* 2005; Fielding *et al.* 2011). The resulting model fits to the data are shown in Figure B1. Although the overall mortality levels in the Malawian setting (van Oosterhout *et al.* 2005) are higher than those in Uganda (Mermin *et al.* 2008), Côte d'Ivoire (Anglaret *et al.* 2012) and South Africa (Fielding *et al.* 2011), the fitted b parameter values are remarkably consistent across settings: 0.9882 in Malawi, 0.9876 in Uganda, 0.9899 in Côte d'Ivoire and 0.9887 in South Africa. We therefore set the b parameter in our model at the average of these values, 0.9886.

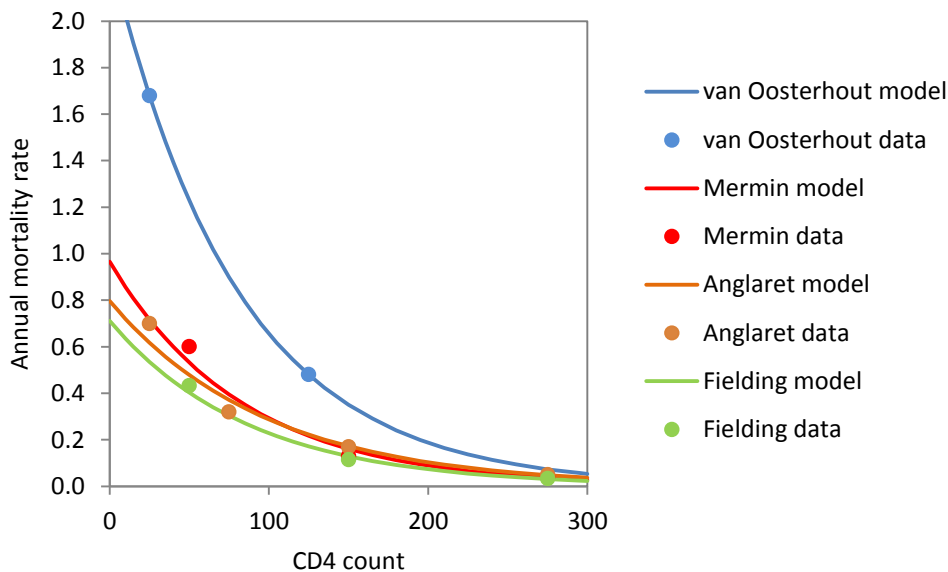


Figure B1: Effect of CD4 count on mortality in the absence of ART

For the purpose of fitting the models to the data points, the average mortality rates reported over different ranges have been taken to apply at the midpoints of the relevant ranges. Mortality data from the 200-350 CD4 range have been included in order to increase the statistical confidence in the fitted parameters.

The a parameter has been set to produce estimates consistent with previously-estimated South African mortality rates in the CD4 200-349 and <200 categories, 0.027 and 0.21 respectively (Johnson 2012). If 0.027 is the average mortality rate that would be expected at a CD4 count of 275/ μl , then substituting these values into equation (B1) together with the previously-estimated value of b gives us $a = 0.645$. (As a validity check, the implied mortality at a CD4

count of 100 is $0.645 \times 0.9886^{100} = 0.205$, which is close to the average of 0.21 that we would expect over the CD4 <200 range.)

Suppose that q_t is the annual mortality rate in untreated adults with CD4 counts <200, in year t . Further suppose that q_0 is the corresponding mortality rate that would have been expected in the absence of any ART rollout, and that q_{\min} is the minimum mortality rate that we would expect if rates of ART initiation were at their maximum. We would expect q_t to decline as the rate of ART initiation increases, as high rates of ART initiation imply that few individuals will progress to very low CD4 counts (<50) without starting ART. In modelling q_t we assume it is exponentially related to r_{t-1} , the rate of ART initiation in the previous year, subject to the maximum of q_0 and the minimum of q_{\min} :

$$q_t = q_{\min} + (q_0 - q_{\min})\exp(-mr_{t-1}), \quad (\text{B2})$$

where m is the assumed exponential parameter. This can be written as

$$A_t = \frac{q_{\min}}{q_0} + \left(1 - \frac{q_{\min}}{q_0}\right)\exp(-mr_{t-1}), \quad (\text{B3})$$

where $A_t \equiv q_t/q_0$ is an adjustment factor applied to the mortality rate that would be expected in the absence of any ART rollout. The ratio q_{\min}/q_0 can be estimated by noting that untreated mortality is at a minimum when all patients start ART soon after their CD4 count drops below 200. Setting $q_{\min} = \mu(200) = 0.065$ and setting $q_0 = 0.21$ yields $q_{\min}/q_0 = 0.31$. The m parameter is difficult to quantify precisely, so a Bayesian approach is adopted to reflect the uncertainty regarding this parameter (discussed further below).

A similar approach is adopted in modelling mortality during the first 6 months after starting ART. Suppose that v_t is the annual mortality rate in adults during their first 6 months after starting ART (with baseline CD4 counts <200), in year t . Further suppose that v_0 is the corresponding mortality rate that would have been expected in the very early stages of the ART rollout, when rates of ART initiation were very low, and that v_{\min} is the minimum mortality rate that we would expect if rates of ART initiation were at their maximum. We would expect v_t to decrease as the rate of ART rollout increases, as higher rates of ART rollout should lead to higher baseline CD4 counts. As before, we assume a relationship of the form

$$B_t = \frac{v_{\min}}{v_0} + \left(1 - \frac{v_{\min}}{v_0}\right)\exp(-mr_{t-1}), \quad (\text{B4})$$

where $B_t \equiv v_t/v_0$. Note that the m parameter is assumed to be the same as that in equation (B2), although one could argue that the relationship with the rate of ART initiation may differ depending on whether one is considering pre-ART mortality or treated mortality. (In the interests of obtaining a parsimonious model fit, we use the same parameter value in equations (B2) and (B4), but the model does allow for different values to be assumed.)

For the purpose of estimating the ratio v_{\min}/v_0 , we will assume that the mortality rate for individuals with baseline CD4 counts of x , $v(x)$, is of the form

$$v(x) = c(d^x). \quad (\text{B5})$$

Studies suggest that in the early stages of South Africa's ART rollout, baseline CD4 distributions were roughly uniform over the range $[0, 200)$ (Lawn *et al.* 2006; Lessells *et al.* 2013), which suggests that we can approximate v_0 using the formula

$$v_0 = \int_0^{200} \frac{1}{200} c(d^x) dx = \frac{c}{200 \ln(d)} (d^{200} - 1). \quad (\text{B6})$$

Since the minimum mortality rate in the first 6 months of ART would be achieved if all patients starting ART at CD4 <200 cells/ μl had initial CD4 counts close to 200, $v_{\min} = v(200) = c(d^{200})$. From this it follows that

$$\frac{v_{\min}}{v_0} = \frac{200 \ln(d)}{1 - d^{-200}}, \quad (\text{B7})$$

which is independent of c . Estimating the ratio v_{\min}/v_0 therefore requires only that we have estimates of the parameter d , which can be obtained from various studies that have estimated the effect of baseline CD4 count on mortality during the first 6 months of ART. Table B1 summarizes relevant studies that have been conducted in South Africa. Although most of these studies report hazard ratios for CD4 intervals, it is possible to convert these into continuous CD4 effects using simple exponential regression models if the mortality hazards are assumed to apply to the average CD4 count over each interval (as in Figure B1). Table B1 shows the estimates of the d parameter that have been obtained by fitting these exponential models in each case. The average value, 0.9917, is substituted into equation (B7) to obtain a v_{\min}/v_0 estimate of 0.39.

Table B1: South African studies of effect of baseline CD4 count on early ART mortality

Study	Population/location	ART durations	Factor by which mortality decreases per unit increase in baseline CD4 (d)
Lawn <i>et al</i> (2006)	Gugulethu programme, Cape Town	<4 months	0.9905
Hoffmann <i>et al</i> (2013)	Aurum community and workplace programmes	13 weeks	0.9928
Boulle <i>et al</i> (2010)	Khayelitsha programme, Cape Town	<3 months	0.9923
Cornell <i>et al</i> (2010)	IeDEA-SA Collaboration	<4 months	0.9874
Mutevedzi <i>et al</i> (2011)	Africa Centre, KwaZulu-Natal, ages <50	<3 months	0.9943
Leisegang <i>et al</i> (2010)	Aid for AIDS programme	<4 months	0.9927
Average			0.9917

For the model of early ART mortality, it is possible to obtain a crude estimate of the m parameter by using data on early mortality from the Western Cape (Boulle *et al.* 2008a), together with estimates of rates of ART initiation in the province (Adam and Johnson 2009). Table B2 shows the estimated probability of death during the first 6 months after starting ART, for patients starting ART in each calendar year, as well as rates of ART initiation derived from the previously-published model of ART coverage. Fitting a simple regression model of the form given in equation (B4) to the estimates of v_t and r_t in Table B2 yields an estimate of the m parameter equal to 8.79, if v_0 is set to 0.28 and the ratio v_{\min}/v_0 is set to 0.39. (The rate of 0.28 was chosen as it is close to the rate estimated in 2001, when the ART rollout in the Western Cape had just started.) It is likely that this m estimate is an over-estimate, as the recording of mortality in patient record systems has become less complete over time as an increasingly high proportion of patients has been classified ‘lost to follow-up’ (Cornell *et al.* 2010), and in other settings where vital registration has remained relatively complete, reductions in early mortality have been more moderate (Lessells *et al.* 2013). This implies that some of the apparent improvement in early ART mortality, which we are attributing to the effect of rising rates of ART initiation, is actually due to declining completeness of death reporting. A more moderate decline in mortality over time would lead to a lower estimate of m , and the 8.79 estimate is therefore likely to be an upper bound. To represent our uncertainty regarding the m parameter, we have chosen a gamma prior with a mean of 5 and a standard deviation of 2.5. The 2.5 and 97.5 percentiles of this distribution are 1.36 and 10.96 respectively, reflecting the substantial prior uncertainty that exists for this parameter.

Table B2: Early ART mortality and ART initiation in the Western Cape province

	2000	2001	2002	2003	2004	2005
6-month cumulative mortality*	-	0.127	0.117	0.096	0.060	0.066
Annual mortality rate (v_t)	-	0.2716	0.2489	0.2019	0.1238	0.1366
Adults starting ART†	158	391	691	2585	5468	8528
Untreated adults with CD4 <200 cells/ μ l or AIDS (mid-year)†	10706	14286	18296	22131	23465	23440
ART initiation rate (r_t)	0.0148	0.0274	0.0378	0.1168	0.2330	0.3638

* From Boulle *et al.* (2008a). † From the model described by Adam and Johnson (2009).

Finally, we define w_t to be the annual mortality rate in ART patients in year t , who have been on ART for durations >6 months, having started ART with an initial CD4 count <200 cells/ μ l. As with v_t , we would expect this rate to decline with respect to t as rates of ART initiation increase. However, we would expect the decline in w_t to be more moderate than that in v_t , since mortality at longer ART durations is not as strongly related to baseline CD4 count as mortality at early ART durations. We define a relation between w_t to and r_t similar to that in equation (B4):

$$w_t = w_{\min} + (w_0 - w_{\min})\exp(-mr_{t-1}), \quad (\text{B8})$$

where w_0 is the mortality rate that would have been expected in the very early stages of the ART rollout, and w_{\min} is the minimum mortality rate that we would expect if rates of ART initiation were at their maximum. As before, we define $C_t \equiv w_t/w_0$, so that

$$C_t = \frac{w_{\min}}{w_0} + \left(1 - \frac{w_{\min}}{w_0}\right) \exp(-mr_{t-1}). \quad (\text{B9})$$

For the purpose of estimating the ratio w_{\min}/w_0 , we use the same assumptions as before to derive a similar formula to that in equation (B7),

$$\frac{w_{\min}}{w_0} = \frac{200 \ln(f)}{1 - f^{-200}}. \quad (\text{B10})$$

where f is the factor by which mortality at durations >6 months reduces, per unit increase in the baseline CD4 count. Estimates of the f parameter are obtained in the same way as before, based on fitting simple exponential regression models to hazard ratio estimates from various published studies (Table B3). There are relatively few such studies, as most studies control for time-updated CD4 count (rather than baseline CD4 count) when assessing the effect of CD4 count on mortality at longer ART durations. Substituting the average estimate of f , 0.9955, into equation (B10) gives an estimate for w_{\min}/w_0 of 0.61. As expected, this is higher than the ratio of 0.39 estimated for v_{\min}/v_0 , reflecting the more modest effect of baseline CD4 count on mortality at longer ART durations.

Table B3: South African studies of effect of baseline CD4 count on late ART mortality

Study	Population/location	ART durations	Factor by which mortality decreases per unit increase in baseline CD4 (f)
Lawn <i>et al</i> (2006)	Gugulethu programme, Cape Town	>4 months	0.9905
Johnson <i>et al</i> (2013)	IeDEA-SA Collaboration, males	>12 months	0.9966
	IeDEA-SA Collaboration, females	>12 months	0.9966
Cornell <i>et al</i> (2010)	IeDEA-SA Collaboration	12-36 months	0.9955
Average			0.9955

Appendix C: Modelling changes in CD4 distributions after ART initiation

Although our model stratifies individuals who have started ART according to their CD4 count at baseline (the time of starting ART), there are some situations in which it is necessary to know what proportions of ART patients are *currently* in different CD4 categories. For example, this is necessary when calibrating the model to cross-sectional surveys of CD4 distributions in HIV-positive individuals. It is also necessary when modelling the frequency of sex and fertility of patients on ART, since both parameters are assumed to depend on patients' current CD4 counts rather than their baseline CD4 counts. This appendix describes an approach to estimating the proportion of ART patients currently in different CD4 categories, for a given baseline CD4 count and a given time since ART initiation.

In setting the model assumptions, we rely primarily on data from three studies of CD4 trajectories after ART initiation: a South African study (Boulle *et al.* 2010), a multi-regional collaboration of ART programmes in developing countries (Nash *et al.* 2008), and a US study (Lok *et al.* 2010). These studies report CD4 trajectories in terms of medians and inter-quartile ranges (IQRs), rather than proportions of patients in the CD4 intervals that we are interested in. Our approach is therefore to fit gamma distributions to the reported medians and IQRs, and then to estimate proportions of patients in the different CD4 categories from the fitted gamma distributions. Gamma distributions are chosen as they are positive-valued and tend to match the positively-skewed shape of observed CD4 distributions better than symmetric normal distributions.

Panel a of Figure C1 shows the gamma distributions fitted to the data in the South African study, and Table C1 shows the means and standard deviations estimated in fitting the gamma distributions to the data. At all ART durations, the gamma distribution provided a good fit to the observed CD4 distribution, and the estimated coefficient of variation was consistently around 0.46. In this study, almost all patients started ART with a CD4 count <200 cells/ μ l, but a small minority started ART with higher CD4 counts because they qualified for ART on clinical grounds. For this reason we have used the reported medians rather than the fitted means when setting the assumed average CD4 levels after ART initiation in patients starting ART with CD4 <200 (the median is slightly less than the mean).

As the South African data relate only to patients starting ART with low CD4 counts, it is necessary to rely on estimated CD4 trajectories in other settings when setting the model assumptions about changes in CD4 counts for patients starting ART at higher CD4 counts. Panels b-d of Figure C1 show the gamma fits to the US data, and the associated parameters are shown in Table C1. Here it is apparent that the coefficient of variation is much lower at baseline (average of 0.15, range 0.11-0.17) than at durations of 3 years or longer (average 0.33, range 0.27-0.45). Although it is not strictly correct to fit gamma distributions to the baseline CD4 distributions, since the actual CD4 distributions at baseline are truncated at the upper and lower limits of the relevant ranges, one obtains similar estimates of the coefficient of variation if one instead assumes baseline CD4 distributions are uniformly distributed over the relevant ranges (0.16 for the CD4 201-350 range and 0.10 for the CD4 351-500 range). At the 7-year ART duration, the gamma distributions appear to provide a relatively poor fit to

the reported CD4 distributions, but this may simply be a reflection of the smaller sample sizes at longer ART durations.

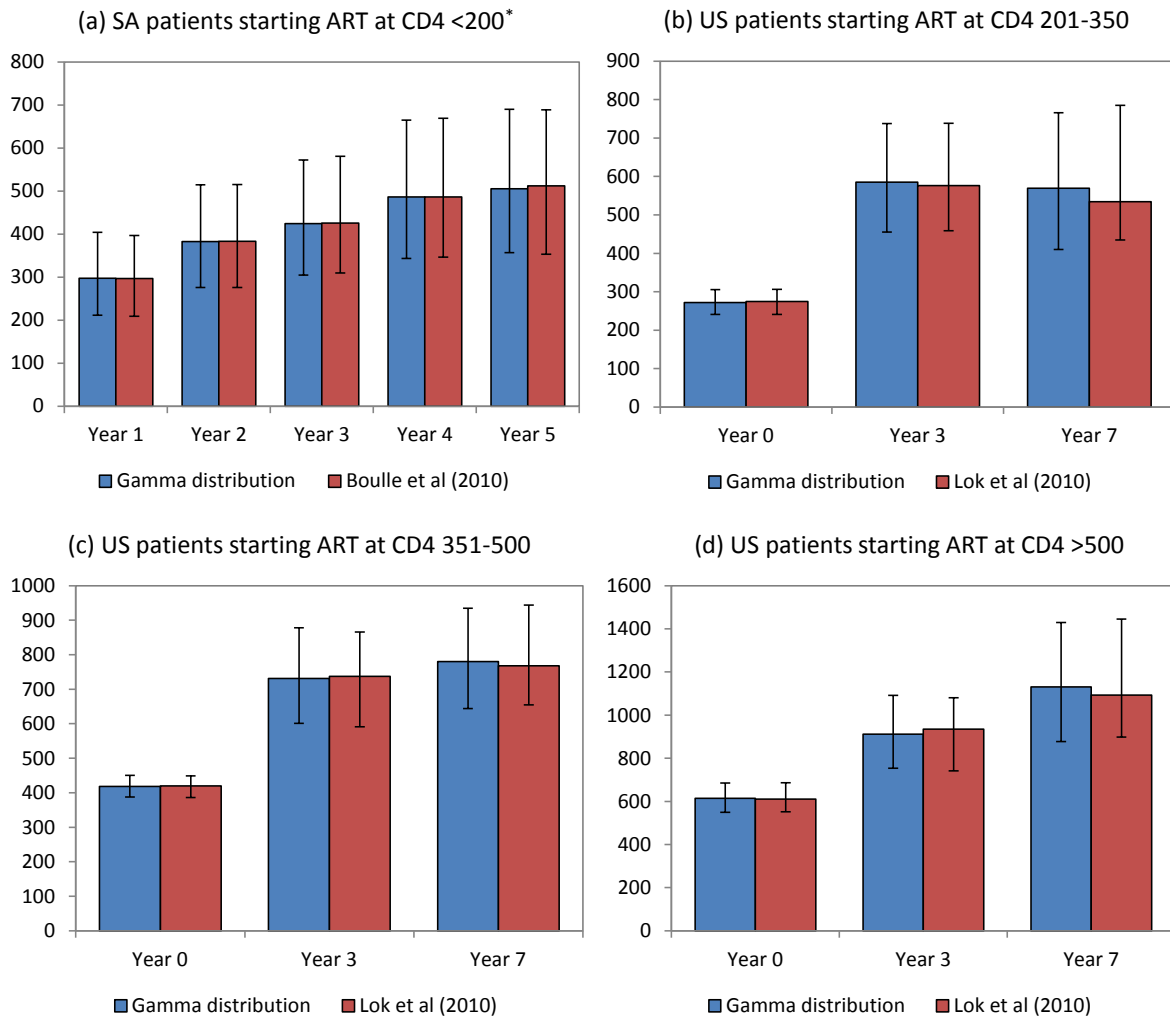


Figure C1: Comparison of reported CD4 distributions and fitted CD4 distributions at different ART durations, for patients starting ART in different CD4 categories

* A small minority of patients started ART at CD4 >200/ μ l because they qualified for ART on clinical grounds.

Data from a multi-centre collaboration of ART programmes in developing countries (Nash *et al.* 2008) are used to set the assumed changes in mean CD4 count for patients starting ART at CD4 counts >200 cells/ μ l. However, Table C2 shows that in patients starting ART with CD4 counts <200, the mean changes in CD4 count in this study are significantly smaller than those observed by Boulle *et al.* This could be because most of the programmes contributing to the multi-centre collaboration do not perform routine viral load monitoring, whereas viral load is routinely monitored in South Africa. Previous research has shown that CD4 recovery appears to be more substantial in programmes that perform viral load monitoring than in those that do not (Keiser *et al.* 2011). Some adjustment therefore needs to be made to the mean changes estimated by Nash *et al.*, in order to make them more applicable to South Africa. We do this by calculating the ratio of the South African CD4 counts to the CD4 counts in the multiregional collaboration, at different ART durations, standardizing on the baseline CD4 counts in the South African study (last row of Table C2).

Table C1: Gamma fits to observed CD4 distributions

Study	Baseline CD4	Years since ART start	Reported CD4 distribution (median, IQR)	Fitted gamma distribution		
				Mean	Standard deviation	Coefficient of variation
<i>Boulle et al</i> (2010)	<200 [*]	1	297 (209-397)	320	149	0.47
		2	383 (276-515)	410	184	0.45
		3	426 (310-581)	455	206	0.45
		4	486 (347-669)	525	248	0.47
		5	512 (353-689)	545	257	0.47
<i>Lok et al</i> (2010)	201-350	0	275 (241-306)	275	48	0.17
		3	576 (459-738)	610	214	0.35
		7	534 (435-785)	610	274	0.45
	351-500	0	420 (386-449)	420	47	0.11
		3	737 (591-866)	750	208	0.28
		7	768 (655-944)	800	218	0.27
	>500	0	610 (552-687)	620	101	0.16
		3	935 (741-1081)	935	253	0.27
		7	1093 (898-1445)	1180	419	0.36

* A small minority of patients started ART at CD4 >200/μl because they qualified for ART on clinical grounds.

Table C2: Changes in mean CD4 count after ART initiation

Study	Mean CD4 count by ART duration (years)					
	0	1	2	3	4	5
<i>Boulle et al</i> (2010) ^a	101	297	383	425.5	486	512
<i>Nash et al</i> (2008) ^b	81	262	318	328	320	304
	180	357	407	417	411	399
	367	492	537	557	566	570
	Ratio of Boulle to Nash estimates (standardized to baseline CD4 of Boulle)	1	1.06	1.14	1.23	1.44

^a Medians are used in place of means, as means were not reported, and as this is consistent with the previous assumption that mean CD4 counts in patients with baseline CD4 <200 are approximately the same as the reported medians for all patients (a small minority of whom start ART at CD4 >200). ^b Estimates are for women starting ART aged 30-39.

For patients starting ART at CD4 counts >200, the procedure for setting the assumed CD4 trajectories is to (a) set the assumed average baseline CD4 count for patients starting ART in each CD4 category, (b) linearly interpolate or extrapolate from the *Nash et al* estimates in Table C2 to calculate the expected CD4 count at each of durations 1-5 as a function of the average baseline CD4 counts in (a), (c) apply the South African adjustment factor from the last row of Table C2 to obtain revised means, (d) set the assumed coefficients of variation in CD4 count at each ART duration, and finally (e) calculate the fraction of patients in each CD4 band at each ART duration if it is assumed that CD4 counts are gamma-distributed with the previously-specified means and coefficients of variation. The key steps in this procedure are summarized in Table C3. In step (a) we assume that baseline CD4 counts are uniformly distributed over each CD4 range, except in the CD4 500+ category, where the mean has been set to 610 based on the estimates of *Lok et al* (2010). Steps (b) and (c) do not apply to the assumptions for patients with baseline CD4 <200, since we obtain the mean CD4 counts for these patients directly from *Boulle et al* (2010). In step (d) we have relied on the coefficient

of variation estimates in Table C1, assuming that in patients who start ART with CD4 >200, the coefficient of variation in CD4 count increases linearly from 0.15 at baseline to 0.33 at ART durations of 3 years and remains stable at this level thereafter.

Table C3: Derivation of proportions of patients in different CD4 categories

	Years since ART initiation					
	0	1	2	3	4	5
Assumed mean CD4 count for						
Baseline CD4 <200	100	297	383	426	486	512
Baseline CD4 200-349	275	450	539	600	703	770
Baseline CD4 350-499	425	564	658	738	882	987
Baseline CD4 500+	610	705	805	909	1102	1255
Assumed CD4 coefficient of variation for						
Baseline CD4 <200	0.46	0.46	0.46	0.46	0.46	0.46
Baseline CD4 200-349	0.15	0.21	0.27	0.33	0.33	0.33
Baseline CD4 350-499	0.15	0.21	0.27	0.33	0.33	0.33
Baseline CD4 500+	0.15	0.21	0.27	0.33	0.33	0.33
Patients starting ART with CD4 <200						
Proportion with current CD4 500+	0.00	0.08	0.22	0.30	0.41	0.46
Proportion with current CD4 350-499	0.00	0.22	0.29	0.30	0.28	0.27
Proportion with current CD4 200-349	0.00	0.44	0.35	0.30	0.24	0.21
Proportion with current CD4 <200	1.00	0.26	0.13	0.10	0.06	0.05
Patients starting ART with CD4 200-349						
Proportion with current CD4 500+	0.00	0.28	0.57	0.66	0.81	0.87
Proportion with current CD4 350-499	0.00	0.58	0.35	0.25	0.16	0.11
Proportion with current CD4 200-349	1.00	0.14	0.08	0.08	0.04	0.02
Proportion with current CD4 <200	0.00	0.00	0.00	0.00	0.00	0.00
Patients starting ART with CD4 350-499						
Proportion with current CD4 500+	0.00	0.69	0.81	0.84	0.93	0.96
Proportion with current CD4 350-499	1.00	0.29	0.17	0.13	0.06	0.04
Proportion with current CD4 200-349	0.00	0.02	0.02	0.03	0.01	0.01
Proportion with current CD4 <200	0.00	0.00	0.00	0.00	0.00	0.00
Patients starting ART with CD4 500+						
Proportion with current CD4 500+	1.00	0.93	0.94	0.94	0.98	0.99
Proportion with current CD4 350-499	0.00	0.07	0.06	0.05	0.02	0.01
Proportion with current CD4 200-349	0.00	0.00	0.00	0.01	0.00	0.00
Proportion with current CD4 <200	0.00	0.00	0.00	0.00	0.00	0.00

In our model, the variable $\psi_d(u | s)$ is the proportion of individuals with current CD4 count in category u , in the cohort of patients who started ART with a CD4 count of s and who have been on ART for d years. In the model, the duration categories are defined over integer ranges rather than at exact time points, but we can use the estimates in Table C3 as approximations to the distributions over integer ranges. For example, the duration category $d = 1$ corresponds to ART initiation in the previous projection year. If we are at the middle of the current projection year, then all individuals in this duration category would have started ART between 0.5 and 1.5 years ago, and if we assume their ART initiation times are uniformly distributed, then their average current duration would be 1 year. This means that

we can take their $\psi_d(u | s)$ values directly from the third column in Table C2 without any need for interpolation or extrapolation.

Appendix D: Adjustments to confidence intervals to reflect model error

The method for sampling from the posterior distribution, as described in section 8.3, provides an estimate of the uncertainty in the model outputs that is due to the uncertainty in the parameters considered in the uncertainty analysis. It does not represent the uncertainty that may be due to other parameters (not included in the uncertainty analysis) and the uncertainty regarding the choice of model structure. To a large extent, these other sources of uncertainty are reflected in the ‘model error’ terms referred to when fitting the model (see sections 8.2.1 and 8.2.4). These ‘model errors’ represent the extent to which the model fails to fit the data, after subtracting random measurement error. Suppose that we wish to estimate a 95% confidence interval for a model output with value X , and the variation in X that we have estimated just by sampling from the posterior distribution is σ_p^2 . If we estimate that the variation in X due to model error is σ_M^2 , then the total variance can be estimated as

$$\sigma_T^2 \equiv \sigma_p^2 + \sigma_M^2,$$

and the 95% confidence interval around X can be calculated as $(X - 1.96\sigma_T, X + 1.96\sigma_T)$, on the assumption that errors are approximately normally distributed. This confidence interval represents the uncertainty around X after taking into account the lack of model fit to previous data. In practice, the estimation of σ_M^2 is complex, for two reasons. Firstly, the model error variances estimated in sections 8.2.1 and 8.2.4 are defined on the logit and log scales respectively, and it is necessary to calculate the model errors on the un-transformed scales. Secondly, the model variances estimated in sections 8.2.1 and 8.2.4 are defined for measurements specific to a particular sex and 5-year age group, but the model outputs that we are interested in are typically based on aggregating results from several 5-year age groups, or combining estimates for males and females. The methods used to deal with these complexities are described in sections D.1 and D.2 for measurements of HIV prevalence and measurements of mortality respectively. Finally, section D.3 explains how we derive estimates of model error for HIV incidence measurements.

D.1 Model error for HIV prevalence measurements

Suppose that we wish to estimate the variance of the model error term for prevalence measure H , which is based on aggregating HIV infections across k 5-year age categories (for now suppose that we are considering a single sex). The HIV prevalence can be expressed as

$$H = \frac{\sum_{i=1}^k N_i H_i}{\sum_{i=1}^k N_i},$$

where N_i is the number of individuals in age group i and H_i is the HIV prevalence in age group i . If we define $p_i = N_i / \sum_j N_j$ then

$$H = \sum_{i=1}^k p_i H_i .$$

If we use the notation $\text{Var}_M[X]$ to represent the variance in X due to model error (equivalent to σ_M^2), then

$$\text{Var}_M[H] = \sum_{i=1}^k \sum_{j=1}^k p_i p_j \text{Corr}_M(H_i, H_j) \sqrt{\text{Var}_M[H_i] \text{Var}_M[H_j]}, \quad (\text{D1})$$

where $\text{Corr}_M(H_i, H_j)$ is the correlation between the model errors in H_i and H_j . If σ_m^2 is the variance of the model error term on the logit scale (as defined in section 8.2.1), then using the delta method we can approximate the variance on the un-transformed scale as

$$\text{Var}_M[H_i] \approx \sigma_m^2 (H_i (1 - H_i))^2 . \quad (\text{D2})$$

The correlation matrix is close to the identity matrix. When examining the model error terms with respect to the 1991-2011 antenatal survey data, it was found that the average value of $\text{Corr}_M(H_i, H_{i+1})$ was 0.24, but for $|i - j| > 1$ the values of $\text{Corr}_M(H_i, H_j)$ were highly variable, with none of the correlation estimates being significantly different from zero. We approximate the variance on the assumption that $\text{Corr}_M(H_i, H_j) = 0$ for $|i - j| > 1$ and $\text{Corr}_M(H_i, H_j) = 0.24$ for $|i - j| = 1$. Equation (D1) then simplifies to

$$\text{Var}_M[H] = \sum_{i=1}^k p_i^2 \text{Var}_M[H_i] + 2 \sum_{i=1}^{k-1} 0.24 p_i p_{i+1} \sqrt{\text{Var}_M[H_i] \text{Var}_M[H_{i+1}]} . \quad (\text{D3})$$

Now suppose that all k age groups are equally sized and the prevalence in all k age groups is the same (i.e. $p_i = 1/k$ and $H_i = H$ for all i). Then equation (D3) simplifies to

$$\text{Var}_M[H] = \left(\frac{1}{k}\right)^2 \sum_{i=1}^k \text{Var}_M[H_i] + 2 \left(\frac{1}{k}\right)^2 \sum_{i=1}^{k-1} 0.24 \sqrt{\text{Var}_M[H_i] \text{Var}_M[H_{i+1}]} \quad (\text{D4})$$

and after substituting equation (D2) into (D4) we obtain

$$\text{Var}_M[H] \approx \left(\frac{1}{k}\right)^2 (k + 2 \times 0.24(k - 1)) \sigma_m^2 (H(1 - H))^2 . \quad (\text{D5})$$

This variance approximation is substantially easier to calculate than the expression in (D3), as it does not require estimates of p_i and H_i . Although it is not realistic to assume homogeneity of age groups, the approximation serves reasonably well for the purpose of variance estimation. For example, when estimating the HIV prevalence in females aged 15-49 in 2008, the exact formula in equation (D3) yields a standard error of 0.0130, while the approximation

in equation (D5) yields a standard error of 0.0126. We therefore use equation (D5) for the purpose of estimating the variance of the model error in respect of HIV prevalence measures.

In the case of prevalence measures that combine estimates for males and females, a similar logic applies. We assume that there is no correlation between the model errors for males and females, based on the model fits to the 2005 and 2008 HSRC survey results (correlation between male and female errors = -0.12). Then if the prevalence measure is based on aggregating k age groups, the variance of the model error term is

$$\begin{aligned}\text{Var}_M[H] &\approx \left(\frac{1}{2k}\right)^2 (2k + 4 \times 0.24(k-1))\sigma_m^2 (H(1-H))^2 \\ &= \frac{1}{2} \left(\frac{1}{k}\right)^2 (k + 2 \times 0.24(k-1))\sigma_m^2 (H(1-H))^2\end{aligned}$$

D.2 Model error for mortality estimates

Suppose that we wish to estimate the variance of the model error term for AIDS mortality measure A , which is based on aggregating AIDS deaths across k 5-year age categories (for now suppose that we are considering a single sex), i.e.

$$A = \sum_{i=1}^k A_i,$$

where A_i is the number of AIDS deaths in 5-year age group i . The variance of the model error is

$$\text{Var}_D[A] = \sum_{i=1}^k \sum_{j=1}^k \text{Corr}_D(A_i, A_j) \sqrt{\text{Var}_D[A_i] \text{Var}_D[A_j]}. \quad (\text{D6})$$

Suppose that in age group i , the total number of deaths (AIDS and non-AIDS causes combined) is B_i . In section 8.2.4, the variance of the model error term (σ_d^2) has been calculated in respect of total deaths on the log scale. Using the delta method, the variance of the model error for total deaths, on the un-transformed scale, is approximately

$$\text{Var}_{D^*}[B_i] \approx \sigma_d^2 B_i^2.$$

If it assumed that the variance of the non-AIDS deaths and AIDS deaths are independent of one another, then a reasonable approximation to the variance of the model error associated with A_i is

$$\text{Var}_D[A_i] \approx \sigma_d^2 B_i^2 \frac{A_i}{B_i} = \sigma_d^2 A_i B_i. \quad (\text{D7})$$

The correlation matrix is again close to the identity matrix. When examining the model error terms with respect to the 1997-2010 recorded death data, it was found that the average value

of $\text{Corr}_{D^*}(B_i, B_{i+1})$ was 0.53, but for $|i - j| > 1$ values of $\text{Corr}_{D^*}(B_i, B_j)$ were generally close to zero. If we assume that $\text{Corr}_D(A_i, A_j) = \text{Corr}_{D^*}(B_i, B_j)$, then we can approximate $\text{Corr}_D(A_i, A_j) = 0.53$ for $|i - j| = 1$ and $\text{Corr}_D(A_i, A_j) = 0$ for $|i - j| > 1$. Substituting these approximations and the formula in (D7) into equation (D6) yields

$$\text{Var}_D[A] \approx \sigma_d^2 \left(\sum_{i=1}^k A_i B_i + 2 \sum_{i=1}^{k-1} 0.53 \sqrt{A_i B_i A_{i+1} B_{i+1}} \right). \quad (\text{D8})$$

Now suppose that the numbers of AIDS deaths and total deaths are the same in all age groups (i.e. $A_i = A/k$ and $B_i = B/k$ for all i). If this is the case, equation (D8) simplifies to

$$\text{Var}_D[A] \approx \left(\frac{1}{k} \right)^2 (k + 2 \times 0.53(k - 1)) \sigma_d^2 AB. \quad (\text{D9})$$

Again, this approximation serves reasonably well even when the numbers of deaths are not the same across all age groups. For example, when estimating total AIDS deaths in males aged 15 and older in 2012, the formula in equation (D8) yields a standard error estimate of 4110, while the more approximate equation (D9) yields a standard error estimate of 3563.

There appears to be only weak correlation between the model mortality errors estimated for males and females (correlation coefficient = 0.12 when considering the male and female errors relative to the recorded death data over the 1997-2010 period). When considering AIDS death outputs that aggregate estimates for males and females, we ignore this correlation and modify equation (D9) as follows:

$$\text{Var}_D[A] \approx \frac{1}{2} \left(\frac{1}{k} \right)^2 (k + 2 \times 0.53(k - 1)) \sigma_d^2 AB.$$

D.3 Model error for HIV incidence estimates

Calculation of model errors in respect of HIV incidence estimates is complex because we do not have direct empirical measurements against which we can compare our model estimates. However, it is possible to use the model error variance estimates derived in sections D.1 and D.2 to obtain approximate estimates of the model error variance in respect of HIV incidence. Firstly, suppose we wish to estimate HIV incidence rate $C(t)$ in year t . The number of new infections in year t is equal to the difference between the total infections at the start of year t and the end of year t , plus the number of AIDS deaths in year t (to be technically correct, we should include non-AIDS deaths in HIV-positive individuals and adjust for migration and ageing, but these adjustments make little difference over 1-year intervals). The HIV incidence rate in year t is then the total number of new infections divided by the number of HIV-negative individuals at the start of the year, i.e.

$$C(t) \approx \frac{H(t)N(t) - H(t-1)N(t-1) + A(t)}{N(t-1)(1 - H(t-1))}, \quad (\text{D10})$$

where $H(t)$ is the HIV prevalence at time t , $A(t)$ is the number of AIDS deaths in year t and $N(t)$ is the number of individuals alive at time t . For the purpose of estimating the variance associated with the model error, we can use the following approximation:

$$\begin{aligned} \text{Var}_I[C(t)] &\approx \text{Var}_I[H(t) - H(t-1) + A(t)/N(t-1)] \\ &\approx \text{Var}_M[H(t)] + \text{Var}_M[H(t-1)] + \text{Var}_D[A(t)]/N(t-1)^2 \\ &\quad - 2\text{Corr}_M(H(t), H(t-1))\sqrt{\text{Var}_M[H(t)] \text{Var}_M[H(t-1)]} \end{aligned} \quad (\text{D11})$$

if it is assumed that the model errors in the HIV prevalence and AIDS mortality estimates are independent of one another. Although it may be realistic to allow for some positive correlation between the model errors in respect of $H(t-1)$ and $A(t)$, this would imply a reduction in the total variance (since we would be deducting a positive covariance term), so we are being conservative by not making any adjustment (i.e. erring on the side of overstating the uncertainty). Although this approximation relies on the exclusion of the $(1 - H(t))$ factor from the denominator in equation (D10), which would bias the incidence estimate, this makes little difference to the calculation of the variance. Based on comparing model errors in estimates of antenatal HIV prevalence over the 1991-2011 period, we estimate the average value of the $\text{Corr}_M(H(t), H(t-1))$ parameter to be 0.72, but with a significant trend towards increasing correlation over time. The following logistic formula was fitted to the data in order to obtain a time trend in the correlation parameter:

$$\text{Corr}_M(H(t+1), H(t)) = \frac{1}{1 - 2 \times (1 - \exp(0.594 + 0.166t))^{-1}}.$$

where t is measured in years after 1990. The remaining variables in equation (D11) are estimated from the approximations in equations (D5) and (D9).