Thembisa version 2.4:
A model for evaluating the impact of HIV/AIDS in South Africa

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Note to readers

This document provides a technical description of Thembisa version 2.4. It outlines the model structure, explains the sources on which the model assumptions are based, and describes the method used to calibrate the model to HIV prevalence data. The primary purpose of this document is to provide additional information on the C++ version of Thembisa 2.4 described in our recent paper "Prospects for HIV control in South Africa: a model-based analysis" (Global Health Action, 2016, 9: 30314).

Certain of the parameters discussed in this document relate only to the analysis of future sources of uncertainty in HIV incidence trends, as summarized in Table 1 of the journal article. The sections of the document relating to these parameters are formatted in green (as shown here). Readers who are interested mainly in understanding the modelling of HIV up to 2015 can skip these sections. This highlighted text also appears in the supplementary material of the journal article, but we have integrated it into this model description in the interests of completeness. One point to note is that pre-exposure prophylaxis (PrEP) for sex workers was announced in March 2016, after our journal article had been submitted for publication. Section 1.3.8.4 of this document describes the uncertainty that existed prior to this date, around the timing of PrEP for sex workers. Similarly, universal ART eligibility was announced by the South African Department of Health in May 2016, after the journal article was accepted for publication. Section 1.2.3 discusses the uncertainty that existed prior to this date, regarding the likely timing of the introduction of universal ART.

Readers should be aware that the demographic parameters in Thembisa version 2.4 are out-of-date and are expected to be revised in the near future.

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1. Model description

1.1 Model of sexual behaviour

The population aged 10 and older 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 and/or commercial sex, 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 or not they are sex workers, and men in the high risk group are assumed to have contact with sex workers. 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 contacts 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 1.1 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 assumed initial proportions of men and women in the high risk group have been set at 35% and 25% respectively, based on studies that have estimated proportions of adults ever engaging in concurrent partnerships [1-3].

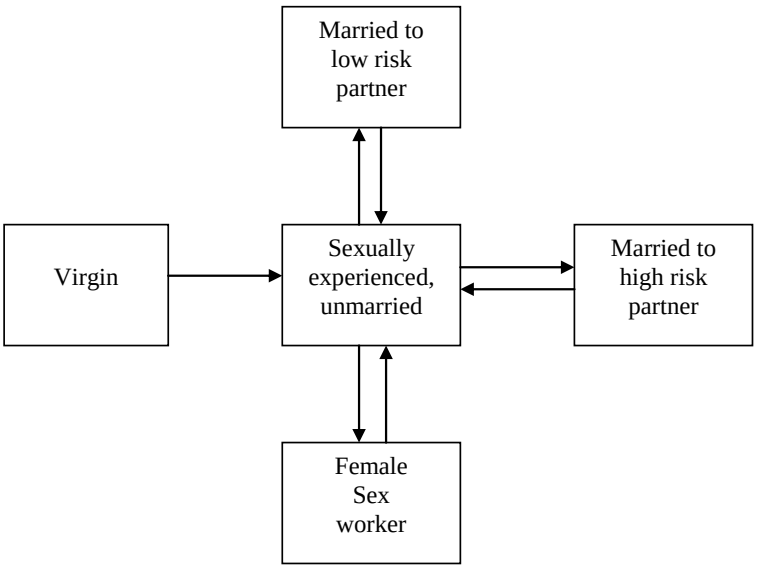

Figure 1.1: Transitions between relationship states
Transitions into and out of sex worker state are relevant only to high risk females.

Table 1.1 summarizes the major sexual behaviour parameters. These parameters are explained in more detail in subsequent sections.

Table 1.1: Sexual behaviour assumptions

Parameter	Men*	Women	Reference
Initial % of population in high risk group	35%	25%	[1-3]
Median age at sexual debut: high risk	17.5	16.5	Calibrated
Weibull shape parameter for time to sexual debut	3.5	4	
Relative rate of short-term partnership formation in married high risk adults (compared to unmarried high risk)	0.33	0.14	Calibrated (see [4])
Mean age difference between partners in short-term relationships	-	3	[5-9]
Standard deviation of age difference in short-term relationships	-	3	
Mean age difference between partners in long-term relationships	-	6	[10]
Standard deviation of age difference in long-term relationships	-	5	
Assortativeness of sexual mixing	-	0.47	Calibrated, [4]

* Male parameters are determined from female parameters in those cases where male parameters are not shown.

1.1.1 Age at sexual debut

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 (Table 1.1). 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 [11-13]. These parameters were chosen to yield estimates of the proportion sexually experienced at each age roughly consistent with the age-specific data from three national surveys [7, 14, 15], as demonstrated in Figure 1.2.

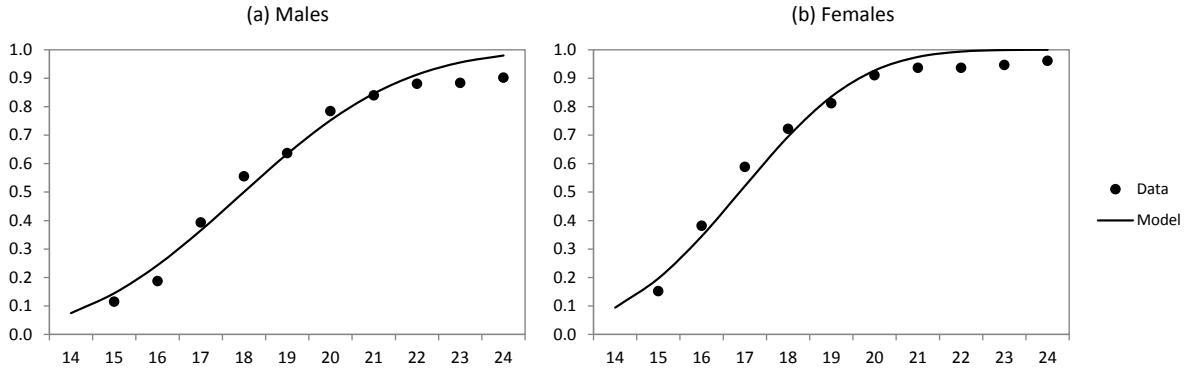

Figure 1.2: Proportion of youth who are sexually experienced, by age and sex
Data in panel (b) have been adjusted to reflect probable under-reporting of sexual experience by young women (assuming that the odds ratio relating true sexual experience to reported average sexual experience is 2).

Rates of sexual debut are assumed to have remained constant up to 2012, given inconsistent evidence of trends from different studies [16-19]. However, we consider possible changes to rates of sexual debut after 2012 in the uncertainty analysis. It is possible that interventions and behaviour change communication programmes may lead to later sexual debut, as has been seen in Uganda, where 27-36% reductions in rates of youth sexual experience were reported [20]. A cash transfer intervention in Malawi was also associated with a 36%

reduction in female rates of sexual debut, although this was not statistically significant [21]. A similar trial in Kenya, which provided support to cover adolescent school costs, also found a 43% reduction in sexual debut that was nearly statistically significant [22]. However, it is also possible that rates of sexual debut may be increasing, in line with the recent HSRC survey results, which found that the proportion of young men who reported sexual debut prior to age 15 increased by 48% between 2008 and 2012 [16]. In the period after 2012, we apply an adjustment factor to the rates of sexual debut that applied in 2011/12, to represent the effect of possible changes in rates of sexual debut. To represent the uncertainty around this adjustment factor, we assign a gamma prior distribution with a mean of 1 and a standard deviation of 0.2. The 2.5 and 97.5 percentiles correspond to a 35% reduction and a 43% increase in sexual debut rates respectively, so that the lower limit corresponds to the reduction that we might optimistically expect if cash transfer interventions/awareness programmes were fully rolled out and were effective, and the upper bound corresponds to a scenario in which the recent HSRC survey results represent a true increase in sexual debut in recent years.

1.1.2 Rates at which non-marital partnerships are formed

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

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

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. The $c_{2,i,l}(20)$ value is 3.3 for women in the high risk group (i = 1) who are unmarried (l = 0), based on previous modelling of rates of partnership formation in South Africa [23]. The λ and α parameters are difficult to determine precisely, and we therefore specify prior distributions to represent the ranges of uncertainty around the mean and standard deviations of the gamma distribution, from which the λ and α parameters are calculated (see Table 1.2). These prior distributions are based on the reported rates of partnership formation in the 2009 National Communication Survey [24]. For unmarried individuals in the low risk group, the rate of non-marital partnership is assumed to be

$$c_{g,2,0}(x) = L_g c_{g,1,0}(x), \quad (2)$$

where L_g is the ratio of the rate of non-marital partnership formation in the low risk group to that in the high 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 (uniform on the interval [0, 1]) to represent the uncertainty regarding the L_g parameter (Table 1.2).

Table 1.2: Prior distributions for sexual behaviour parameters

Parameter	Symbol	Prior mean, std deviation	Prior distribution
Mean of non-marital age adjustment function	α/λ	35, 5	Gamma(49, 1.4)
Standard deviation of non-marital age adjustment function	$\alpha^{0.5}/\lambda$	13, 3	Gamma(18.8, 1.44)
Relative rate of partner acquisition in low risk men	L_1	0.50, 0.29	Uniform(0, 1)
Relative rate of partner acquisition in low risk women	L_2	0.50, 0.29	Uniform(0, 1)
Reduction in unprotected sex after HIV diagnosis	δ_0	0.68, 0.15	Beta(5.90, 2.77)

For married individuals in the high risk group, of sex *g*, the rate of non-marital partnership formation is assumed to be

$$c_{g,1,1}(x) = R_g c_{g,1,0}(x), \quad (3)$$

where R_g is the ratio of the rate of non-marital partnership formation in married high risk individuals to that in unmarried high risk individuals. Values of R_g have been set to 0.33 for males and 0.14 for females (Table 1.1), based on values previously fitted using the STI-HIV Interaction model [4]. No non-marital partnership formation is modelled in married low risk individuals, as the low risk group would (by definition) not engage in concurrent partnerships.

Finally, male rates of non-marital relationship formation are calculated to be consistent with the assumed rates at which females form new non-marital partnerships. Further mathematical details are provided elsewhere [25].

1.1.3 Marriage and divorce

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 [23], 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. Rates of divorce are estimated from published divorce statistics in 2004 [26], applying a multiple of 2 to the crude rates to reflect known biases in divorce statistics [27]. Age-specific rates of marriage and divorce are shown in Table 1.3.

Although rates of marriage in South Africa have been steadily declining over the last few decades [28-31], the model assumes that age-specific marriage rates have been constant up to 2011/12. A number of factors have been suggested as reasons for the low and declining rates of marriage in South Africa, including the rising cost of *lobolo* (bride wealth), increasing employment opportunities for women, and the historic effects of apartheid legislation, which prevented African couples from settling permanently in 'white' urban areas [28, 29]. It is possible that interventions might reverse the downward trend in marriage rates, for example, increasing access to finance for men who cannot afford *lobolo*, increasing employment opportunities in rural communities (which would lead to less labour migration) and promoting marriage through behaviour change communication programmes. However, there have been no studies to evaluate the effect of such interventions. In the light of this uncertainty, we adopt the same approach as used to model uncertainty regarding changes in

sexual debut: in the period after 2012, we apply an adjustment factor to the rates of marriage that applied in 2011/12, and to represent the uncertainty around this adjustment factor, we assign a gamma prior distribution with a mean of 1 and a standard deviation of 0.2.

Table 1.3: Age-specific behavioural parameters

Age	Annual rate of marriage		Annual rate of divorce		Annual rate of sex worker contact in unmarried high risk males	Proportion of sex workers at each age
	Males	Females	Males	Females		
15	0.0000	0.0000	0.0000	0.0000	0.02	0.9%
16	0.0026	0.0073	0.0000	0.0033	0.07	1.4%
17	0.0043	0.0224	0.0009	0.0071	0.20	2.0%
18	0.0058	0.0354	0.0047	0.0104	0.50	2.6%
19	0.0080	0.0465	0.0081	0.0134	1.06	3.2%
20	0.0123	0.0562	0.0112	0.0161	2.02	3.7%
21	0.0197	0.0650	0.0139	0.0183	3.50	4.1%
22	0.0313	0.0730	0.0165	0.0201	5.62	4.5%
23	0.0475	0.0807	0.0188	0.0215	8.44	4.7%
24	0.0674	0.0879	0.0211	0.0226	12.01	4.8%
25	0.0890	0.0943	0.0230	0.0233	16.27	4.9%
26	0.1090	0.0993	0.0246	0.0237	21.14	4.9%
27	0.1235	0.1022	0.0257	0.0241	26.46	4.8%
28	0.1302	0.1025	0.0262	0.0244	32.05	4.7%
29	0.1309	0.1008	0.0262	0.0245	37.68	4.5%
30	0.1297	0.0980	0.0259	0.0246	43.14	4.2%
31	0.1290	0.0949	0.0255	0.0244	48.21	4.0%
32	0.1278	0.0918	0.0250	0.0239	52.72	3.7%
33	0.1268	0.0891	0.0245	0.0230	56.50	3.4%
34	0.1259	0.0868	0.0240	0.0219	59.46	3.2%
35	0.1241	0.0841	0.0233	0.0206	61.52	2.9%
36	0.1215	0.0811	0.0225	0.0193	62.67	2.6%
37	0.1187	0.0780	0.0217	0.0182	62.93	2.4%
38	0.1161	0.0749	0.0210	0.0177	62.36	2.1%
39	0.1135	0.0718	0.0204	0.0174	61.02	1.9%
40	0.1108	0.0686	0.0197	0.0172	59.02	1.7%
41	0.1079	0.0655	0.0190	0.0168	56.47	1.5%
42	0.1051	0.0626	0.0182	0.0163	53.48	1.3%
43	0.1027	0.0601	0.0175	0.0154	50.17	1.2%
44	0.1004	0.0578	0.0167	0.0144	46.64	1.0%
45	0.0982	0.0556	0.0160	0.0133	42.99	0.9%
46	0.0961	0.0535	0.0153	0.0123	39.31	0.8%
47	0.0941	0.0513	0.0145	0.0113	35.67	0.7%
48	0.0924	0.0491	0.0138	0.0105	32.14	0.6%
49	0.0908	0.0469	0.0131	0.0098	28.76	0.5%
50	0.0893	0.0448	0.0124	0.0091	25.57	0.4%
51	0.0879	0.0428	0.0117	0.0083	22.59	0.4%
52	0.0866	0.0408	0.0110	0.0077	19.85	0.3%
53	0.0853	0.0388	0.0102	0.0071	17.34	0.3%
54	0.0842	0.0369	0.0093	0.0065	15.06	0.2%
55	0.0831	0.0351	0.0085	0.0060	13.02	0.2%
56	0.0821	0.0333	0.0077	0.0055	11.20	0.2%
57	0.0812	0.0315	0.0070	0.0050	9.59	0.2%
58	0.0803	0.0297	0.0064	0.0045	8.18	0.1%
59	0.0794	0.0280	0.0058	0.0040	6.94	0.1%

Although the model allows for sexual activity at ages 60 and older, assumptions are not shown.

1.1.4 Commercial sex

Sexually experienced men in the high risk group are assumed to visit sex workers at annual rate $w_l(x)$, which depends on their current 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 married men (l = 1) [32] 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

$$\begin{aligned} w_l(x) &= K \frac{\lambda_1^{\alpha_1}(x-10)^{\alpha_1-1}\exp(-\lambda_1(x-10))}{\lambda_1^{\alpha_1}(21.5-10)^{\alpha_1-1}\exp(-\lambda_1(21.5-10))} 0.25^l \\ &= K \times \left(\frac{x-10}{11.5}\right)^{\alpha_1-1} \exp(-\lambda_1(x-21.5)) \times 0.25^l, \end{aligned} \quad (4)$$

where K is 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 [33].) 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, roughly consistent with observed client age distributions in the early stages of South Africa's HIV epidemic [34, 35]. Finally, the K parameter has been set to 3.5, which ensures that the total male demand for commercial sex is roughly consistent with the number of South African sex workers estimated in a recent national study [36], assuming that the average sex worker has 750 client contacts per annum [37-44]. (Some downward adjustment is made to the survey estimate to take into account differences in definitions of commercial sex.) The model estimates substantial age variation in the rate at which men visit sex workers, with the rate reaching as high as 63 contacts per annum in unmarried high risk males aged 37 (Table 1.3). Men in the low risk group are assumed to have no contact with sex workers.

Women are assumed to enter commercial sex only from the unmarried high risk group (Figure 1.1), with the rate of entry determined to be sufficient to meet the male demand for commercial sex. The rate of entry into commercial sex is also assumed to vary in relation to age, with the age-specific rates being determined in such a way that the age distribution of the sex worker population remains constant over time. This distribution is assumed to be of gamma form, with mean 29 years and standard deviation 9 years (Table 1.3), based on surveys of South African sex workers [5, 39, 41-48]. Women are assumed to retire from commercial sex at a rate of 0.33 per annum [39, 40, 42].

1.1.5 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) [49]. The ε parameter is difficult to determine from 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 [4].

1.1.6 Preferences regarding partner age

The symbol $f_{g,l}(y \mid x)$ 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 gamma distributions. For married women aged *x*, the *preferred* age distribution of the marital partners is assumed to have a mean of (*x* + 6), and a standard deviation of 5 years. This gamma distribution is adjusted to take into account relative numbers of available men at different ages. These assumptions yield marital partner age distributions consistent with those observed in the 1998 Demographic and Health Survey (DHS). Mathematically, the probability that a married woman aged *x* has a husband between the ages of *y* and *y* + 1 is

$$f_{2,1}(y \mid x) \equiv \int_{y}^{y+1} \frac{\left(\lambda_2(x)+\xi(x)\right)^{\alpha_2(x)}\left(t-\min(x)\right)^{\alpha_2(x)-1}}{\Gamma\left(\alpha_2(x)\right)\exp\left(\left(\lambda_2(x)+\xi(x)\right)\left(t-\min(x)\right)\right)}dt\,, \qquad (5)$$

where $\lambda_2(x)$ and $\alpha_2(x)$ are the parameters of the gamma distribution (calculated from the mean, variance and minimum age), $\xi(x)$ is the average rate of decline in the number of available men per year of increase in age (for women aged *x*), and 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). The $\xi(x)$ parameters are updated dynamically each year as the population pyramid changes.

For women who are aged *x* and in non-marital relationships, the age distribution of non-marital partners is assumed to have a mean of (*x* + 3), and a standard deviation of 3 years, consistent with partner age distributions reported by young women in various South African studies [5-9]. As for marital relationships, this distribution is adjusted to take into account the actual number of men available at each age. In sex worker-client contacts, clients and sex workers are assumed to have no age preferences.

Proportions of men who choose their partners from different ages ($f_{1,l}(y \mid x)$) 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 elsewhere [25].

Although the model assumes that age preferences in non-marital relationships have been stable over time, recent surveys suggest that age differences may have increased at young ages: the proportion of young women who report a partner age difference of 5 years or more has been estimated at 34-40% in recent surveys [15-17], in contrast to the level of 18.9% estimated in the model based on earlier data [5-9]. However, at the same time there have been behaviour change programmes to discourage young women from having relationships with older men. For example, the "Sugar daddies destroy lives" campaign was launched in

KwaZulu-Natal in 2012, and a study in this province has found evidence of significant reductions in partner age differences reported by young women [50]. Cluver *et al* [51] have also found that adolescent South African girls in households that were receiving child support grants (CSGs) were 71% less likely to report having older partners (>5 year age difference) than girls in households that are not receiving CSGs. A trial of a cash transfer intervention in Malawi has also shown that providing cash payments to young women reduces their likelihood of reporting a partner over the age of 25 by 79% [21]. This suggests that both the recent increases in access to the CSG (with the age of eligibility increasing from 16 to 18 in 2011) and the potential future introduction of economic empowerment/cash transfer programmes for young women could lead to reductions in average partner age differences.

To represent the uncertainty regarding changes in age-disparate relationships, we assign a gamma prior distribution to represent the range of possible future average partner age differences in short-term relationships, with this distribution having a mean of 3 years (the same as in the baseline scenario) and a standard deviation of 1 year. This allows for the possibility that mean partner age differences could either increase (in line with the trends observed in recent surveys) or decrease (in response to interventions). The standard deviation of the distribution of partner age differences is assumed to increase or decrease in proportion to the mean. The 2.5 and 97.5 percentiles of the distribution of mean partner ages are at 1.37 years and 5.25 years respectively. With a mean and standard deviation of 1.37 years, the probability of a more than 5 year age difference would be 2.6% (86% lower than the baseline, and thus consistent with the reductions that we might optimistically expect if cash transfer interventions were introduced and had effectiveness similar to the previously-cited studies). With a mean and standard deviation of 5.25 years, the probability of a more than 5 year age difference would be 38.6% (consistent with the levels of 34-40% reported in recent surveys).

1.1.7 Coital frequencies

The average number of sex acts per non-spousal relationship is assumed to be 18. This is consistent with an average coital frequency of 3 acts per month in non-spousal relationships [7, 9, 52, 53] and an average non-marital relationship duration of 6 months [23]. In marital 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 [23].

1.1.8 Condom usage

Rates of condom use are assumed to depend on age, sex, type of relationship and knowledge of HIV-positive status. Rates of condom usage are also assumed to change over time; 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 [54]. 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 (time is measured in years since 1985). 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 $\gamma_{2,l}(x,t)$:

$$\ln\left(\frac{\gamma_{2,l}(x,t)}{1-\gamma_{2,l}(x,t)}\right)=\ln\left(\frac{\gamma^*}{1-\gamma^*}\right)+\chi_l+\nu_l(x-20)+\varsigma_l(t) \qquad (6)$$

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;

$\exp(\varsigma_l(t))$ = the odds of using a condom in year *t*, relative to that in 1998, for relationship type *l*.

In the period up to 2011, the $\varsigma_l(t)$ function is a linear combination of a constant term and two cumulative Weibull distribution functions. The constant term represents the initial rate of condom usage, prior to the start of the HIV epidemic in South Africa, the first Weibull distribution corresponds to the increase in condom usage following the introduction of HIV communication programmes in the mid-1990s, and the second Weibull distribution represents the reversal in condom usage rates in recent years. Due to the uncertainty regarding condom usage trends after 2012 (discussed below), a different formula is used to model patterns of condom usage after 2012. In mathematical terms,

$$\varsigma_l(t)=\begin{cases}\kappa_l^1+\left(\kappa_l^2-\kappa_l^1\right)\left(1-0.5^{(t/M_l^1)^{Q_l}}\right)-\left(\kappa_l^2-\kappa_l^3\right)\left(1-0.5^{(t/M_l^2)^{2Q_l}}\right) & \text{if } t\le 26\\ \varsigma_l(26)(31-t)/5+\kappa_l^4(t-26)/5 & \text{if } 26<t\le 30\\ \kappa_l^4 & \text{if } t>30\end{cases} \qquad (7)$$

where *t* is time in years since 1985, and the other variables are defined as follows:

κ_l^1 represents the initial rate of condom use in relationship type *l*, in 1985 (relative to the baseline in 1998);

$\kappa_l^2-\kappa_l^1$ represents the increase in condom use in relationship type *l*, following initial HIV communication programmes;

$\kappa_l^2-\kappa_l^3$ represents the reduction in condom use in relationship type *l*, following reductions in condom promotion/risk compensation;

κ_l^4 represents the ultimate rate of condom use in relationship type *l*, after 2015;

M_l^1 = the median for the first Weibull distribution;

M_l^2 = the median for the second Weibull distribution;

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

The values assumed for these parameters, and the data sources on which they are based, are summarized in Table 1.4. Although several of the model parameters were initially calibrated to match proportions of women reporting condom use at last sex in national surveys, this was found to lead to implausible HIV incidence trends [4], and the calibrated parameters were therefore adjusted downward so that the modelled proportions of women using condoms were closer to the proportion of women who reported using condoms for contraceptive purposes.

Table 1.4: Condom usage assumptions in period up to 2012

Parameter	Symbol	Value	Source
'Baseline' condom usage	γ^*	0.104	[10], calibrated
OR for condom use in marital relationships (1998)	$\exp(\chi_1)$	0.46	[10]
OR for condom use in commercial sex (1998)	$\exp(\chi_2)$	6.0	[5, 45]
OR for condom use per year increase in age	$\exp(\nu_l)$	0.975†	[10, 55]
OR for condom use in 1985 (relative to 1998)			
Marital and non-marital relationships	$\exp(\kappa_1^1)$	0.07	[56]
Commercial sex	$\exp(\kappa_2^1)$	0.17	[35]
Maximum OR for condom use (relative to 1998)			
Non-marital relationships	$\exp(\kappa_0^2)$	4.6	[7, 8, 15], calibrated
Marital relationships	$\exp(\kappa_1^2)$	2.16	
Commercial sex	$\exp(\kappa_2^2)$	3.8	[48, 57], calibrated
OR for condom use after reversal of behaviour change (relative to 1998)			
Non-marital relationships	$\exp(\kappa_0^3)$	2.14	Set to square root of $\exp(\kappa_l^2)$
Marital relationships	$\exp(\kappa_1^3)$	1.47	
Commercial sex	$\exp(\kappa_2^3)$	3.8	No evidence of condom reduction
Shape parameter: speed of behaviour change			
Non-marital relationships	Q_0	3.6	Calibrated
Marital relationships	Q_1	3.24	Calibrated
Commercial sex	Q_2	3.8	Calibrated
Median time to reversal of behaviour change (in years since 1985)	M_l^2	26	Calibrated

† The same assumption applies for marital and non-marital relationships, but the parameter is set to 1 for sex worker-client interactions. OR = odds ratio.

The parameter M_l^1 is calculated as a function of the remaining parameters:

$$M_l^1 = 13\left\{\left(\ln\left[\kappa_l^3 + \left(\kappa_l^2 - \kappa_l^3\right)0.5^{(13/M_l^2)^{2Q_l}}\right] - \ln\left(\kappa_l^2 - \kappa_l^1\right)\right) \Big/ \ln(0.5)\right\}^{-1/Q_l} \quad (8)$$

The resulting trends in women's condom use, by relationship type, are shown in Figure 1.3. To ensure that male and female assumptions are consistent, the probability that an HIV-negative man uses a condom in a marital or non-marital relationship is calculated as

$$\gamma_{1,l}(x,t) = \sum_{y} f_{1,l}(y \mid x)\gamma_{2,l}(y,t), \qquad (9)$$

where $f_{1,l}(y \mid x)$ 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.

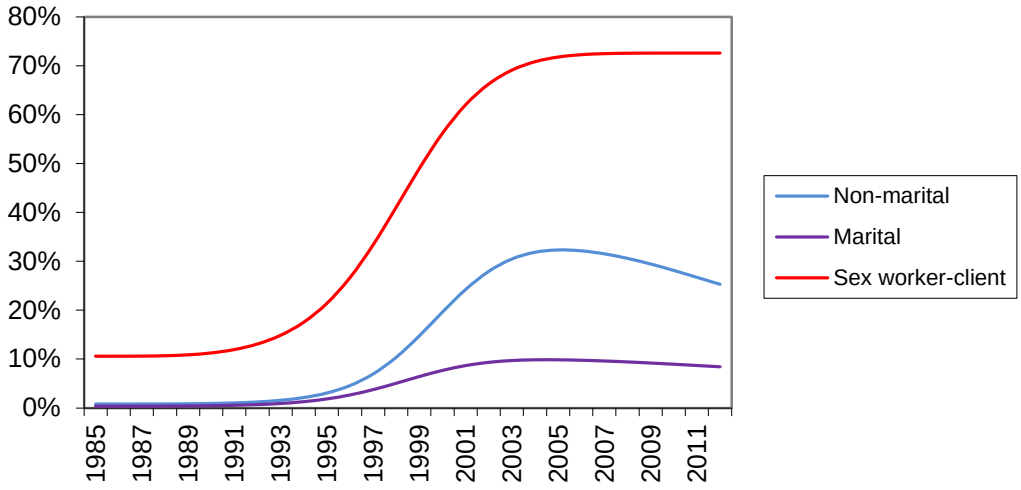

Figure 1.3: Trends in proportion of sex acts that are protected among 20-year old HIV-negative women having sex with HIV-negative or undiagnosed positive partners
Rates are adjusted to take into account knowledge of HIV status and ART (see sections 1.1.10 and 1.1.11).

There is much uncertainty regarding potential future trends in condom usage. In a worst case scenario, condom usage may continue to decline in future. There have already been significant cuts in funding for HIV communication programmes [54], and future budget constraints could lead to further reductions in funding for these programmes. Even if there are no reductions in funding, it is possible that rates of condom usage may decline due to reduced fear of HIV in the era of highly effective and easily accessible treatment – so-called 'risk compensation' or 'treatment optimism'. Studies from other African countries have documented increases in risk behaviour in the general population (or HIV-negative population) associated with ART optimism and ART rollout [58-60], and it is thus possible that similar changes in behaviour may be occurring in South Africa.

On the other hand, there are several ways in which levels of condom usage could be increased. Previous South African studies have shown that levels of condom usage are strongly associated with levels of exposure to HIV communication programmes [17, 61] as well as lifeskills programmes in schools [62], and renewed emphasis on condoms through HIV communication programmes and lifeskills programmes could therefore lead to greater condom use. In the most recent national HIV communication survey [17], the median level of reported condom use at last sex was 50%, while the level of condom use in the 10% of respondents with the highest level of exposure to HIV communication programmes was 63%; this suggests that the odds of condom usage could be increased by a factor of 1.7 if levels of exposure to HIV communication programmes were increased to those currently achieved in the top decile.

In addition to the need for general HIV communication programmes, there may also be a need for more targeted approaches to promote condom usage in specific high risk groups. For example, a recent meta-analysis estimated that community empowerment initiatives in sex workers increase the odds of condom usage among sex workers and their clients by a factor of 3.27 (95% CI: 2.32-4.62) [63]. Although 94% of South African female sex workers reported using condoms with their last client in a recent national survey [48], non-use of condoms is significantly associated with being drunk (OR 2.6, 95% CI: 1.7-3.8). This suggests that substance abuse programmes for sex workers may be particularly important in increasing their consistency of condom use. Mathematical modelling also suggests that decriminalization of commercial sex could lead to substantial reductions in HIV incidence through its effect on sex workers' ability to negotiate consistent condom use with their clients [64].

To represent the uncertainty regarding future trends in condom usage, we assign gamma prior distributions to the $\exp\left(\kappa_l^4\right)$ parameter. For each relationship type, the gamma mean is set to the $\exp\left(\zeta_l\,(26)\right)$ parameter, and the standard deviation is set in such a way that the 2.5 percentile of the gamma distribution corresponds to 1. This means that on average condom usage is projected to remain stable after 2011, but in the most pessimistic scenarios, condom usage would be unlikely to fall below the levels in 1998 (when HIV communication programmes and condom distribution were still at relatively low levels). The 97.5 percentiles of the distributions for marital and non-marital relationships are 2.79 and 6.47 respectively (1.57 and 2.06 times the corresponding baseline values, and thus roughly consistent with the odds ratio of 1.7 that might optimistically be assumed if high levels of exposure to HIV communication programmes were achieved). For sex worker condom usage, the 97.5 percentile of the odds ratio is 8.44, which is 2.2 times the baseline value, and thus roughly consistent with the value that would be expected if it were optimistically assumed that community empowerment efforts were rolled out and reached 50% of sex workers (0.5 + 0.5 × 3.27 = 2.14).

1.1.9 Effect of CD4 count on level of sexual activity

The model assumes that coital frequencies in HIV-positive individuals decline as they enter more advanced stages of HIV disease. It is assumed that the frequency of sex in HIV-positive adults with CD4 counts ≥500/μl is the same as would be expected in HIV-negative adults with the same characteristics. The frequency of sex is assumed to be reduced by 8% in individuals with CD4 counts of 350-499/μl, by 24% in individuals with CD4 counts of 200-349/μl, and by 45% in individuals with CD4 counts of <200/μl (relative to individuals with CD4 counts of ≥500/μl in all cases). These assumptions are based on meta-analyses of various studies that have assessed either differences in sexual behaviour or differences in the incidence of pregnancy between CD4 stages [65-71]; results of the individual studies are shown in Figure 1.4.

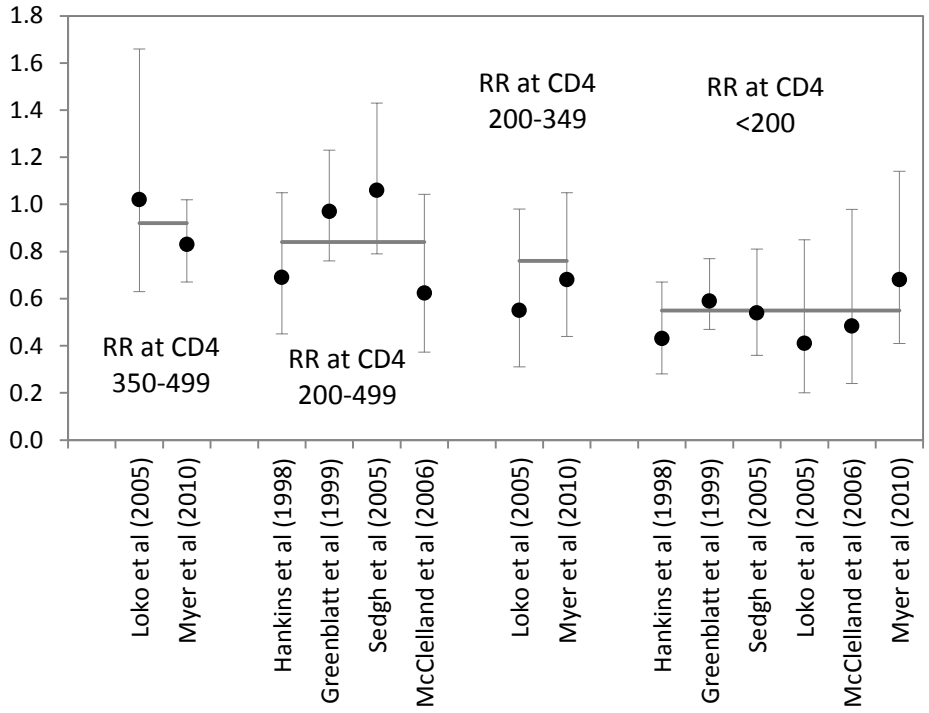

Figure 1.4: Comparison of model assumptions about relative frequency of sex at different CD4 levels and empirical estimates

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 category 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, it is assumed 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 [72], 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.

1.1.10 Effect of knowledge of HIV status on sexual behaviour

Most evidence suggests that HIV testing does not significantly affect sexual behaviour or HIV incidence in individuals who receive negative test results [73-76], and the model therefore assumes no change in behaviour following an HIV-negative test result. However,

studies from developing countries show that HIV-positive diagnoses usually lead to significant declines in unprotected sex, with the reductions varying between 10% and 95% (average reduction 68%) [75, 77-79]. Given the range of variation across studies, we have specified a prior distribution to represent the uncertainty regarding the percentage reduction in unprotected sex after HIV diagnosis, with a mean of 68% and standard deviation of 15% (see Table 1.2).

It is possible that certain interventions could lead to greater reductions in unprotected sex following diagnosis. For example, Cornman *et al* [80] found that in a South African healthcare setting, HIV-positive patients who were randomized to receive special risk reduction counselling reported roughly 90% less unprotected sex with partners of negative or unknown HIV status compared to HIV-positive patients who did not receive the counselling. The same authors found that when repeating the intervention in a larger trial, the reduction in unprotected sex with partners of negative/unknown status was slightly more modest, 59% after 18 months [81]. However, in another South African trial involving a similar intervention, there was no reduction in unprotected sex in women who received special counselling over a 3-month period [82]. In other African settings, facilitated disclosure of HIV status to sexual partners has been shown to significantly increase levels of disclosure [83], which is likely to also be important in reducing levels of unprotected sex in HIV-diagnosed individuals. Given the intensive nature of these counselling interventions, it is unlikely that they would reach all HIV-diagnosed individuals.

To model the effect of HIV diagnosis on sexual risk behaviour, we define $\delta(t)$ to be the reduction in unprotected sex in HIV-diagnosed individuals, relative to undiagnosed individuals, in year t. The symbol δ_0 represents the reduction associated with current South African programmes and policies, while δ_1 represents the additional reduction that might be expected in future if new counselling and facilitated disclosure interventions were introduced. In mathematical terms,

$$\delta(t) = \begin{cases} \delta_0 & \text{if } t < 2015 \\ 1-(1-\delta_0)(1-\delta_1 I_0(t) G) & \text{if } t \geq 2015 \end{cases} \quad (10)$$

where $I_0(t)$ is a function indicating whether the new interventions have been introduced by year t (1 if the interventions have been introduced, 0 otherwise), and G is the fraction of HIV-diagnosed individuals who are covered by the intervention once it is introduced. Due to the uncertainty regarding these new interventions, we assign three separate prior distributions: one to represent the uncertainty regarding the timing of the new interventions, one to represent the uncertainty regarding the coverage (G) and one to represent the uncertainty regarding the δ_1 parameter. The prior for the time to the introduction of the new interventions (in years after 2015) is a Weibull distribution with a median of 10 years and a shape parameter of 0.55. The prior for the coverage parameter is uniform on the interval (0, 1), reflecting the uncertainty regarding the level of coverage that would be possible. Finally, the prior distribution on the δ_1 parameter is a beta distribution with a mean of 0.5 and a standard deviation of 0.22; the mean corresponds to the average of the percentage reductions in unprotected sex in the three previously-described South African trials [80-82], and the standard deviation was chosen so that the upper 97.5 percentile would correspond to the 90% reduction observed in the most promising of these three trials.

1.1.11 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 [84], 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.

Coital frequencies after ART initiation are assumed to depend only on current CD4 count, as described in section 1.1.9, with no effect of ART after controlling for current CD4 count. This is because most African studies show that after controlling for measures of disease severity, ART does not significantly affect frequency of sexual activity [85-87].

The assumed proportion of sex acts that are protected in year *t*, in an HIV-treated adult of age *x* and sex *g*, in relationship type *l*, is

$$1-\left(1-\gamma_{g,l}(x,t)\right)\left(1-\delta(t)\right)\left(1-h\right), \qquad (11)$$

where $\gamma_{g,l}(x,t)$ is the corresponding rate of condom use in HIV-negative individuals (discussed in section 1.1.8), $\delta(t)$ represents the reduction in unprotected sex following diagnosis (discussed in section 1.1.10), and h represents the additional reduction in unprotected sex following ART initiation. The h parameter has been set to 0.32, based on a recent meta-analysis [88], which found that in high-quality studies receipt of ART was associated with a significant reduction in unprotected sex (OR 0.68, 95% CI: 0.58-0.79). Low-quality studies were excluded, as these tend not to control for time since diagnosis and thus tend to conflate the effects of HIV diagnosis and ART on levels of condom usage.

1.2 Model of HIV disease progression and mortality in adults

HIV-infected adults are assumed to progress through five stages of HIV infection in the absence of ART. An initial acute infection phase, lasting for three months, is followed by four stages of increasing immunosuppression (CD4 count ≥500 cells/μl, 350-499 cells/μl, 200-349 cells/μl and <200 cells/μl). Individuals are further classified according to whether they have been diagnosed HIV-positive, with rates of diagnosis changing over time and varying in relation to age, sex and CD4 stage. Adults who have been diagnosed HIV-positive are assumed to start ART at a rate that changes over time, as ART rollout expands and treatment eligibility criteria change [89]. Once individuals have started ART, they are stratified by their time since ART initiation and baseline CD4 category. The model of HIV disease progression, diagnosis and ART initiation is illustrated in Figure 1.5.

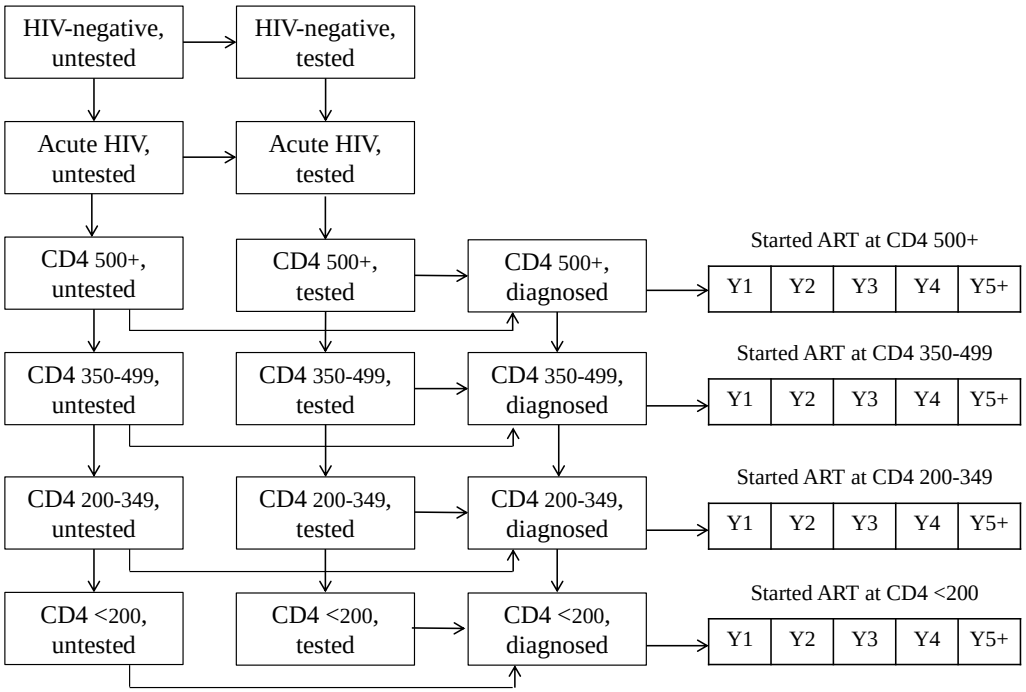

Figure 1.5: Multi-state model of survival in HIV-positive adults

1.2.1 HIV disease progression and mortality prior to ART initiation

In untreated individuals, 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 = males, 2 = females) who are aged *x*. This is calculated as

$$\lambda_{g,s}(x) = \lambda_s \varpi^{g-1}(1+k)^{(x-30)/10}, \tag{12}$$

where λ_s is the rate that applies in men aged 30, ϖ is the factor by which HIV disease progression is adjusted in women, and *k* is the proportional increase in the rate of disease progression per 10-year increase in age. Similarly, we define the symbol $\mu_{g,s}(x)$ to be the annual HIV-related mortality rate in HIV state *s* in untreated individuals of sex *g* who are aged *x*. This is calculated as

$$\mu_{g,s}(x) = \mu_s \varpi^{g-1}(1+k)^{(x-30)/10}, \tag{13}$$

where μ_s is the HIV mortality rate that applies in men aged 30. The adjustment factors for the effects of age and sex on HIV disease progression are thus the same as the adjustment factors for the corresponding effects on HIV-related mortality. As HIV-positive women tend to have lower viral loads [90-92] and lower rates of CD4 decline [93] than HIV-positive men, and as

studies suggest a lower mortality rate in HIV-positive women than in HIV-positive men in the pre-ART era [92, 94-96], the ϖ parameter has been set to 0.9, consistent with age-adjusted hazard ratios of 0.89 in the CASCADE collaboration [97] and 0.91 in the Alpha network [94]. (Although it could be argued that these studies fail to exclude non-HIV mortality and thus overstate the extent of sex differences, CASCADE data actually suggest an even more substantial difference when non-HIV mortality is excluded [96].)

Evidence suggests that increasing age is associated with both increasing rates of CD4 decline [98, 99] and increasing mortality in HIV-positive adults [100-103]. The *k* parameter has been set to 0.27, based on calibration of the model to age-specific mortality data in South Africa [25]. The same calibration exercise was used in setting the λ_s and μ_s parameters, which are shown in Table 1.5. Assumptions about the relative lengths of time spent in different CD4 stages were also determined by calibrating the model to cross-sectional surveys of CD4 distributions in HIV-positive adults [104-110], and assumptions about relative rates of mortality by CD4 stage were based on the assumption of negligible HIV-specific mortality at CD4 counts >350 cells/μl and a mortality hazard ratio of 0.13 for individuals with CD4 counts of 200-349, when compared to individuals with CD4 counts <200 cells/μl [89].

Table 1.5: Parameters by HIV disease stage

Parameter	Acute HIV	CD4 range 500+	350-499	200-349	<200	Source
Average time (in years) to next stage, in absence of ART* ($1/\lambda_s$)	0.25	3.16	2.13	3.20	-	Calibrated
Annual HIV mortality rate, in absence of ART* (μ_s)	0.00	0.00	0.00	0.035	0.272	Calibrated
Annual incidence of OIs, in absence of ART						[111, 112]
All WHO stage III and IV OIs	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	
Relative infectiousness if untreated (I_s)	10	1	1	2	7	[113-115]
Annual male HIV mortality after ART initiation, by baseline CD4‡						
1st 6 months of ART	-	0.0002	0.0016	0.0146	0.2554	[116]
Months 7-18	-	0.0009	0.0050	0.0132	0.0613	
Months 19-30	-	0.0027	0.0085	0.0116	0.0306	
Months 31-42	-	0.0042	0.0076	0.0076	0.0202	
Months 43+	-	0.0049	0.0063	0.0063	0.0166	
Annual female HIV mortality after ART initiation, by baseline CD4‡						
1st 6 months of ART	-	0.0001	0.0016	0.0159	0.2072	[116]
Months 7-18	-	0.0008	0.0045	0.0101	0.0490	
Months 19-30	-	0.0020	0.0057	0.0057	0.0235	
Months 31-42	-	0.0027	0.0034	0.0034	0.0141	
Months 43+	-	0.0025	0.0025	0.0025	0.0103	

* Parameters are specified for 30-year old males, and age and sex adjustments are made in the process of calibrating the model to reported death data. ‡ Parameters are adjusted to take into account age effects and effects of increasing baseline CD4 counts over time. OI = opportunistic infection.

1.2.2 HIV testing and diagnosis

As shown in Figure 1.5, the population aged 10 and older is divided into three HIV testing history groups (never tested, previously tested negative and previously tested positive). Three

types of HIV testing are modelled: testing in antenatal clinics, testing of HIV patients with opportunistic infections (OIs), and testing for other reasons. The annual rate at which sexually-experienced individuals get tested is assumed to depend on their HIV stage (s), age (x), sex (g), HIV testing history (i) and the calendar year (t):

$$\tau_{g,i,s}(x,t) = b(t)A_g(x,t)r_i + \Omega_s d_i(t) + F_{g,s}(x,t)\nu_i(t) \quad (14)$$

where $b(t)$ is the base rate of HIV testing in year t, in individuals who do not have any HIV symptoms and are not pregnant; $A_g(x,t)$ is an adjustment factor to represent the effect of age and sex on the base rate of test uptake; r_i is an adjustment factor to represent the effect of testing history; Ω_s is the annual incidence of OIs in CD4 stage s; $d_i(t)$ is the fraction of OI patients who are tested for HIV in year t; $F_{g,s}(x,t)$ is the fertility rate in sexually experienced women aged x, in HIV stage s, during year t (set to zero for men); and $\nu_i(t)$ is the proportion of pregnant women who receive HIV testing in year t. The function used to represent the effect of age and sex on the uptake of HIV testing is

$$A_g(x,t) = B_g(t)\left(\frac{x}{25}\right)^{\alpha_g - 1}\exp\left(-\sigma_g\left(x-25\right)\right), \quad (15)$$

where $B_g(t)$ is a time-dependent sex adjustment factor, and α_g and σ_g are coefficients for the effect of age on the rate of HIV test uptake. The parameterization of the model is described in detail elsewhere [117]. Briefly, the model parameters have been estimated using a Bayesian procedure that incorporates three data sources: total numbers of HIV tests performed in the South African public and private health sectors (2002-2012), proportions of individuals testing for HIV who test positive, and proportions of adults who report previous HIV testing in three national surveys [7, 8, 16], stratified by age, sex and HIV status. The calibration procedure allows for potential bias in self-reporting of previous HIV testing. The prior distributions in the Bayesian analysis are based on observed patterns of HIV testing by age and sex [61, 118] and observed increases in rates of testing in previously-tested individuals [46, 119, 120]. The assumed incidence of OIs by HIV stage (Ω_s) is shown in Table 1.5, and the assumed proportions of OIs tested for HIV are shown in Table 1.6. Assumptions regarding fertility rates and the effect of HIV on fertility are described in section 1.5.2, and the assumed fractions of pregnant women tested for HIV are also shown in Table 1.6.

Table 1.6: Assumed proportions of patients tested for HIV and linked to ART

Year	Antenatal testing ($v_i(t)$)		Testing of OI patients ($d_i(t)$)		Linkage to ART in pregnancy ($l_2(s,t)$)	
	Rate	Sources	Rate	Sources	Rate	Sources
Pre-1999	0.0%		5%		0.0%	
1999-00	0.9%		5%		0.0%	
2000-01	2.9%		5%		1.9%	
2001-02	7.5%	[121]	5%		2.5%	
2002-03	15.6%	[122, 123]	5%		2.5%	
2003-04	31.3%		5%		3.6%	
2004-05	42.0%	[124]	8%	[125]	12.6%	
2005-06	54.5%	[126]	20%	[127]	22.6%	[128]‡
2006-07	72.2%	[129]	31%	[127]	29.1%	
2007-08	84.0%	[130]	40%	[127, 131]	35.5%	[132]‡
2008-09	89.0%	[133]	45%	[127, 131]	44.5%	[134]‡
2009-10	93.0%		50%	[127]	55.0%	
2010-11	97.0%	[135]	55%	[136]	64.1%	[137]
2011-12	98.0%	[138]	60%		75.4%	[137]
2012-13	98.0%*		65%†		80.0%	

* Rates are assumed to remain constant at 98% after 2013. † Rates are assumed to increase by 5% per annum until an ultimate rate of 90% is reached in 2017. ‡ Adjusted to take into account differences in access to ART between provinces.

In calibrating the model to historic data, the average estimate for the base rate, $b(t)$, in 2011/12, is 0.3 [117]. This represents the average annual rate of testing in women aged 25 who are asymptomatic and not pregnant, who have not previously been tested for HIV. South Africa aims to maintain roughly stable annual numbers of HIV tests in the public health sector after 2013, with the target set at 10 million HIV tests per annum, similar to the number of 9.9 million tests performed in 2011/12 [139]. However, there may have been some reduction in numbers of HIV tests in recent years; numbers of HIV tests performed among 15-49 year olds in public health facilities have been reported at 9.0 million in 2012/13 [139] and at 6.7 million in 2013/14 [140]. This could be a reflection of testing fatigue, or reductions in resources to support HCT campaigns. On the other hand, there are a number of ways in which HCT uptake could be increased in future. Do *et al* [141], for example, show that 4 social marketing programmes in South Africa have had a significant impact on HCT uptake, and estimate that for each unit increase in exposure to these programmes, the odds of HIV testing in 2011/12 was increased by 3% (or 6.7% if accounting for indirect effects). Taking into account that the average exposure score over 2009-2012 was 4.16 and the theoretical maximum score was 9, this suggests a maximum increase of 37% ($1.067^{(9 - 4.16)} - 1$) in the odds of HIV testing if social marketing of HCT were fully scaled up. The introduction of self-testing kits could also lead to increases in the uptake of HIV testing [142]. To represent the uncertainty regarding future trends in the $b(t)$ rate, we assign a beta distribution with a mean of 0.25 and a standard deviation of 0.06 to represent the rate that applies from 2016 onwards. The 2.5 and 97.5 percentiles of this distribution are 0.15 and 0.38 respectively; the former represents a worst case scenario in which the reductions in HCT uptake over the 2011-2014 period continue over the next two years, at the average annual rate of 13% observed; the latter represents an optimistic scenario in which the odds of HIV testing in 2011/12 is increased by 37% (which is equivalent to a 30% increase in the rate of testing).

Although the base rate of HIV testing in women is estimated to have increased in the decade up to 2010/11, the relative rate of male HIV testing at age 25, $B_0(t)$, is estimated to have declined from 0.83 in 2002/03 to 0.68 in 2010/11 [117]. This may be because the HCT campaigns of recent years have been conducted mainly through public health facilities, which

are attended mostly by women. Recent national surveys suggest that the male-to-female testing ratio may have continued to decline in the post-2010 period [143]. On the other hand, it is possible that new HCT interventions might lead to increases in HIV testing in men specifically. For example, incentivized HCT programmes through mobile HCT clinics may be important in reaching unemployed men who often do not attend fixed health facilities [144]. Mobile HCT is associated with relatively high rates of male participation in urban South Africa, with proportions of male clients ranging from 48-61% (median 52%), in comparison to proportions of 40-50% (median 43%) in fixed health facilities [145-147]. A recent systematic review identified a number of other potential strategies for increasing male uptake of HCT, including promotion of testing of partners of women attending antenatal clinics, offering HIV testing in bars, and promotion of testing of partners of newly-diagnosed individuals [148]. Changing clinic opening hours may also make HCT more accessible to employed men [149]. To represent the uncertainty around the future values of the $B_0(t)$ parameter, we assign a gamma prior to the parameter value in 2017/18. This distribution has a mean of 0.68 (assuming on average no change from the baseline) and a standard deviation of 0.07. The 2.5 and 97.5 percentiles of this distribution are 0.55 and 0.82 respectively. The lower bound corresponds to a worst case scenario, in which the male-to-female testing ratio continues to decline at the same rate that it has over the 2002-2010 period. The upper bound corresponds to an optimistic scenario in which the ratio returns to the levels estimated in 2002.

In the period after 2015, the model also allows for potential additional increases in HIV testing due to home-based counselling and testing (HBCT). This involves extending equation (14) to include an additional term:

$$\tau_{g,i,s}(x,t) = b(t)A_g(x,t)r_i + \Omega_s d_i(t) + F_{g,s}(x,t)v_i(t) + I_1(t)\pi\,, \qquad (16)$$

where $I_1(t)$ is an indicator of whether HBCT has been introduced up to year t (0 if not, 1 otherwise) and π is the average annual rate of testing through HBCT campaigns. Although a number of African studies have shown that HBCT is highly acceptable [150], few studies have reported on the fraction of the total population that is reached and tested through HBCT campaigns. In a randomized trial conducted in a South African community [151], the fraction of the population who reported having ever tested for HIV increased from 31% to 69% over a 14-month period, suggesting an annual testing rate of 0.69 (-ln((1-0.69)/(1-0.31))×12/14), if it is optimistically assumed that all testing that occurred during the 14-month period was due to the home-based testing programme. Lower rates of testing might be expected in field settings, where fewer resources are likely to be committed to the intervention than in a randomized trial. We assign a gamma distribution to represent the uncertainty around the π parameter. This distribution has a mean of 0.35 and a standard deviation of 0.15, with 2.5 and 97.5 percentiles at 0.12 and 0.70 respectively. The mean and standard deviation have thus been chosen so that the upper bound corresponds to what we might optimistically expect if conditions similar to those in the randomized trial prevailed, while the lower bound reflects minimal uptake of HBCT. It is unclear whether HBCT is likely to be introduced in South Africa in future, and we have therefore modelled the introduction of HBCT in the same way as other new interventions, assigning a Weibull distribution with a median of 10 years and a shape parameter of 0.55 to represent the uncertainty around the time to the introduction of HBCT (in years after 2015).

1.2.3 Adult 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 link to care and start ART shortly after HIV diagnosis.) Table 1.7 summarizes the assumed proportions of HIV-positive adults in different categories who are eligible to receive life-long ART, and shows how this has changed over time. 'Eligibility to receive ART' here means only that the relevant guidelines recommended ART initiation in these patients [152-155] – this does not reflect the actual proportion of patients who started ART when they became eligible. In some of the periods the assumed eligible proportion has been set to 50% because the change in guideline occurred midway through the relevant period. For patients with CD4 counts of 200-349 cells/μl, the model allows for non-zero access to ART prior to official guideline changes, as some NGO-supported programmes and private sector programmes applied higher CD4 eligibility thresholds [156-158], and these adjustments are necessary to bring the model estimates in line with reported fractions of ART initiators in the CD4 200-349 category [159].

Table 1.7: Proportions of adult patients assumed to be eligible to receive lifelong ART

	2000-2003*	2003-2009	2009-2010	2010-2011	2011-2012	2012-2014	2014-2015	Post-2015
WHO stage IV or CD4 <200	100%	100%	100%	100%	100%	100%	100%	100%
Pulmonary TB, CD4 200-349	10%	10%	50%	100%	100%	100%	100%	100%
WHO stage III, CD4 350+	0%	0%	0%	0%	0%	100%	100%	100%
Pregnant women, CD4 200-349	10%	10%	50%	100%	100%	100%	100%	100%
Pregnant women, CD4 350+	0%	0%	0%	0%	0%	0%	50%	100%
Asymptomatic, non-pregnant, CD4 200-349	10%	10%	10%	20%	80%	100%	100%	100%
Asymptomatic, non-pregnant, CD4 350-499	0%	0%	0%	0%	0%	0%	50%	100%
Asymptomatic, non-pregnant, CD4 500+	0%	0%	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. † Eligibility can change in the uncertainty analysis.

It is unclear if and when South African ART eligibility criteria will be extended to include all HIV-positive individuals (regardless of CD4 count, pregnancy or clinical stage). The START and TEMPRANO trials have both found that immediate ART initiation leads to better health outcomes than ART deferred according to previous guidelines [160, 161], and based on this the WHO has issued new guidelines recommending universal ART eligibility [162]. It is likely that South African ART eligibility criteria will change to be consistent with WHO guidelines, although it is possible that local eligibility will not change, particularly if there concerns about the fiscal implications of further expansion of eligibility criteria. We adopt the same approach as before to represent the uncertainty, assigning a Weibull distribution to represent the uncertainty regarding the timing of the change in eligibility criteria (in years after 2015), with a median of 10 years and a shape parameter of 0.55.

The number of adults of sex *g* who initiate ART in the same month as diagnosis, in year *t*, is modelled as

$$S_g^0(t) = \sum_{i=0}^{1}\sum_{s=2}^{5}\sum_{x=15}^{90} N_{g,i,s}(x,t)\left\{b(t)A_g(x,t)r_i l_0(s,t) + \Omega_s d_i(t) l_1(s,t)\right\} + \sum_{i=0}^{2}\sum_{s=2}^{5}\sum_{x=15}^{49} N_{g,i,s}(x,t)F_{g,s}(x,t)\nu_i(t)l_2(s,t) \quad , \qquad (17)$$

where $N_{g,i,s}(x,t)$ is the number of individuals of age x and sex g, in HIV stage s and with HIV testing history i at the start of year t; $l_0(s,t)$ is the fraction of newly-diagnosed, asymptomatic, non-pregnant individuals in HIV stage s who start ART within a month of being diagnosed; and $l_1(s,t)$ and $l_2(s,t)$ are the corresponding fractions of OI patients and pregnant women respectively who start ART immediately after diagnosis (other symbols are defined in the same way as in equation (14)). Although the calculation is presented as an annual total for ease of comparison with equation (14), the actual model calculations of numbers starting ART are performed at monthly time steps, using monthly rates of HIV testing in place of annual rates of testing. Note that the summation excludes individuals in the acute phase of HIV infection (s = 1), since it is assumed that most rapid tests would return negative results during this disease stage. The summation also excludes individuals who were previously diagnosed (i = 2), although previously-diagnosed pregnant women are included if they are retested and are ART-eligible.

1.2.3.1 Linkage to ART after diagnosis during pregnancy

The assumed fractions of ART-eligible pregnant women who start ART during pregnancy are shown in Table 1.6. Assumptions for the early years are based on studies in the Western Cape [128, 132, 134], but are adjusted downward to take into account the lower rate of access to ART in other provinces in the early stages of the ART programme (applying the ratio of the ART initiation rate in women in the Western Cape to that estimated nationally). Assumptions for the more recent years are obtained from national statistics, which showed the proportion increasing to 75.4% in 2011/12 [137]. It is likely that this proportion increased in subsequent periods, following the introduction of WHO option B at the start of 2013, which eliminated the need for CD4 testing prior to ART initiation and thus simplified the ART initiation process. The Department of Health target is to ultimately increase the proportion of HIV-positive mothers initiating ART during pregnancy to 100% [139], but this may be unrealistic given the challenges associated with ART initiation in pregnancy, and given that some women do not receive any antenatal care prior to delivery. Linkage rates as high as 95% have been reported [163], and these might be considered a best case scenario. To represent the uncertainty regarding the proportion of women who start ART prior to delivery, following an HIV diagnosis in 2016 ($l_2(s, 2016)$), we assign a beta prior with a mean of 90% and a standard deviation of 4% (2.5 and 97.5 percentiles of 81% and 96% respectively). The mean and standard deviation have thus been chosen so that the upper limit on the confidence interval corresponds to the best case scenario, while the lower limit reflects negligible improvement relative to the baseline.

1.2.3.2 Linkage to ART after HIV diagnosis in OI patients

Few studies have reported on rates of linkage to ART specifically in those patients who are diagnosed in the course of management of an OI. However, relatively high rates of linkage might be expected, given that (a) such patients are likely to be fast-tracked through the patient

preparation process (since CD4 testing is not required prior to ART initiation), and (b) symptomatic patients are likely to be more motivated to start ART [164-166]. In one Cape Town study the rate of linkage in OI patients was found to be similar to that in pregnant patients [134]. We have therefore set the assumptions about the $l_1(s,t)$ parameters to be the same as the assumptions for women who are diagnosed positive during pregnancy ($l_2(s,t)$), in the period up to 2011/12 (Table 1.6). In subsequent years the rate of linkage to ART is assumed to remain constant at 80%.

1.2.3.3 Linkage to ART after HIV diagnosis in non-pregnant, asymptomatic adults

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 [167]. 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 × 0.80 × 0.67). We have therefore set the rate of linkage to care in 2012/13 ($l_0(s,2012)$) to 0.4, for all individuals who are ART-eligible. This is half of the rate assumed for OI patients, consistent with relative rates of linkage to ART in a Cape Town study conducted from 2004 to 2009 [134]. We have therefore set the $l_0(s,t)$ parameters for years prior to 2012 to be half of the rates assumed for OI patients.

The rate at which newly-diagnosed adults link to ART could change in future, for two reasons. Firstly, the introduction of point-of-care (POC) CD4 testing would mean that patients could have their CD4 count determined at the same time that HIV diagnosis occurs, and this would reduce drop-out. For example, Larson *et al* [168] found that the introduction of POC CD4 testing led to an increase in linkage to care following HIV diagnosis in South Africa (RR 1.25, 95% CI: 1.00-1.57), and Govindasamy *et al* [169] found that the proportion of CD4-tested individuals who received their test results increased from 73% to 98% (RR 1.34) following the introduction of POC testing. This suggests a theoretical increase from 40% to 52% if a RR of 1.3 is assumed (mid-way between the RR values of the two studies). Secondly, the switch to universal ART eligibility would obviate the need for baseline CD4 testing. This could theoretically increase the proportion of newly-diagnosed individuals starting ART from 40% to 67% (removing the factors of 0.75 and 0.8 from the calculation in the previous paragraph). In the period after 2015, we model the rate of linkage to care in asymptomatic, non-pregnant adults as

$$l_0(s,t) = 0.4 \times \left(1 - I_2(t)\right)\left(1 - I_3(t)\right) + \left(I_2(t) + I_3(t) - I_2(t)I_3(t)\right)l_0^M \qquad (18)$$

where $I_2(t)$ is an indicator of whether POC CD4 testing has been introduced up to year t (1 if so, 0 otherwise); $I_3(t)$ is similarly an indicator of whether universal ART eligibility has been introduced; and l_0^M is the proportion starting ART immediately after diagnosis, after the introduction of POC CD4 testing or universal ART eligibility. Based on the South African evidence reviewed, we model the uncertainty regarding the l_0^M parameter by assigning to this parameter a beta distribution with a mean of 60% and a standard deviation of 10%. The mean

of this distribution is midway between the 52% and 67% estimates, and the 2.5 and 97.5 percentiles of the distribution are at 40% and 79% respectively. The standard deviation has thus been chosen so that in a worst case scenario the interventions would lead to no improvement in linkage to ART, while in a best case scenario the interventions would increase linkage to care to levels similar to those in pregnant women and OI patients (80%).

Uncertainty regarding the time to the adoption of POC CD4 testing (in years after 2015) is modelled in the same way as other new interventions, using a Weibull distribution with a median of 10 years. This determines in which years $I_2(t) = 1$.

1.2.3.4 ART initiation in previously-diagnosed adults who did not link to ART soon after diagnosis, up to mid-2014

In the period up to mid-2014, the modelled rates of ART initiation in previously-diagnosed adults are calculated from reported numbers of adults starting ART in each period. Suppose that in the period up to mid-2014, $S_g(t)$ is the estimated number of adults of sex g starting ART in month t. Further suppose that $S_g^0(t)$ is the number who started ART immediately after HIV diagnosis in month t, calculated as shown in equation (17) but converting the annual total into a monthly number. Let $N_{g,s}(x,t)$ be the number of HIV-diagnosed individuals in CD4 category s, who are ART-naive 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 primarily on the observed relative rates of ART initiation in ART-eligible individuals in different CD4 categories [170], and are consistent with the relative rates at which individuals enrolled in pre-ART care return for regular CD4 testing [93, 156].) We wish to estimate the monthly rate at which previously-diagnosed individuals in the CD4 <200/μl category initiate ART, $\rho_g(t)$. We estimate this by noting that

$$\begin{aligned} S_g(t) - S_g^0(t) &= \sum_{x=15}^{90}\sum_{s=1}^{5} N_{g,s}(x,t)\int_0^1 \rho_g(t) J_s(t) \exp\left(-\left(\mu_{g,s}(x,t) + \rho_g(t) J_s(t)\right)u\right) du \\ &\approx \sum_{x=15}^{90}\sum_{s=1}^{5} N_{g,s}(x,t)\rho_g(t) J_s(t)\left(1 - 0.5\left(\mu_{g,s}(x,t) + \rho_g(t) J_s(t)\right)\right) \end{aligned} \qquad (19)$$

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.

The assumed values of $S_g(t)$, expressed as annual totals, are summarized in Table 1.8. These are estimated by combining data from the public sector, private sector and NGO programmes. Surveys of private sector and NGO programmes have been conducted every two years, to determine total numbers of patients currently receiving ART [171]. Reporting of patient totals in the public sector has changed over time; early reporting systems provided information only on numbers of patients cumulatively enrolled into ART programmes, but since late 2009 most provinces have switched to reporting numbers of patients *currently*

receiving ART [137, 172]. To estimate the number of new initiates in each period from the reported numbers of current patients, we have fitted a simplified model to the data, which allows for mortality [173] and ART interruptions [174]. This model has been fitted separately for each province, and the results presented in Table 1.8 are the aggregated totals for the whole country.

Table 1.8: Assumed annual numbers of patients starting ART in South Africa, and implied average treatment delays in previously-diagnosed patients with CD4 counts <200 cells/µl

	Men (15+)	Women (15+)	Children (<15)	Implied ART delay ($1/\rho(t)$)	
				Men (15+)	Women (15+)
Pre-2000	0	0	0	-	-
2000-01	2 808	3 553	464	217.4	238.1
2001-02	4 476	5 664	740	181.8	208.3
2002-03	5 340	6 757	883	196.1	238.1
2003-04	7 953	11 442	2 246	161.3	181.8
2004-05	22 852	44 318	6 595	68.0	54.9
2005-06	43 258	84 447	13 730	52.6	37.3
2006-07	54 579	104 965	15 076	62.9	41.3
2007-08	76 045	147 733	19 341	54.1	32.9
2008-09	115 407	216 722	30 972	32.9	20.3
2009-10	158 492	285 854	34 754	22.4	13.9
2010-11	185 562	355 024	43 143	19.4	10.4
2011-12	180 271	353 763	36 676	32.5	16.7
2012-13	185 843	342 701	28 999	40.0	17.4
2013-14	155 801	283 732	23 547	50.0	19.6

1.2.3.5 ART initiation in previously-diagnosed adults who did not link to ART soon after diagnosis, after mid-2014

Because we do not yet have data on the absolute numbers starting ART after mid-2014, we specify the $\rho_g(t)$ parameters directly for this period. These parameters can also be expressed in terms of average delays (in months) between diagnosis and ART initiation, if the individual does not link to ART soon after ART initiation ($1/\rho_g(t)$). The average delays implied by our assumed absolute numbers are shown in the last two columns of Table 1.8. Our baseline simulations suggest that in women with CD4 counts of <200 cells/µl, this average delay was around 10 months in 2010/11 but gradually increased to just under 20 months in the more recent periods, possibly as a result of 'crowding out' of sicker patients as ART eligibility criteria have expanded to include healthier patients. However, these results should be interpreted with caution, as the estimates are sensitive to assumptions about linkage to care after diagnosis (sections 1.2.3.1-1.2.3.3), which are difficult to determine precisely. In the period since 2009, the delay in men was on average around 2 times that in women (the ratio was substantially lower in the early 2000s, when men had better access to ART through private healthcare). Mujugira *et al* [170] found that among East African adults who were previously diagnosed and were subsequently determined to have CD4 counts <200 cells/µl, the average delay to ART initiation was around 6 months (with no significant difference between men and women). However, this is likely to be a lower bound on the delay that would apply in practice, (a) because the study was conducted in the context of a randomized trial, in which patients were intensively counselled and monitored; and (b) because most of

those with CD4 counts <200 cells/μl had only recently become eligible for ART, so the cohort included relatively few individuals who were diagnosed in previous periods, who might have chosen to delay ART until they were at a more advanced stage of disease. It is likely that delays would be longer in field settings, where access to services may be limited. There is concern that South Africa's public sector ART programme may be over-stretched and that limited future availability of resources might effectively lead to restricted ART access, even if the guidelines officially endorse early ART initiation [175]. To represent the uncertainty regarding likely future delays, we assign a gamma prior distribution to the mean time to ART initiation in women with CD4 <200 cells/μl who have not previously started ART. This prior distribution has a mean of 18 months and a standard deviation of 8 months (with 2.5 and 97.5 percentiles at 5.9 and 36.7 months respectively). The mean thus corresponds to the baseline estimates in 2012-13 and 2013-14, and the standard deviation has been chosen so that in a best case scenario rates of ART initiation would be similar to those in the East African trial. The upper limit of 36.7 months corresponds to a worst case scenario in which treatment delays return to those seen in 2005/6, when the public sector ART programme was still in its early stages. The average delay in men is assumed to be 2 times that in women, consistent with the model estimates over the period from mid-2009 to mid-2014.

1.2.4 Mortality after ART initiation in adults

HIV-related mortality after ART initiation is assumed to depend on age, sex, baseline CD4 category and time since ART initiation. The mortality rates specified in Table 1.5 relate to individuals who are aged 35, and these mortality rates are assumed to increase by factors of 1.12 and 1.09 per 10-year increase in age, in men and women respectively. For the most part these parameters have been determined from a model fitted to data from the IeDEA Southern Africa collaboration [116]. However, the IeDEA-SA data relate mainly to individuals who start ART with CD4 counts below 350 cells/μl, and the few patients starting ART at higher CD4 counts are mostly patients who started ART because they qualified on the basis of HIV-related symptoms. Although we lack South African data on mortality in asymptomatic patients starting ART at higher CD4 counts, observational data from high income countries suggest that untreated patients with CD4 counts above 250 cells/μl have similar long-term mortality rates, as long as they start ART before their CD4 count declines below 250 cells/μl [176]. We have therefore set the mortality rates of patients starting ART at higher CD4 counts in such a way that the predicted long-term mortality rate in untreated patients with CD4 counts above 500 cells/μl is roughly the same regardless of whether they start ART immediately, defer ART to when their CD4 count drops below 500, or defer ART to when their CD4 count drops below 350.

Within the group of patients starting ART at CD4 counts <200 cells/μl there is substantial heterogeneity in mortality depending on the exact baseline CD4 value. Although the model does not explicitly model variation in mortality rates by CD4 count below the 200 cells/μl cut-off, mortality rates are adjusted to take into account the rate of ART initiation, since high rates of ART initiation would imply that (a) most individuals starting ART at CD4 <200 cells/μl do so soon after their CD4 count falls below 200, and (b) most untreated individuals with CD4 <200 cells/μl have CD4 counts close to 200. We therefore calculate the theoretical minimum mortality rates that would be expected (both in untreated individuals with CD4 <200 and in treated individuals starting ART with CD4 <200) if ART was started soon after the CD4 count dropped below the 200 threshold. The difference between the mortality rate in

Table 1.5 and the theoretical minimum is reduced by a factor of $\exp\left(-m\rho_g(t^-)\right)$ in year *t*, where $\rho_g(t^-)$ is the average rate of ART initiation in the 3 years prior to year *t*, in adults of sex *g* with CD4 <200 cells/μl, and *m* is a scaling factor. This scaled difference is added to the minimum mortality rate to determine the modelled mortality rate in year *t*. For the purpose of this analysis, the *m* scaling parameter has been fixed at 4.71, the posterior mode estimated when the model was fitted to South African mortality data [25]. The adjustments are made only to those ART-naïve adults with CD4 counts <200 cells/μl and those treated adults with baseline CD4 counts <200 cells/μl.

1.3 Model of heterosexual HIV transmission

HIV transmission probabilities per act of sex are difficult to determine with a high degree of precision. We therefore specify prior distributions to represent the uncertainty regarding average transmission probabilities from untreated adults to their HIV-susceptible partners, then specify various adjustments to represent the effects of known cofactors on HIV transmission.

1.3.1 The effect of sex and relationship type

The symbol $\beta_{g,l}$ represents the average HIV transmission probability, in a single act of unprotected sex, from an untreated HIV-positive individual of sex *g*, to an HIV-negative partner in relationship type *l*. Table 1.9 summarizes the assumed prior distributions for these parameter values. Although empirical estimates suggest high female-to-male transmission probabilities per act of unprotected sex in unmarried men [177, 178], these are likely to be over-estimates, as they do not reflect possible male acquisition of HIV infection through sex worker contact, which is often substantially under-reported [179]. The prior distribution for the $\beta_{0,0}$ parameter has therefore been set in such a way that the mean (0.008) is below the empirical estimates (0.016 and 0.0128) but the 97.5 percentile of the distribution (0.015) is close to the empirical estimates. Beta distributions are used for all of the specified priors.

Table 1.9: Assumed probabilities of HIV transmission per act of sex

Relationship type	Symbol	Male-to-female			Female-to-male[c]		
		Mean	Std dev.	Ref.	Mean	Std dev.	Ref.
CSW-client relationships	$\beta_{g,2}$	0.001[a]	-	[180, 181]	0.008[b]	-	-
Short-term relationships	$\beta_{g,0}$	0.012	0.005	[182, 183]	0.008	0.003	[177, 178]
Long-term relationships	$\beta_{g,1}$	0.002	0.00075	[91, 184, 185]	0.002	0.00075	[91, 184, 185]

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.

1.3.2 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 [186, 187] and when present in the HIV-infected partner [188]. Although Thembisa does 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 is appropriate, depending on the risk groups of the HIV-infected partner and the HIV-susceptible partner. The transmission probabilities specified in Table 1.9 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 by definition high risk). The parameter $\Theta_{g,i,l,j}$ is 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. These parameter values have been estimated from a previously-published model of STI-HIV interactions in South Africa [189], and are shown in Table 1.10.

Table 1.10: Assumed multiples by which HIV transmission probabilities are increased depending on partner risk groups

	Short-term contacts		Marital contacts	
	HIV+ male partner	HIV+ female partner	HIV+ male partner	HIV+ female partner
High risk male, high risk female	1.23	1.20	1.62	1.38
High risk male, low risk female	1.25	1.14	1.57	1.35
Low risk male, high risk female	1.08	1.09	1.33	1.24
Low risk male, low risk female	1.00	1.00	1.00	1.00

1.3.3 The effect of HIV stage and antiretroviral treatment

Table 1.5 shows how relative levels of HIV infectiousness are assumed to differ by CD4 count in untreated adults. Although we do not express these assumptions in terms of differences in viral load between CD4 stages, we do make assumptions about viral load distributions and HIV infectiousness as a function of viral load for the purpose of calculating average levels of infectiousness after ART initiation. Suppose that random variable $X_{a,s}$ is the difference between the maximum viral load and the actual viral load, on the logarithmic scale, in individuals with ART status *a* (0 = untreated, 1 = treated) and CD4 stage *s* (in untreated individuals, *s* refers to the current CD4 stage, while in treated individuals *s* refers to the CD4 stage at the time of ART initiation). The maximum viral load is set to 6 on the $\log_{10}$ scale (although higher values are possible, these have little effect on the HIV transmission dynamics in which we are interested). Variable $X_{a,s}$ is assumed to be Weibull-distributed, with parameters $\omega_{a,s}$ and ϕ. The probability of viral suppression (a viral load of less than 400 copies/ml) in treated individuals is thus

$$\exp\left(-\omega_{1,s}\left(6-\log 400\right)^{\phi}\right), \tag{20}$$

from which it follows that if $V_s(t)$ is the probability of viral suppression in year *t*,

$$\omega_{1,s} = \frac{-\ln(V_s(t))}{(6-\log 400)^{\phi}}. \quad (21)$$

In fitting Weibull distributions to viral load data from both treated [107, 110] and ART-naïve South Africans [190], we have found that a ϕ parameter of 1.5 produces reasonable fits. In the period up to mid-2013, the $V_5(t)$ parameter (representing the rate of viral suppression in patients starting ART with CD4 <200 cells/μl) has been set to 0.77, based on data from South Africa's public sector ART programme [172] (a similar estimate of 0.75 was estimated for 2012 in a recent analysis of data from the National Health Laboratory Service [191]). Substituting $V_s(t) = 0.77$ into equation (21) yields a $\omega_{1,5}$ estimate of 0.042. Based on fitting the Weibull model to the median and inter-quartile range of viral loads prior to ART initiation in South Africans who almost all had CD4 counts of <200 cells/μl [190], we estimate the $\omega_{0,5}$ parameter to be 0.635.

We assume that if x is the difference between the maximum viral load and the actual viral load (on the logarithmic scale), the HIV transmission risk per act of sex is

$$c\exp\left(-\theta x^{\phi}\right), \quad (22)$$

where c is the maximum HIV transmission risk (when $x = 0$) and parameter θ determines the extent of the association between viral load and HIV transmission risk. Including $\phi > 1$ in the above equation ensures that the effect of viral load is less substantial at higher viral load levels than at lower viral load levels [192]. For reasons of mathematical convenience, explained below, we use the same value of $\phi = 1.5$ as estimated in the model of viral load distributions. The θ parameter is estimated by noting that if the factor by which infectiousness increases, per unit increase in viral load, is of the order of 2.5 [91, 193, 194], this implies that

$$\frac{-\frac{d}{dx}\left[c\exp\left(-\theta x^{\phi}\right)\right]}{c\exp\left(-\theta x^{\phi}\right)} = \ln(2.5). \quad (23)$$

From this it follows that $\theta\phi x^{\phi-1} = \ln(2.5)$. Substituting $\phi = 1.5$ and $x = 2$ [91, 193] yields $\theta = 0.432$. The average HIV transmission probability, for patients with ART status a and CD4 stage s, is then

$$\int_0^{\infty} \omega_{a,s}\phi x^{\phi-1}\exp\left(-\omega_{a,s}x^{\phi}\right)c\exp\left(-\theta x^{\phi}\right)dx = c\int_0^{\infty}\omega_{a,s}\phi x^{\phi-1}\exp\left(-\left(\theta+\omega_{a,s}\right)x^{\phi}\right)dx$$
$$= \frac{c\omega_{a,s}}{\omega_{a,s}+\theta}. \quad (24)$$

The advantage of using the same value of $\phi = 1.5$ in the modelled relationship between viral load and HIV transmission risk is thus that it ensures a simple mathematical expression for the average probability of HIV transmission. From equation (24), the ratio of the infectiousness after ART initiation to that prior to ART initiation is

$$R_s = \frac{\omega_{1,s}}{\omega_{1,s} + \theta} \Big/ \frac{\omega_{0,s}}{\omega_{0,s} + \theta} . \quad (25)$$

Substituting the values of $\omega_{1,5}$ = 0.042 and $\omega_{0,5}$ = 0.635 into this equation yields an R_5 estimate of 0.149. This is somewhat higher than the relative risk estimates of 0.04-0.08 estimated from randomized controlled trials [114, 195], but lower than the relative risk of 0.36 estimated in a recent meta-analysis of observational studies [196]. For patients who start ART at higher CD4 counts, data show that although they have lower baseline viral loads [104], they also have lower rates of virological failure after ART initiation [197], which suggests similar relative reductions in infectiousness across baseline CD4 categories. It is therefore assumed that the relative reduction in infectiousness is the same in all patients starting ART (i.e. $R_s = R_5$ for $s < 5$). Rates of viral suppression in patients who start ART at CD4 counts >200 cells/μl are calculated from equation (25), assuming that average viral load levels in untreated patients decrease by 0.18 for each 100-cell increase in the CD4 cell count [104] (which determines the $\omega_{0,s}$ values).

The model allows for uncertainty in future rates of viral suppression. Although a 77% rate of viral suppression has been assumed as the baseline, an 86% rate of viral suppression has been measured at 12 and 24 months after ART initiation in South African programmes participating in the IeDEA Southern Africa collaboration [173]. This higher rate of viral suppression probably reflects better access to resources in IeDEA programmes. A recent systematic review of ART adherence interventions in Africa estimates that SMS reminders and intensified adherence counselling in combination with treatment supporters could increase the odds of viral suppression by 1.55 (95% CI: 1.01-2.38) and 1.46 (95% CI: 1.09-1.97) respectively [198]. If such interventions were introduced in South Africa and an odds ratio of 2 were assumed (towards the upper end of the quoted 95% confidence intervals), this would yield an increase in viral suppression from 77% to 87%. Recent data from KwaZulu-Natal, collected following the introduction of adherence interventions, suggest viral suppression rates of between 85% and 90% in people who reported being on ART [110]. Another approach to defining a 'best case scenario' is to consider the 0.04 relative rate of transmission observed in the HPTN052 trial, when comparing individuals who started ART early to those in whom ART was deferred [195]. Substituting R_5 = 0.04 and $\omega_{0,5}$ = 0.635 into equation (25) yields an $\omega_{1,5}$ estimate of 0.011, which is equivalent to a virological suppression rate of 94% (from equation (21)).

Although these interventions suggest potential improvements in viral suppression in future, there are also a number of factors that may contribute to deteriorating viral suppression. There is particular concern that drug stockouts are becoming more frequent as the South African ART programme expands [199]. Increasing drug resistance could lead to declines in viral suppression; for example, Phillips *et al* [200] predict based on mathematical modelling that if levels of primary drug resistance in patients starting ART are around 5-10% (a level that is probably plausible for South Africa [201]), the rate of viral suppression one year after ART initiation will decline from 77% to 63% over 15 years, in the absence of any changes to drug regimens and patient monitoring. Data from a South African community suggest a viral suppression rate of only 66% in individuals who reported that they were receiving ART [107], possibly due to low levels of adherence in this community. With this baseline, Phillips *et al* predict that a long-term viral suppression rate of 52% would be more likely [200], which we consider a 'worst case' scenario. To represent the uncertainty regarding future viral

suppression, we assign a beta prior to the ultimate rate of viral suppression that applies in 2017 and future years. This beta prior has a mean of 0.77 and a standard deviation of 0.11 (with 2.5 and 97.5 percentiles of 0.52 and 0.94 respectively). The mean of 0.77 corresponds to the baseline assumption for 2012/13 [172], and the standard deviation has been chosen so that the upper and lower limits of the 95% confidence interval correspond to the best- and worst-case scenarios respectively.

1.3.4 Condom effectiveness

Condoms are assumed to be 90% effective in preventing HIV transmission. Although this is slightly higher than the rates of around 80% that have been estimated empirically [91, 202], it is likely that empirical estimates are biased downward due to over-reporting of condom usage [203, 204].

1.3.5 Age-related factors

Young women are at a biologically increased risk of HIV acquisition due to the high prevalence of cervical ectopy in adolescence and young adulthood [205-207], and relatively low levels of protective lactobacilli [208]. The model makes allowance for this heightened susceptibility by assuming that the HIV transmission risk per act of sex is increased by a factor of $Z_g(x)$, relative to adults aged 25 and older, in individuals of sex g and age x. The function $Z_g(x)$ is defined as

$$Z_g(x) = \begin{cases} (1+Z_g)^{25-x} & \text{for } x < 25 \\ 1 & \text{for } x \geq 25 \end{cases}. \qquad (26)$$

The Z_2 parameter (for females) is set equal to 0.15, based on studies that have quantified the effect of age on HIV transmission probabilities in women [209-211]. For males, there does not appear to be strong evidence of age variation in the risk of HIV acquisition per sex act [91, 210], and the Z_1 parameter has therefore been set to zero.

1.3.6 Mathematical model of heterosexual transmission

We define $\Gamma(s)$ to be the frequency of sex in untreated HIV disease stage s, relative to that in uninfected individuals (these parameters are estimated in section 1.1.9). The previously-defined $\beta_{g,l}$ 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

$$\beta_{g,l} = \beta^*_{g,l} \frac{\sum_{s=1}^{3} \frac{I_s \Gamma(s)}{\lambda_s} + \frac{I_4 \Gamma(4)}{\lambda_4 + \mu_4} + \frac{\lambda_4}{\lambda_4 + \mu_4} \times \frac{I_5 \Gamma(5)}{\mu_5}}{\sum_{s=1}^{3} \frac{\Gamma(s)}{\lambda_s} + \frac{\Gamma(4)}{\lambda_4 + \mu_4} + \frac{\lambda_4 \Gamma(5)}{(\lambda_4 + \mu_4)\mu_5}}, \quad (27)$$

where the I_s factors are the relative levels of infectiousness (Table 1.5), and the CD4 decline parameters (λ_s) and mortality parameters (μ_s) are those specified in section 1.2.1. 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

$$I^*_2 = \frac{\sum_{s=1}^{3} \frac{\Gamma(s)}{\lambda_s} + \frac{\Gamma(4)}{\lambda_4 + \mu_4} + \frac{\lambda_4 \Gamma(5)}{(\lambda_4 + \mu_4)\mu_5}}{\sum_{s=1}^{3} \frac{I_s \Gamma(s)}{\lambda_s} + \frac{I_4 \Gamma(4)}{\lambda_4 + \mu_4} + \frac{\lambda_4}{\lambda_4 + \mu_4} \times \frac{I_5 \Gamma(5)}{\mu_5}}. \quad (28)$$

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 ART-naïve and 1 implying ever 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 ART-naïve individuals $I^*_s(0) = I^*_s$. For ART-experienced individuals who started ART in HIV disease stage *s*, the relative infectiousness is $I^*_s(1) = I^*_s(\iota_d + (1-\iota_d)R_s)$, where ι_d is the proportion of ART-experienced adults surviving to duration *d* after ART initiation, who are interrupting ART, and R_s is the relative infectivity after ART initiation (as defined in equation (25)). The ι_d parameters have been set to 0.024 for the first 6 months after ART initiation, 0.072 for months 7-18, 0.088 for months 19-30, 0.081 for months 31-42 and 0.067 for longer ART durations, based on a model of ART interruptions in South Africa [174].

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. As in section 1.2.2, 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

$$G(v,a) = (1-\delta(t))(1-h)^a, \quad (29)$$

where the $\delta(t)$ and *h* parameters represent the reductions in unprotected sex due to HIV diagnosis and ART initiation respectively (see sections 1.1.10 and 1.1.11).

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*, with duration *d* since first ART initiation, to the frequency of sex in HIV-negative individuals. In the case of ART-naïve individuals (*a* = 0 and *d* = 0), $Y(0,s,0) = \Gamma(s)$. In the case of ART-experienced individuals, we define

$$Y(1,s,d) = \iota_d \Gamma(s) + (1-\iota_d)\sum_{s'=2}^{5} \psi_d(s' \mid s)\Gamma(s'), \quad (30)$$

where $\psi_d(s' \mid s)$ is the proportion of surviving 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 are in ART duration category *d*. Individuals who interrupt ART are assumed to experience a return to baseline CD4 levels [90], and the frequency of sex is thus assumed to be a function only of the *current* CD4 count. The $\psi_d(s' \mid s)$ values are estimated from studies of CD4 distributions after ART initiation [212-214], and the assumed values are shown in Table 1.11.

Table 1.11: Proportions of treated patients in different CD4 categories

	Time since ART initiation (months)				
	0-6	7-18	19-30	31-42	43+
Patients starting ART with CD4 <200					
Proportion with current CD4 500+	0.00	0.08	0.22	0.30	0.41
Proportion with current CD4 350-499	0.01	0.22	0.29	0.30	0.28
Proportion with current CD4 200-349	0.20	0.44	0.35	0.30	0.24
Proportion with current CD4 <200	0.79	0.26	0.13	0.10	0.06
Patients starting ART with CD4 200-349					
Proportion with current CD4 500+	0.00	0.28	0.57	0.66	0.81
Proportion with current CD4 350-499	0.26	0.58	0.35	0.25	0.16
Proportion with current CD4 200-349	0.73	0.14	0.08	0.08	0.04
Proportion with current CD4 <200	0.01	0.00	0.00	0.00	0.00
Patients starting ART with CD4 350-499					
Proportion with current CD4 500+	0.28	0.69	0.81	0.84	0.93
Proportion with current CD4 350-499	0.65	0.29	0.17	0.13	0.06
Proportion with current CD4 200-349	0.06	0.02	0.02	0.03	0.01
Proportion with current CD4 <200	0.00	0.00	0.00	0.00	0.00
Patients starting ART with CD4 500+					
Proportion with current CD4 500+	0.91	0.93	0.94	0.94	0.98
Proportion with current CD4 350-499	0.09	0.07	0.06	0.05	0.02
Proportion with current CD4 200-349	0.00	0.00	0.00	0.01	0.00
Proportion with current CD4 <200	0.00	0.00	0.00	0.00	0.00

For the purpose of calculating average transmission probabilities, we define $N^r_{g,i,l,j}(x)$ 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 $X^r_{g,i,l,j}(x,a,s,v,d)$ 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 1.12.

Table 1.12: Definitions of HIV-positive states

ART status (a)	HIV stage (s)	Testing history (v)	ART duration (d)	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 – all other infections are assumed to be diagnosed following acute infection.

As in recent modelling of herpes transmission [215], the model is parameterized in terms of a force (or 'hazard') of transmission per sex act, which is then converted into a cumulative hazard, given the expected number of sex acts in the relationship. For an HIV-positive individual with state covariates (a, s, v, d), the cumulative hazard for HIV transmission, per short-term partnership with a partner in risk group j, is

$$\begin{aligned} &n_{g,0}(x)Y(a,s,d)\beta_{g,0}I_s^*(a)\Theta_{g,i,0,j}\left(1-\left[1-\left(1-\gamma_{g,0}(x,t)\right)G(v,a)\right]E\right) \\ &= n_{g,0}(x)Y(a,s,d)\beta_{g,0}I_s^*(a)\Theta_{g,i,0,j}\left\{\left(1-\gamma_{g,0}(x,t)\right)G(v,a)E+\left(1-E\right)\right\} \end{aligned} \quad (31)$$

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 1.1.8), and E is

the condom efficacy parameter. From this we can calculate the probability of HIV transmission per short-term partnership:

$$1-\exp\left(-n_{g,0}(x)Y(a,s,d)\beta_{g,0}I_s^*(a)\Theta_{g,i,0,j}\left\{\left(1-\gamma_{g,0}(x,t)\right)G(v,a)E+\left(1-E\right)\right\}\right). \quad (32)$$

The rate at which individuals transmit HIV, per short-term partnership with a partner in risk group *j*, averaged across the HIV disease stages defined in Table 1.12, is defined as

$$T_{g,i,l,k}^{0,r}(j,x)=\sum_{a,s,v,d}X_{g,i,l,k}^{r}(x,a,s,v,d)n_{g,0}(x)Y(a,s,d)\beta_{g,0}I_s^*(a)\Theta_{g,i,0,j} \times\left\{\left(1-\gamma_{g,0}(x,t)\right)G(v,a)E+\left(1-E\right)\right\}. \quad (33)$$

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 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

$$1-\exp\left(-T_{g,i,l,k}^{0,r}(j,x)\right), \quad (34)$$

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

$$U_{g,i}^{0}(j,x)=1-\frac{\sum_{r,l,k}N_{g,i,l,k}^{r}(x)c_{g,i,l}(x)\exp\left(-T_{g,i,l,k}^{0,r}(j,x)\right)}{\sum_{r,l,k}N_{g,i,l,k}^{r}(x)c_{g,i,l}(x)}, \quad (35)$$

where $c_{g,i,l}(x)$ is the annual rate at which new non-spousal relationships are formed (as defined in section 1.1.2). 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

$$U_{g,i}^{1}(j,x) = 1 - \frac{\sum_{r} N_{g,i,1,j}^{r}(x)\exp\left(-T_{g,i,1,j}^{1,r}(j,x)\right)}{\sum_{r} N_{g,i,1,j}^{r}(x)}, \tag{36}$$

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

$$U_{1,1}^{2} = \frac{\sum_{r,l,k,x} N_{1,1,l,k}^{r}(x) w_l(x) T_{1,1,l,k}^{2,r}(1)}{\sum_{r,l,k,x} N_{1,1,l,k}^{r}(x) w_l(x)}, \tag{37}$$

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

$$P_{g,i,l}^{0}(x) = 1 - \exp\left(-\frac{c_{g,i,l}(x)}{12} Z_g(x) \sum_{y=10}^{90} f_{g,0}(y \mid x) \times \left[\rho_{g,i,0}(1,t) U_{3-g,1}^{0}(i,y) + \rho_{g,i,0}(2,t) U_{3-g,2}^{0}(i,y)\right]\right) \tag{38}$$

where $f_{g,0}(y \mid x)$ is the proportion of short-term partners who are aged *y*, $\rho_{g,i,0}(j,t)$ is the proportion of partners who are in risk group *j*, 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

$$P_{g,i,1,j}^{1}(x) = 1 - \exp\left(- Z_g(x) \sum_{y=10}^{90} f_{g,1}(y \mid x) U_{3-g,j}^{1}(i,y)\right). \tag{39}$$

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

$$P_{1,1,l}^{2}(x) = 1 - \exp\left(-\frac{w_l(x)}{12} Z_1(x) \sum_{y=10}^{90} N_{2,1,2}^{0}(y) T_{2,1,2}^{2,0}(1,y) \Big/ \sum_{y=10}^{90} N_{2,1,2}^{0}(y)\right), \tag{40}$$

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

$$P_{2,1,2}^{2}(x) = 1 - \exp\left(-\frac{C}{12} Z_2(x) U_{1,1}^{2}\right), \tag{41}$$

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

1.3.7 Extensions to represent effect of male circumcision

Men who are circumcised are assumed to have a 60% lower probability of HIV transmission than uncircumcised men, per act of sex with an HIV-positive partner (the transmission probabilities in Table 1.9 relate to uncircumcised men) [216-219]. Male circumcision is assumed to have no effect on male-to-female rates of HIV transmission.

The rate at which men get circumcised is assumed to be composed of two parts: the 'background' rate of male circumcision that would be expected in the absence of any efforts to promote male circumcision as an HIV prevention strategy, and the rate of male circumcision due to medical male circumcision (MMC) campaigns. In modelling the former, a cumulative Weibull distribution is used to represent the age-related changes in the prevalence of male circumcision prior to 2008. It is assumed that the prevalence of male circumcision at age x is determined by the function

$$p(x) = a + (b-a)\left(1 - 0.5^{(x/m_1)^{\phi}}\right), \tag{42}$$

where a is the proportion of males who are circumcised soon after birth, b is the maximum cumulative uptake of male circumcision in the absence of MMC promotion, 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 (including those who are circumcised at the time of birth), it is useful to parameterize the model in terms of this overall median circumcision age, m_2, noting that

$$m_1 = m_2\left(\frac{\ln\left(b/(2(b-a))\right)}{\ln(0.5)}\right)^{-1/\phi} \qquad \text{for } \frac{b}{2} > a\,. \tag{43}$$

Parameters a and b are set at 0.105 and 0.42 respectively. The shape parameter ϕ is set at 4.5, and the median age at circumcision m_2 is set at 18, the median age at circumcision reported by Africans in the 2002 HSRC survey [220]. Most of these parameters have been set so that the model is consistent with reported rates of male circumcision by age in national surveys [55, 220, 221], after correcting the self-reported data to take into account known biases in the reporting of male circumcision [222-227]. The two national surveys used in the parameterization were conducted in 2002 and 2003, and thus represent the situation prior to the promotion of male circumcision as an HIV prevention strategy. Figure 1.6 shows the model calibration.

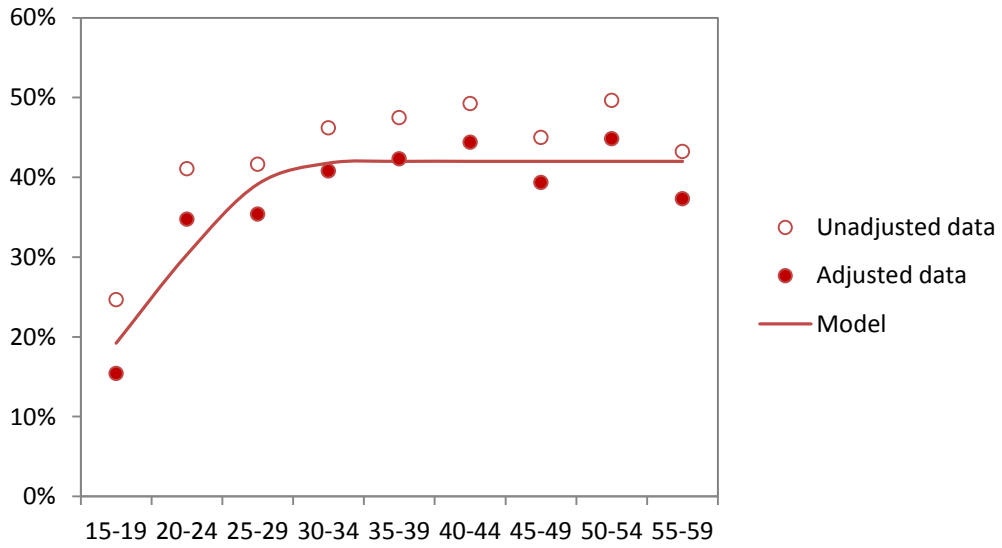

Figure 1.6: Fraction of men who are circumcised, by age
Unadjusted data represent the average of the results from national surveys in 2002 and 2003 [55, 220, 221]. Adjusted estimates are calculated on the assumption that the sensitivity and specificity of self-reported male circumcision status (relative to true status) are 96.4% and 88.4% respectively.

The annual probability that uncircumcised men aged x would get circumcised in the absence of MMC campaigns is calculated from the $p(x)$ values defined previously using the equation

$$\psi(x) = 1 - \frac{1 - p(x+1)}{1 - p(x)}. \qquad (44)$$

The symbol $\eta_{i,l}(x,t)$ is defined as the probability that HIV-negative men in risk group i, of marital status l, who are aged x and uncircumcised at the start of year t, get medically circumcised through MMC campaigns. This is calculated as

$$\eta_{i,l}(x,t) = R(t)\left[1 - \exp\left(-c_{1,i,l}(x)\right)\right] \ , \qquad (45)$$

where $R(t)$ is the maximum probability in year t and $c_{1,i,l}(x)$ is the rate at which short-term partners are acquired in men aged x, who are in risk group i and of marital status l. The term in square brackets represents the annual probability of having at least one short-term partner, and it is therefore assumed that the annual rate of MMC uptake is proportional to this probability [228]. In the period up to 2013/14, the $R(t)$ values are calculated from the reported annual total numbers of MMC operations performed through MMC campaigns (summarized in Table 1.13). Suppose that in year t, the reported number of medical male circumcisions performed as part of the MMC promotion drive is $\Lambda(t)$. If we define $N_{i,l}(x,t)$ to be the number of uncircumcised HIV-negative men aged x at the start of year t, who are in risk group i and are of marital status l, then we obtain

$$\Lambda(t) \approx \sum_i \sum_l \sum_x N_{i,l}(x,t) \times \eta_{i,l}(x,t)\left(1 - 0.5 \times \psi(x)\right), \qquad (46)$$

from which it follows that

$$R(t) \approx \frac{\Lambda(t)}{\sum_i \sum_l \sum_x N_{i,l}(x,t)\left(1-\exp\left(c_{g,i,l}(x)\right)\right)\left(1-0.5\times\psi(x)\right)}. \quad (47)$$

Table 1.13: Annual numbers of MMC operations performed through MMC campaigns

Year	Pre-2008	2008/09	2009/10	2010/11	2011/12	2012/13	2013/14
Operations	0	5 190	9 168	131 117	347 973	422 262	331 668

Source: World Health Organization [229], Department of Health [139, 140]

Based on equation (47), the model estimates the annual probability of MMC in 2013/14, for men in short-term relationships, to be 0.15. The Department of Health target is to increase the number of MMC operations to 1 000 000 per annum from 2014/15 [139], which would be equivalent to a roughly 0.68 probability of MMC uptake in men in non-marital relationships in 2014/15. These increases in MMC operations could potentially be achieved through a number of novel MMC promotion methods. For example, MMC campaigns during school holidays may be particularly important in boosting the uptake of MMC at young ages [230], while payments to compensate for time off work may be particularly important in motivating older men to get circumcised [231]. There also appears to be a strong association between men's self-reported exposure to HIV communications programmes and their intentions to get circumcised [17], which suggests that HIV communication programmes may be important in generating demand for MMC. Promotion of MMC to men seeking VCT may also be effective [232].

However, there are a number of reasons why it may be overly optimistic to set the future annual probability of MMC uptake to 0.68. Most importantly, there is likely to be a degree of intervention saturation, which has not been taken into account in the target setting. In the face of declining numbers of uncircumcised men, the absolute numbers of MMC operations may well decline. This would be particularly likely if many of the men who are currently uncircumcised belong to ethnic groups such as the Xhosa, in which MMC is considered culturally unacceptable [233, 234], or if most of the remaining uncircumcised men are at low HIV risk and are unlikely to see much benefit in getting circumcised. In the 2012 National Communication Survey [17], the fraction of uncircumcised men who said that they definitely intended to get medically circumcised in the next 12 months was only 2-4% in the Eastern Cape and Western Cape, the two provinces with the highest proportions of Xhosa speakers. This might be considered a lower bound on the future rate of MMC uptake in men in non-marital relationships, if most of the remaining uncircumcised men were resistant to the idea of MMC for cultural reasons.

We assign a beta prior distribution to reflect the uncertainty regarding the ultimate annual probability of MMC uptake in men in non-marital partnerships. This beta prior has a mean of 0.30 and a standard deviation of 0.17, which gives 2.5 and 97.5 percentiles at 0.04 and 0.68 respectively. The mean and standard deviation have thus been chosen so that the upper and lower confidence limits correspond to worst case and best case scenarios respectively ('best case' corresponding to the meeting of government targets).

1.3.8 Extensions to represent effect of pre-exposure prophylaxis (PrEP)

1.3.8.1 Effectiveness of PrEP

Randomized controlled trials published to date have yielded conflicting estimates of the effectiveness of PrEP. We assign a beta prior distribution to represent the uncertainty regarding future average levels of PrEP effectiveness. As in our previous work [235], we set the mean and standard deviation of this distribution at 40% and 24% respectively, so that there is a wide range of possible effectiveness parameters simulated (2.5 and 97.5 percentiles are at 3% and 88% respectively). The mean corresponds to the average efficacy level in the studies of PrEP in heterosexual adults that have been published to date [236-240]. The upper limit of the confidence interval corresponds to the most optimistic estimates of PrEP efficacy in heterosexual adults; in the Partners PrEP trial, detectable levels of study drug in blood plasma were associated with efficacy levels of 86% and 90% in individuals receiving tenofovir and truvada respectively [236]. The 3% lower limit corresponds to the levels of efficacy in the FEM-PrEP trial (6% efficacy [239]) and the VOICE trial (zero efficacy [238]). The variation in efficacy is a reflection of variation in adherence, and it is possible that individuals may be more motivated to use the drugs consistently in future once their efficacy is established. In addition, new PrEP delivery methods are currently being investigated, including long-acting injectable PrEP and vaginal rings [241, 242], which would require less frequent action on the part of the user.

1.3.8.2 Risk compensation

Although data from randomized trials generally do not show evidence of risk compensation in PrEP recipients [236, 237, 239], 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 PrEP trial data, a statistically significant 10% increase was noted in unprotected extramarital sex, amongst individuals who were receiving open-label PrEP [243]. Another recent microbicide acceptability study found that women were resistant to the idea of using both condoms and microbicides simultaneously [241]. This suggests that some reduction in condom use could occur. However, in a study of men who have sex with men (MSM) and transgender women who were offered PrEP following news of its efficacy, unprotected anal intercourse declined similarly over the course of the study in those who chose to receive PrEP and those who did not take PrEP [244]. We assign a beta prior distribution to represent the uncertainty around the average percentage reduction in condom usage that occurs in users of PrEP. This distribution has a mean of 10% and a standard deviation of 10% (with 2.5 and 97.5 percentiles at 0% and 37% respectively). The mean thus corresponds to the data from the Partners PrEP trial, while the standard deviation has been chosen so that the lower limit corresponds to negligible risk compensation.

1.3.8.3 PrEP discontinuation

Rates at which individuals discontinue PrEP are highly variable between studies, ranging from rates of 0.23 per annum in American MSM [245] to rates of 0.45 and 0.80 per annum in studies that have followed individuals following the completion of randomized controlled

trials of PrEP [243, 244]. The model assumes that individuals who start PrEP discontinue PrEP at a rate of 0.5 per annum, corresponding roughly to the average of the estimates from the three cited studies.

1.3.8.4 Adoption of PrEP by sex workers

Few studies have investigated the acceptability of PrEP among sex workers. In a study of sex workers in four countries (Kenya, India, Peru and Ukraine), Eisingerich *et al* [246] found that more than 90% of sex workers reported that they would probably or definitely use PrEP if it was available. In another Kenyan study, 80% of sex workers and MSM reported that they would use PrEP if it was found to be effective [247]. However, stated acceptability may differ from actual uptake. Among MSM attending STI clinics in San Francisco, who were offered PrEP, only 49% accepted the offer [245]. Sex workers may avoid PrEP if they are concerned that it provides no protection against other STIs and pregnancy. Even if PrEP is highly acceptable, actual levels of uptake may be low if PrEP promotion programmes struggle to reach women engaging in commercial sex; this is likely given that commercial sex is currently criminalized in South Africa. We assign a gamma distribution to represent the uncertainty regarding the annual rate at which sex workers adopt PrEP if it is available to them. This gamma distribution has a mean of 0.3 and a standard deviation of 0.2; with this mean uptake of 0.3 per annum, the average PrEP coverage in sex workers would be approximately 26% (0.3/(0.3 + 0.5 + 1/3), given an assumed PrEP discontinuation rate of 0.5 per annum and an assumed average duration of commercial sex of 3 years). The 2.5 and 97.5 percentiles of the prior distribution (0.04 and 0.80 respectively) correspond to PrEP coverage levels of 5% and 49% respectively. The mean and standard deviation have thus been chosen in such a way that the upper bound on the confidence interval corresponds to an optimistic scenario in which all sex workers have access to PrEP and have rates of PrEP coverage similar to those observed in MSM in San Francisco who had been offered PrEP, while the mean of the distribution yields a PrEP coverage level that is roughly half of that [245].

It is uncertain if and when PrEP would be promoted among sex workers. Although PrEP is not formally endorsed in the 2012-16 National Strategic Plan and in government target setting, the SANAC strategic plan for sex workers does mention the need to pilot PrEP programmes in sex workers [248], and the Department of Health has commissioned work to explore the cost-effectiveness of a PrEP promotion strategy for sex workers. The South African Medicines Control Council has not yet licensed tenofovir for use as a prophylactic agent. We assume that the time to PrEP introduction among sex workers (in years from 2015) is Weibull distributed with a median of 10 years and a shape parameter of 0.55 (implying a 30% chance that PrEP is made available to sex workers before 2018).

1.3.8.5 Adoption of PrEP by youth

Although self-reported willingness to use PrEP among South African youth appears similar to the high levels reported among sex workers [246], actual uptake may again be very different. Although youth are an easier population to access than sex workers, there are important concerns that still need to be resolved regarding the safety of tenofovir and truvada in adolescents, especially in relation to bone mineral density. There are potentially also legal obstacles to offering PrEP to adolescents below the age of majority. We model the uncertainty regarding the likely uptake of PrEP in sexually active youth (ages 15-24) using the same approach as for sex workers, i.e. assigning a gamma prior with a mean of 0.3 to

represent the annual rate at which youth would initiate PrEP if it were available. The timing of the introduction of PrEP for youth is also modelled in the same way as that for sex workers, i.e. using a Weibull distribution with a median of 10 years to represent the uncertainty regarding the time to the promotion of PrEP for youth (after 2015).

1.4 Model of mother-to-child transmission and paediatric HIV

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). HIV survival rates in HIV-infected children are assumed to depend on whether infection is acquired perinatally or postnatally.

1.4.1 Perinatal transmission

The model of mother-to-child transmission has been described elsewhere [249], and key parameters are summarized in Table 1.14. Perinatal transmission probabilities are assumed to depend on the mother's HIV disease stage and the type of antiretroviral prophylaxis that she receives. Proportions of women who receive testing for HIV and proportions of women who start long-term ART (if they are ART-eligible) have both been presented in Table 1.6.

1.4.1.1 Short-course antiretroviral prophylaxis

Of women who test positive during pregnancy but do not start long-term ART, 71% are assumed to receive single-dose nevirapine (sd NVP) in the period up to 2011/12. A fraction $D(t)$ of these women also receive short-course AZT (dual therapy), and the fraction of women not receiving sd NVP who receive short-course AZT is assumed to be proportional to $D(t)$. The fraction of diagnosed women not starting long-term ART, who receive some form of short-course ARV prophylaxis, is thus $0.71 + (1 - 0.71) \times D(t) \times 0.79$, where 0.79 is the assumed constant of proportionality (Kate Kerber, personal communication, based on national survey data [250]). The $D(t)$ parameters are assumed to increase from zero in 2002/3 up to 90% in the 2010-2012 period [250, 251].

Table 1.14: Mother-to-child transmission assumptions

Parameter	Value (mean)	Standard deviation*	Source
Transmission rate at/before birth, from chronically-infected women with no ARV prophylaxis, with			
CD4 >500	13.4%	-	Meta-analysis of published studies [252]
CD4 350-500	15.2%	-	
CD4 200-349	25.8%	-	
CD4 <200	35.0%	-	
Transmission rate at/before birth, from acutely-infected women with no ARV prophylaxis	35.0%	8.0%	Meta-analysis [249]
% of HIV-diagnosed women who receive single-dose nevirapine, if not starting ART	71.0%	-	Kate Kerber (pers. comm.), based on national survey data [250]
% reduction in perinatal MTCT if mother receives single-dose nevirapine only	40.0%	-	[253]
% reduction in perinatal MTCT if mother receives short-course zidovudine only	65.0%	-	[254]
% reduction in perinatal MTCT if mother receives single-dose nevirapine + short-course zidovudine	85.0%	5.0%	[255, 256]
Transmission rate at/before birth, from women on long-term ART pre-conception	0.6%	-	[257-259]
Probability of MTCT from chronically-infected mothers, per year of mixed feeding	14.0%	2.5%	Meta-analysis [260], adjusted to reflect effect of excluding EBF
Probability of MTCT from acutely-infected mothers, per month of mixed feeding	16.0%	3.0%	Derived from meta-analysis [249]
Ratio of postnatal transmission risk per month of EBF to postnatal transmission risk per month of mixed feeding	50.0%	15.0%	[261, 262]
% reduction in monthly postnatal MTCT risk if child receives extended nevirapine prophylaxis	60.0%	-	[263-265]
% reduction in monthly postnatal MTCT risk if mother receives long-term ART	80.0%	-	[266-270]

* Standard deviations are shown only for those parameters that are included in the uncertainty analysis. EBF = exclusive breastfeeding; MTCT = mother-to-child transmission.

In the period from the end of 2012 to the end of 2014, WHO option B has been official policy in South Africa, and since the start of 2015, option B+ has been official policy. However, there has been a lack of clarity regarding the provision of short-course antiretroviral prophylaxis to women who – for whatever reason – do not start long-term ART during pregnancy. Western Cape guidelines recommend that pregnant HIV-positive women who are not able to start long-term ART immediately should receive AZT prophylaxis, and if an HIV-positive mother presents in labour but is not on ART, short-course ARV prophylaxis should be initiated [271]. However, recent national guidelines make no mention of short-course antiretroviral prophylaxis [272]. Recent data from Botswana show that the introduction of WHO Option B in Botswana has led to an *increase* in the fraction of HIV-positive women who receive no ARV prophylaxis during pregnancy [273], which suggests that women who do not start long-term ART are less likely to be offered short-course ARV prophylaxis than they were previously. The simplification of PMTCT and the lack of clarity regarding the provision of short-course ARV prophylaxis probably mean that some antenatal clinics might *only* offer long-term ART, as has been the case in Malawi following the introduction of WHO Option B+. In addition, the mothers who do not start long-term ART despite being offered therapy are likely to be a select group, different from the mothers who qualified only for short-course ARV prophylaxis in the period up to 2012 (i.e. if they have refused long-term ART, they might be as likely to refuse short-course ARV prophylaxis). We have

therefore assigned a uniform (0, 1) prior distribution to represent the uncertainty regarding the relative rate of short-course ARV uptake in the post-2012 period, in women who do not start long-term ART. The choice of a vague prior reflects the lack of data regarding the relative rate of short-course ARV uptake since the switch to WHO options B and B+. If $J(t)$ is the relative rate of short-course ARV uptake in year t, then the proportion of diagnosed women not starting long-term ART, who receive some form of short-course ARV prophylaxis, is

$$0.71J(t)+\left(1-0.71J(t)\right)D(t)J(t)\times 0.79\,. \qquad (48)$$

Reductions in mother-to-child transmission probabilities due to different forms of antiretroviral prophylaxis are shown in Table 1.14. There is uncertainty regarding the combined efficacy of sd NVP and short-course AZT, and a beta prior distribution has therefore been specified to represent the uncertainty around this parameter.

1.4.1.2 Initiation of long-term ART

For women who start ART during pregnancy, in CD4 stage s, the probability of perinatal transmission is assumed to be of the form

$$a+b_s R^x\,, \qquad (49)$$

where a is the minimum transmission risk (the risk that might be expected in women who started ART prior to conception), b_s is the difference between the maximum and minimum transmission risk (the maximum being that which applies if ART is initiated just prior to delivery), R is the factor by which the difference reduces per week of ART prior to delivery, and x is the number of weeks of ART received prior to delivery. If $g(x)$ is the probability density function describing the distribution of ART durations in the baseline scenario (before any interventions to improve ART initiation during pregnancy), and this density is assumed to be of gamma form, then the average probability of perinatal transmission in the baseline scenario is

$$\begin{aligned}\int_0^\infty g(x)\left(a+b_s R^x\right)dx &= a+b_s\int_0^\infty \frac{\lambda(t)^\alpha x^{\alpha-1}\exp\left(-\lambda(t)x\right)}{\Gamma(\alpha)}R^x dx \\ &= a+b_s\left(\frac{\lambda(t)}{\lambda(t)-\ln(R)}\right)^\alpha . \qquad (50)\end{aligned}$$

where α and $\lambda(t)$ are the parameters of the gamma distribution. Based on South African data sources [257, 258, 274, 275], the mean and standard deviation of the gamma distribution in the baseline scenario have been set to 10.6 weeks and 8 weeks respectively (α = 1.7556 and $\lambda(t)$ = 0.1656 for t < 2010), and the R parameter has been set to 0.9. Parameter a has been set to 0.006, the average transmission risk from studies that evaluated the perinatal transmission rate from mothers who started ART prior to conception [257-259] (Table 1.14).

The remaining b_s parameter is estimated by equating expression (50) to the known average perinatal transmission probability that existed in the baseline scenario. This is calculated separately for women who started ART during pregnancy with CD4 <200 (s = 5) and women

who started ART in pregnancy at higher CD4 counts ($s < 5$); based on previous research these average transmission probabilities are assumed to be 0.031 and 0.015 respectively [257, 258, 266-268, 270, 274, 276, 277]. The resulting estimates of the b_s parameter are 0.059 and 0.021 respectively.

It is likely that there has already been some improvement in the average duration of ART, relative to the baseline scenario. The South African 2010 PMTCT guidelines recommended integration of ART provision into PMTCT services [278], which led to more rapid initiation of ART during pregnancy. For example, Van Schalkwyk *et al* [275] found that the median duration of ART prior to delivery increased from 7.7 weeks in the 2008-9 period to 13.1 weeks in 2010 following the introduction of the new guidelines. A similar median of around 12 weeks has been observed in the period following 2010 in the Eastern Cape, and even higher rates of ART uptake were measured from 2012 [279]. Stinson *et al* [280] documented a more substantial difference (about 7 weeks) in the median time to ART initiation when comparing the ART referral model to the integrated ART model. There have also been steady improvements over time in the mean gestational age at first antenatal booking; for example, the Department of Health [139] reports that the proportion of mothers who had their first antenatal visit before 20 weeks gestation has increased from 37.5% in 2010/11 to 50.6% in 2013/14. It is therefore assumed that the mean duration of ART increased by 50% in 2010-12 (relative to the mean duration in the pre-2010 period). This means setting $\lambda(t) = 0.1104$ over the 2010-2012 period, which leads to a 22% reduction in the probability of perinatal transmission from mothers with initial CD4 counts <200 cells/μl. Following the introduction of WHO option B at the start of 2013, it is likely that the delay in ART initiation would have been reduced even further, since the removal of the CD4 restriction would have eliminated the delay associated with CD4 testing. In a best case scenario, we might expect a doubling of the mean duration of ART relative to the pre-2010 period, i.e. an average of 21 weeks of ART, which is what might be expected if the mean gestational age at the first antenatal visit was around 18 weeks and all HIV-positive women were to start ART immediately upon diagnosis. In a more conservative scenario we might expect no improvement over the 50% increase achieved in the 2011-2012 period. To represent the uncertainty surrounding the percentage increase in mean ART duration, we assign a gamma prior distribution with a mean of 70% and a standard deviation of 14% (2.5 and 97.5 percentiles of 45% and 100% respectively).

1.4.1.3 HIV incidence in pregnancy and retesting in late pregnancy

The first antenatal visit is assumed to occur at 23 weeks gestation [10, 281, 282] and delivery at 39 weeks [282], on average, so that the average time in which a woman seronegative at her first visit can acquire HIV before delivery is 20 weeks if a 4-week window period is assumed [283]. The probability that a pregnant woman seronegative at her first antenatal visit acquires HIV before delivery is therefore calculated as the annual HIV incidence rate in pregnant women multiplied by a factor of 0.38 (20/52). The probability that a woman who acquires HIV in late pregnancy transmits HIV perinatally is difficult to determine precisely, and a prior distribution with a mean of 35% has been specified to represent the uncertainty regarding this parameter (Table 1.14). This probability applies if the woman receives no antiretroviral prophylaxis.

In the period up to 2006, there is assumed to have been no retesting prior to delivery of mothers HIV-negative at their first antenatal visit. Recent studies suggest that the proportion

of women testing negative who get tested again in late pregnancy has been steadily increasing over time [284, 285], with the most recent data suggesting a retesting frequency of 46% in 2011 [285]. In a best case scenario, this proportion may rise to 100%, but in a more conservative scenario, this proportion might change relatively little from the rate of 45% assumed for the 2011/2012 period. We assign a beta prior distribution to represent the range of uncertainty around the proportion of women who are offered retesting in late pregnancy, with this beta prior having a mean of 75% and a standard deviation of 12% (2.5. and 97.5 percentiles at 48% and 94% respectively). Women who are diagnosed HIV-positive following retesting are assumed to be as likely to receive short-course ARV prophylaxis and long-term ART as women who are diagnosed at their first antenatal visit.

1.4.2 Postnatal HIV transmission

1.4.2.1 Infant feeding practices up to 2011

Among HIV-negative mothers and undiagnosed HIV-positive mothers, 86.7% are assumed to breastfeed, and in those who breastfeed the duration of breastfeeding is modelled using a Weibull distribution with a median of 18 months and a shape parameter of 2 [10]. All of these women are assumed to practise mixed feeding, as exclusive breastfeeding (EBF) was rare prior to the introduction of PMTCT programmes [10, 286]. Of women who were diagnosed HIV-positive antenatally in the period up to 2011, it is assumed 56% avoided breastfeeding completely [135], 30% practised EBF and 14% practised mixed feeding [287]. HIV-diagnosed women who practised EBF are assumed to have done so for a median of 2 months (up to a maximum of 6 months), after which 30% are assumed to have discontinued breastfeeding completely and the remainder practised mixed feeding (i.e. continued breastfeeding while introducing complementary feeds), for a median of 7 months [287-289]. The median duration of mixed feeding in HIV-diagnosed mothers is assumed to be the same regardless of whether mixed feeding was provided from birth or following a period of EBF.

1.4.2.2 Infant feeding practices after 2011

The benefits of EBF have been increasingly emphasized following the Tshwane declaration [290], with guidelines recommending 6 months of EBF for all mothers (as well as continued mixed feeding after 6 months) and the phasing out of the free provision of formula milk for HIV-positive mothers. The proportion of HIV-diagnosed women who avoid breastfeeding is assumed to have declined from 56% in 2010/11 to 20% in 2013/14, in line with data from a series of national PMTCT surveys [291]. It is also likely that there has been some increase in the median duration of EBF over time, although there are currently no data to determine the extent of this change. We assign a gamma prior distribution to represent the uncertainty regarding the median duration of EBF from 2013, the year in which the impact of the change in infant feeding policy is assumed to reach its maximum. This gamma distribution has a mean of 4 months and a standard deviation of 1 month (2.5 and 97.5 percentiles at 2.29 and 6 months respectively, assuming EBF does not continue for more than 6 months). The mean and standard deviation have thus been chosen so that the lower bound on the confidence interval corresponds to a ‘worst case’ case scenario, in which there is little change relative to the baseline scenario, and the upper bound corresponds to a ‘best case’ scenario, in which the median duration of EBF is consistent with that recommended in national guidelines.

It is also assumed that the proportion of mothers who stop breastfeeding completely (as distinct from introducing solids) at the time of ceasing EBF is likely to have declined from the baseline of 30%. To represent the uncertainty regarding the likely magnitude of the decline, we assign a beta prior distribution to the fraction of mothers discontinuing EBF who stop breastfeeding completely. This distribution has a mean of 15% and a standard deviation of 6% (2.5. and 97.5 percentiles at 5% and 28% respectively). The lower bound of the 95% confidence interval thus corresponds to a 'best case' scenario in which 95% of women continue to breastfeed after introducing solids, while the upper bound corresponds to a 'worst case' scenario in which there is negligible improvement relative to baseline.

1.4.2.3 Postnatal transmission probabilities

Table 1.14 summarizes the assumptions regarding postnatal HIV transmission probabilities, per month of breastfeeding. Exclusive breastfeeding is assumed to be associated with a reduced risk of transmission relative to mixed feeding, while women who seroconvert during breastfeeding are assumed to be at a significantly increased risk of transmitting HIV to their infants. The duration of this period of increased postnatal transmission risk is assumed to be an average of 3 months after the date of HIV acquisition, consistent with the assumed average duration of acute infection (Table 1.5).

Following the revision to the South African PMTCT guidelines in 2010 [278], HIV-positive mothers who breastfed but did start ART were provided with extended nevirapine prophylaxis to administer to their infants during the breastfeeding period. Although there is a lack of data on the uptake of this prophylaxis, it is assumed that 80% of all breastfed children whose HIV-positive mothers are not on ART receive this prophylaxis.

The modelling of the uptake of long-term ART in pregnant HIV-positive women has been described in section 1.2.3. In addition to this, in the period between the start of 2013 and the end of 2014 (prior to adoption of WHO Option B+), women who were not eligible for long-term ART were eligible for short-term ART (triple-drug therapy) for the duration of pregnancy and the breastfeeding period. The rate of short-term ART uptake during pregnancy is assumed to have been the same as the rate of long-term ART uptake in the corresponding year.

The assumption of an 80% reduction in postnatal transmission rates in women on ART (Table 1.14), relative to breastfeeding mothers who are untreated, is calculated as one less the ratio of the average monthly postnatal transmission risk in five studies (0.0018) to the average monthly transmission risk of 0.0097 for untreated mothers, estimated when a similar model was previously fitted to South African data [252]. However, the model of postnatal transmission is simplistic because it implicitly assumes that all mothers who initiate ART during pregnancy remain on ART throughout the breastfeeding period. There is concern that rates of retention in care may be poor in the post-partum period, particularly in the context of WHO option B+ [292, 293]. In a recent study conducted in Cape Town it was found that 28% of mothers who initiated ART during pregnancy dropped out of ART care during the 6 months after delivery [293]. If it were conservatively assumed that all of these women stopped ART for the entire duration of the breastfeeding period, the reduction in postnatal transmission would be only 80% × (1 – 0.28) = 58%. On the other hand, it is possible that the ART adherence interventions described in section 1.3.3 could contribute to improvements in viral suppression in future, and hence lead to further reductions in postnatal transmission

rates. The effect of plasma viral load on perinatal and postnatal transmission rates [294] is similar to that on heterosexual transmission probabilities [91, 193, 194], and hence the 96% reduction in HIV transmission probabilities due to ART in the HPTN 052 trial [195] should – in theory – also be possible in the context of postnatal HIV transmission. A beta distribution is used to represent the uncertainty regarding the future reduction in the postnatal HIV transmission risk due to ART. This distribution has a mean of 0.8 (the same as the baseline value) and a standard deviation of 0.1 (2.5 and 97.5 percentiles at 57% and 95% respectively). The standard deviation has thus been chosen so that the upper and lower limits of the 95% confidence interval correspond to the best case and worst case scenarios respectively.

1.4.3 Paediatric HIV survival

The structure of the paediatric HIV survival model is illustrated in Figure 1.7, and a detailed description of the model of paediatric HIV survival has been published previously [295]. Briefly, HIV-infected children are assumed to progress from an early disease stage to a late disease stage in the absence of ART (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 [296]). HIV-related mortality in untreated children is assumed to occur only in the late disease stage. Children who are infected postnatally are assumed to have a slower rate of progression from early disease to late disease, but after progression to late disease and after ART initiation, age-specific mortality rates are assumed to be the same regardless of timing of transmission.

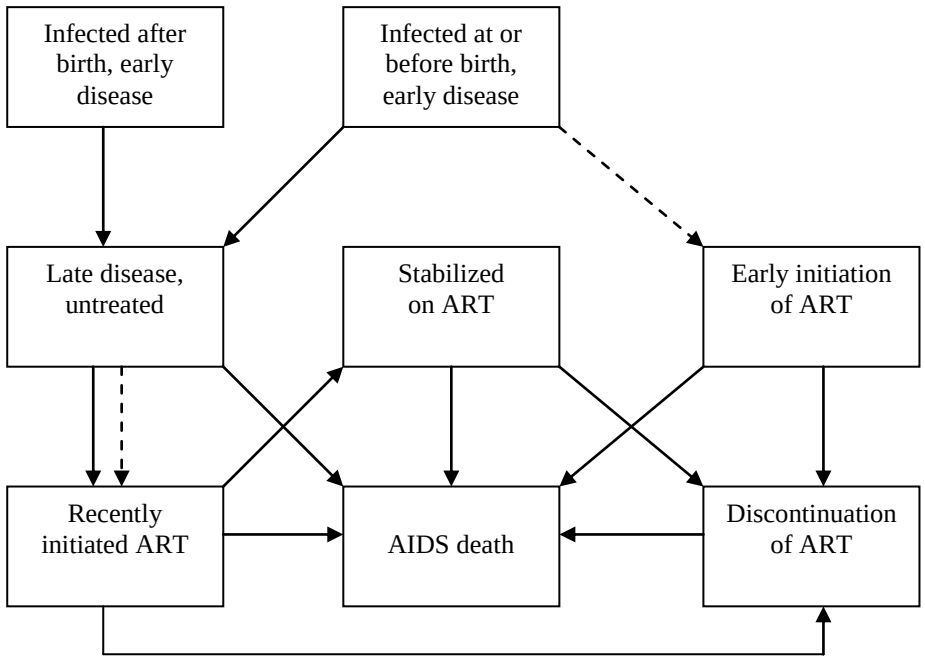

Figure 1.7: Multi-state model of HIV survival in HIV-positive children
All children are assumed to experience non-AIDS mortality rates that vary by age and sex (not shown). Dashed arrows represent ART initiation at 2 months of age, following PCR screening at 6 weeks.

Since the rate of progression to late disease declines as children age, the time to reaching late disease is assumed to follow a Makeham distribution, with the hazard rate in perinatally-infected children aged x being

$$\eta(x) = G_p + \left(H_p \times c^x\right), \tag{51}$$

where G_p is the annual rate of progression in older children, H_p is the excess rate of progression in neonates, and c is the factor by which the excess rate of progression is reduced per year of age. Children who acquired HIV postnatally are assumed to progress to late disease at rate $\theta\eta(x)$, where θ is a constant scaling factor. As these parameters are difficult to determine precisely, we specify prior distributions to represent the uncertainty around their values. The prior distributions and the data sources on which they are based are summarized in Table 1.15.

Table 1.15: Paediatric HIV survival assumptions (ages <10)

Parameter	Symbol	Value	Standard deviation†	Source
Children infected at/before birth				
Annual rate of progression to late disease in older children	G_p	0.40	0.10	θG_p = 0.14 is consistent with rates of progression observed by Charlebois *et al* [297] in children aged ≥1 year
Excess annual rate of progression to late disease in neonates	H_p	2.00	0.25	[298, 299]
Excess progression reduction factor, per year of age	c	0.25	-	[298-301]
Relative rate of progression to late disease if infected after birth	θ	0.35	0.15	[302-305]
Children in late disease, untreated				
Annual rate of AIDS mortality in older children	G_m	0.12	0.03	[306, 307]
Excess annual rate of AIDS mortality in neonates	H_m	3.50	0.35	Based on fitting model to mortality data from children diagnosed with HIV-related symptoms at different ages [307]
Excess mortality reduction factor, per year of age	d	0.05	-	
Relative rate of AIDS mortality in children who started ART after progression to late disease				Based on fitting model to mortality data from IeDEA Southern Africa Collaboration [308]
'High risk' phase	Φ_0	0.95	-	
'Stabilized' phase	Φ_1	0.10	-	
Children who started ART while in early disease				
Relative rate of excess early AIDS mortality	P	0.40	-	Based on fitting model to data from early ART trial [298]

* Standard deviations are shown only for those parameters included in the uncertainty analysis. All prior distributions are assumed to be gamma in form, except for the θ prior, which is assigned a beta distribution (since θ is assumed to be between 0 and 1).

In the absence of ART, children in the late disease stage are assumed to die from AIDS at rate $\mu(x)$ at age x. As this mortality rate appears to decline with increasing age [306, 307], a Makeham distribution is again used to model the time from reaching late disease to death. It is therefore assumed that the AIDS-related mortality rate is of the form

$$\mu(x) = G_m + \left(H_m \times d^x\right), \tag{52}$$

where G_m is the annual rate of mortality that would be expected in older children in late disease, H_m is the excess AIDS mortality rate in neonates, and d is the factor by which this excess mortality risk declines per year of age. Prior distributions to represent the uncertainty around these parameters are summarized in Table 1.15.

Children who start ART after having progressed to late disease are assumed to remain in a 'high risk' phase for an average period of three months after starting ART, if they do not die. After 'stabilizing' on ART, these children are assumed to experience lower mortality rates. The rates of AIDS mortality in the 'high risk' and 'stabilized' states are assumed to be $\Phi_0\mu(x)$ and $\Phi_1\mu(x)$ respectively, and are thus higher in children receiving ART at young ages than in children on ART at older ages. The mortality rate in children who start ART in early disease, $\psi(x)$ at age x, is calculated as

$$\psi(x) = \Phi_1\left(G_m + \left(P \times H_m \times d^x\right)\right), \tag{53}$$

where P is the factor by which the excess early mortality rate is reduced as a result of early ART initiation. Although the model allows for children to interrupt ART (Figure 1.7), there is uncertainty about how much of the loss to follow-up that is reported is actually due to treatment interruptions, and rates of ART interruption have therefore been set to zero for the purpose of this analysis.

The model assumes that a proportion of children born to HIV-positive mothers receive PCR testing for HIV around the time of their 6-week immunization visit. Of these, a proportion of those eligible for ART are assumed to start ART. Mathematically, the number of perinatally-infected infants who start ART at the age of 2 months following PCR screening, is assumed to be

$$S^0(t) = \sum_{s=0}^{2} N_s(2,t)V(t)\pi_s E_s(t)l\,, \tag{54}$$

where $N_s(2, t)$ is the number of perinatally-infected infants at the age of 2 months, in stage s of infection; $V(t)$ is the fraction of children born to HIV-positive mothers who receive PCR testing in year t; π_s is the sensitivity of the PCR in infants in stage s; $E_s(t)$ is the fraction of children who are eligible to receive ART in year t, in stage s of infection; and l is the fraction of ART-eligible diagnosed infants who link to ART care soon after diagnosis. Stages 0 and 1 correspond to infants in early disease who were antenatally PMTCT-unexposed and PMTCT-exposed respectively, and stage 2 corresponds to infants in the late stage of HIV disease (all ART-naïve). The time-dependent parameters are summarized in Table 1.16. Rates of PCR testing are based on public sector statistics [137], adjusted to reflect under-count due to late immunization [309, 310] and over-count due to non-return of test results to caregivers [311-313]. Sensitivity levels have been set at 76%, 81% and 100% for stages 0, 1 and 2 respectively, based on a previous model of perinatal transmission [314], assuming that all infants who are tested for HIV would at least have received NVP prophylaxis postnatally [278]. Although children in late disease have been eligible for ART since 2004 [152], ART eligibility for infants in early disease only became official policy in 2010 [315], with some earlier provision following the 2008 WHO guideline revision [316]. The fraction of eligible, diagnosed infants who link to care has been set to 80% [313].

Table 1.16: 6-week diagnosis and ART eligibility in perinatally-infected infants

	Pre-2004	2004-2006	2006-2007	2007-2008	2008-2009	2009-2010	2010-2011	2011-2012	Post-2012
Fraction tested ($V(t)$)	0.0%	0.0%	8.5%	19.1%	29.5%	40.1%	53.0%	60.8%	68.9%
Early ART eligibility ($E_0(t)$, $E_1(t)$)	0.0%	0.0%	0.0%	0.0%	20.0%	60.0%	100.0%	100.0%	100.0%
Late ART eligibility ($E_2(t)$)	0.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

If HIV is not diagnosed soon after birth, it is assumed to be diagnosed only at a later age, after the child has progressed to late disease. Similar to the approach adopted in modelling ART initiation in adults, the approach is to calculate the rate of ART initiation in children in late disease from the reported total numbers of children starting ART in month t ($S(t)$), after subtracting the model estimate of the number of children starting ART due to diagnosis at the time of 6-week screening. Similar to equation (19),

$$\begin{aligned} S(t) - S^0(t) &= \sum_{x=0}^{179} \sum_{s=2,4} N_s(x,t) \int_0^1 \rho(t) \exp\left(-\left(\mu(x) + \delta(x,t) + \rho(t)\right) u\right) du \\ &\approx \sum_{x=0}^{179} \sum_{s=2,4} N_s(x,t) \rho(t) \left(1 - 0.5\left(\mu(x) + \delta(x,t) + \rho(t)\right)\right) \end{aligned} \quad (55)$$

where $S(t)$ is the total number of children (aged <15) starting ART in month t; $N_4(x, t)$ is the number of postnatally-infected children aged x months, who are in late disease but ART-naive; $\rho(t)$ is the monthly rate of ART initiation in month t, in children who are in late disease; and $\delta(x,t)$ is the rate of non-AIDS mortality at age x in year t. Equation (55) is a quadratic in $\rho(t)$, and can thus be solved on a monthly basis, for those periods in which absolute numbers of children starting ART are specified. The assumed total numbers of children starting ART are shown in Table 1.8 for each year up to mid-2014 (monthly numbers are calculated by dividing these annual totals by 12).

In the period after mid-2014, the rate of ART initiation is calculated based on assumed average times to ART initiation (in months) after progressing to late disease. The baseline results suggest that over the 2013-14 period the average treatment delay ($1/\rho(t)$) was approximately 45 months, and this same parameter value has been assumed in the post-2014 period.

Transitions from the paediatric HIV disease categories to the adult HIV disease stages are modelled on the assumption that late disease is equivalent to a CD4 count of <200 cells/μl in older children, to be consistent with the definition of late disease [296]. This means that on reaching age 10, children who are in the late HIV stage and ART-naïve get moved into the CD4 <200/μl category, and 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. 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.

1.5 Demographic assumptions

At the time of producing the model, the individual-level data from the 2011 Census had yet to be released and analysed. Most of the current demographic assumptions are thus the same as those in the ASSA2008 AIDS and Demographic model [317], with some adjustments (described below). The model will be updated to take into account the improved demographic estimates once these are finalized, but the impact of these changes on the epidemiological outputs (where expressed as rates and proportions) is expected to be limited.

1.5.1 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.

1.5.2 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 [318]. 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

$$F(x,t)\Gamma(s)^q, \tag{56}$$

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 1.1.9). 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 [319, 320]. 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

$$F(x,t)Y(1,s,d)^q \tag{57}$$

where $Y(1,s,d)$ is the relative frequency of sex in the cohort of individuals who started ART with a CD4 count of *s*, *d* years previously (as defined in equation (30)). 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, consistent with what has been observed in a number of studies of the incidence of pregnancy in Africa [69, 259, 321, 322].

For the purpose of calculating the HIV-negative fertility rate, $F(x,t)$, we define $N^i_{a,s,d}(x,t)$ 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

$$\overline{F}(x,t) = \frac{F(x,t)\left[N^1_{0,0,0}(x,t) + \sum_{s=1}^{5} N^1_{0,s,0}(x,t)\Gamma(s)^q + \sum_{s,d} N^1_{1,s,d}(x,t)Y(1,s,d)^q \right]}{\sum_{i,a,s,d} N^i_{a,s,d}(x,t)} \tag{58}$$

and this equation is then used to solve for $F(x,t)$, given the $\overline{F}(x,t)$ value. 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 fertility, converging toward an ultimate set of fertility rates. These assumptions about declining future non-HIV fertility 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.

1.5.3 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.

1.5.4 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 [318]. 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 rest of the South African population.

2. Statistical analysis

The model is calibrated to historic HIV prevalence data using a two-step Bayesian procedure: the first step involves calibrating the model to adult HIV prevalence data and the second involves calibrating the model to paediatric HIV prevalence data. Once the calibration is completed, the uncertainty analysis to explore the effect of potential future determinants of HIV incidence is performed. Although prior distributions are specified for both calibration steps and for the uncertainty analysis, each step considers a different group of priors, with all other parameter values being held constant. The sections that follow describe the different steps in more detail.

2.1 Calibration step 1: Model fitting to adult HIV prevalence data

2.1.1 Prior distributions

The parameters that are allowed to vary in the first calibration step, and the corresponding prior distributions chosen to represent the uncertainty around these parameters, are summarized in Table 2.1. Most of these prior distributions have been explained previously (see section references in last column), except in the case of the initial HIV prevalence in women in the high risk group (this parameter 'seeds' the epidemic). 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 [323], 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 [324]. 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 [325].

Table 2.1: Prior distributions for parameters considered in calibration to adult HIV prevalence data

	Prior distribution	Prior mean, std deviation	Ref.
Mean of non-spousal sex age adjustment function	Gamma (49, 1.4)	35, 5	1.1.2
Std deviation of non-spousal sex age adjustment function	Gamma (18.8, 1.44)	13, 3	1.1.2
Relative rate of partner acquisition in low-risk men	Uniform (0, 1)	0.50, 0.29	1.1.2
Relative rate of partner acquisition in low-risk women	Uniform (0, 1)	0.50, 0.29	1.1.2
Reduction in unprotected sex after HIV diagnosis	Beta (5.90, 2.77)	0.68, 0.15	1.1.9
Female-to-male transmission probability in short-term/ non-spousal partnerships	Gamma (5.68, 468)	0.008, 0.003	1.3.1
Male-to-female transmission probability in short-term/ non-spousal partnerships	Gamma (5.68, 468)	0.012, 0.005	1.3.1
Female-to-male transmission probability in long-term/ spousal partnerships	Gamma (7.09, 3540)	0.002, 0.00075	1.3.1
Male-to-female transmission probability in long-term/ spousal partnerships	Gamma (7.09, 3540)	0.002, 0.00075	1.3.1
Initial HIV prevalence in high risk women, ages 15-49	Uniform (0, 0.002)	0.001, 0.00058	2.1.1

2.1.2 Likelihood definition

The model is calibrated to three HIV prevalence data sources: antenatal clinic survey data, household survey data and sex worker survey data. The likelihood for all three data sources is simply the product of the likelihood calculated for each individual data source, as detailed below.

2.1.2.1 Likelihood definition for antenatal clinic survey data

The model is fitted to antenatal HIV prevalence data from national surveys that have been conducted from 1997 to 2012 (survey data collected prior to 1997 have not been included, as these early antenatal surveys were based on convenience samples and reported 95% confidence intervals did not include survey design effects). We include HIV prevalence estimates for 5 age groups (15-19, 20-24, 25-29, 30-34 and 35-39).

Suppose that $H_{x,t}(\boldsymbol{\varphi})$ is the model estimate of HIV prevalence in pregnant women aged x to $x + 4$, in year t, where the vector $\boldsymbol{\varphi}$ represents the values of the model input parameters. This is calculated from equation (58) as

$$H_{x,t}(\boldsymbol{\varphi}) = 1 - \frac{\sum_{j=x}^{x+4} F(j,t) N^{1}_{0,0,0}(j,t)}{\sum_{j=x}^{x+4} \overline{F}(j,t) \sum_{i,a,s,d} N^{i}_{a,s,d}(j,t)}. \qquad (59)$$

The corresponding prevalence of HIV actually measured in the antenatal survey is represented by $y_{x,t}$. It is assumed that if $\boldsymbol{\varphi}$ 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 arises due to the exclusion of women receiving private antenatal care from the sample and other behavioural factors. 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 (representing the error that may arise due to the assumption that the antenatal bias is constant over time and constant with respect to age). More formally, it is assumed that

$$\log\left(\frac{y_{x,t}}{1-y_{x,t}}\right) = \log\left(\frac{H_{x,t}(\boldsymbol{\varphi})}{1-H_{x,t}(\boldsymbol{\varphi})}\right) + b + m_{x,t} + \varepsilon_{x,t}, \tag{60}$$

where b is the antenatal bias parameter, $m_{x,t} \sim N\left(0, \sigma_m^2\right)$ and $\varepsilon_{x,t} \sim N\left(0, \sigma_{x,t}^2\right)$. 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 $\boldsymbol{\varphi}$, the antenatal bias parameter is estimated using the formula

$$\hat{b} = \frac{1}{80}\sum_{x}\sum_{t=1997}^{2012}\left(\log\left(\frac{y_{x,t}}{1-y_{x,t}}\right) - \log\left(\frac{H_{x,t}(\boldsymbol{\varphi})}{1-H_{x,t}(\boldsymbol{\varphi})}\right)\right). \tag{61}$$

The $\sigma_{x,t}^2$ values are estimated from the 95% confidence intervals that have been published for the various survey estimates. Once these $\sigma_{x,t}^2$ values have been obtained, the σ_m^2 parameter is estimated using the formula

$$\hat{\sigma}_m^2 = \frac{1}{80}\sum_{x}\sum_{t}\left(\log\left(\frac{y_{x,t}}{1-y_{x,t}}\right) - \log\left(\frac{H_{x,t}(\boldsymbol{\varphi})}{1-H_{x,t}(\boldsymbol{\varphi})}\right) - \hat{b}\right)^2 - \sigma_{x,t}^2. \tag{62}$$

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

$$L(\mathbf{y} \mid \boldsymbol{\varphi}) = \prod_{x}\prod_{t}\left(2\pi\left(\hat{\sigma}_m^2 + \sigma_{x,t}^2\right)\right)^{-0.5} \exp\left[-\frac{\left(\text{logit}\left(y_{x,t}\right) - \text{logit}\left(H_{x,t}(\boldsymbol{\varphi})\right) - \hat{b}\right)^2}{2\left(\hat{\sigma}_m^2 + \sigma_{x,t}^2\right)}\right], \tag{63}$$

where $\mathbf{y}$ represents the matrix of $y_{x,t}$ values, across age bands 15-19 to 35-39, and across calendar years 1997 to 2012.

2.1.2.2 Likelihood definition for household survey 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 [7], 2008 [8] and 2012 [326]. HIV prevalence levels in each survey are estimated by 5-year age group (from 15-19 up to 55-59) and by sex. 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 [327, 328], in which it is assumed that household prevalence data provide an unbiased estimate of HIV prevalence in the general population. The model error term is omitted because it is not necessary if the survey estimates are truly unbiased. However, even if the household survey estimates were biased, the 95% confidence intervals around the household prevalence estimates are very wide, relative to the confidence intervals around the antenatal survey estimates, and the model error would therefore be small relative to the survey error.

2.1.2.3 Likelihood definition for sex worker survey data

Table 2.2 summarizes the HIV prevalence data from surveys of sex workers, which have been used in model calibration. Unlike the antenatal surveys and the household surveys, the surveys of commercial sex workers have been conducted in specific communities, and cannot be considered representative of sex workers nationally. It is therefore necessary to allow for potential heterogeneity in HIV prevalence between commercial sex workers surveyed in different communities, using different sampling techniques. We use the notation t_i, n_i and p_i to represent the time of the i^{th} survey, the sample size of the i^{th} survey and the HIV prevalence measured in the i^{th} survey respectively.

Table 2.2: Studies of HIV prevalence in South African sex workers

Study	Location	Year (t_i)	Sample size (n_i)	Prevalence of HIV (p_i)
Ramjee *et al* [180]	Truck stops between Durban and Johannesburg	1996	416	50%
Dunkle *et al* [40]	Johannesburg	1996	295	46.4%
Leggett *et al* [329]	Johannesburg, Durban, Cape Town	1998*	249	42.6%
Williams *et al* [5]	Carletonville	1998	121	68.6%
Ndhlovu *et al* [330]	Carletonville	2001	101	78%
van Loggerenberg *et al* [43]	Durban	2004	775	59.6%
Luseno & Wechsberg [46]	Pretoria	2005	276	59.1%
Greener *et al* [331]	Durban	2012	349	66.9%

* The study date was not stated, and has been assumed to be three years prior to the date of publication, based on average publication delays in other STI prevalence surveys [332].

For the purpose of defining the likelihood function, suppose that $C(t_i, \boldsymbol{\varphi})$ represents the model estimate of HIV prevalence in sex workers in the year of the i^{th} study, where the vector $\boldsymbol{\varphi}$ again represents the values of the model input parameters. The difference between the logit-transformed model estimate of HIV prevalence and the logit-transformed observed prevalence is assumed to be composed of a 'random effect' (representing the true difference in HIV prevalence between the HIV prevalence in sex workers nationally and the prevalence in sex workers in the community being studied) and a 'random error' term (representing the binomial sampling variation due to the limited sample size). More formally, it is assumed that

$$\log\left(\frac{p_i}{1-p_i}\right) = \log\left(\frac{C(t_i,\boldsymbol{\varphi})}{1-C(t_i,\boldsymbol{\varphi})}\right) + r_i + \varepsilon_i, \tag{64}$$

where $r_i \sim N(0,\sigma_r^2)$ and $\varepsilon_i \sim N(0,\sigma_i^2)$. The variance of the random error term, σ_i^2, is estimated by noting that the sample variance of p_i is $p_i(1-p_i)/n_i$, and after logit-transformation, the Taylor approximation to the value of the sample variance of logit(p_i) is

$$\hat{\sigma}_i^2 = \frac{1}{n_i p_i (1-p_i)}. \tag{65}$$

Hence the variance of the random effects term can be estimated using the equation

$$\hat{\sigma}_r^2 = \frac{1}{8}\sum_{i=1}^{8}\left(\log\left(\frac{p_i}{1-p_i}\right) - \log\left(\frac{C(t_i,\boldsymbol{\varphi})}{1-C(t_i,\boldsymbol{\varphi})}\right)\right)^2 - \frac{1}{n_i p_i (1-p_i)}. \tag{66}$$

The likelihood function in respect of the commercial sex worker prevalence data is then

$$L(\mathbf{p} \mid \boldsymbol{\varphi}) = \prod_{i=1}^{5}\left(2\pi\left(\hat{\sigma}_r^2 + \hat{\sigma}_i^2\right)\right)^{-0.5} \exp\left[-\frac{\left(\text{logit}\left(p_i\right) - \text{logit}\left(C(t_i,\boldsymbol{\varphi})\right)\right)^2}{2\left(\hat{\sigma}_r^2 + \hat{\sigma}_i^2\right)}\right], \tag{67}$$

where **p** is the vector of p_i values.

2.1.3 Posterior simulation

The posterior distribution was simulated numerically using Incremental Mixture Importance Sampling (IMIS) [333]. Following the recommendations of Raftery and Bao [333], an initial set of 10 000 parameter combinations was randomly drawn from the prior distributions in Table 2.1 and the likelihood was calculated for each. Importance sampling was then used to draw a second sample of 1 000 parameter combinations from the region of the parameter space with the highest likelihood values, and the procedure was repeated iteratively, updating the importance sampling distribution at each step to reflect the region of the parameter space with the highest likelihood values, until the algorithm converged on a posterior sample that was sufficiently heterogeneous. A posterior sample of 1 000 parameter combinations was drawn, and means and 95% confidence intervals were calculated from this sample.

2.1.4 Results of calibration to adult HIV prevalence data

Table 2.3 compares the prior and posterior means for the 10 parameters that are allowed to vary when fitting the model to the adult HIV prevalence 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.

Table 2.3: Comparison of prior and posterior distributions for parameters considered in calibration to adult HIV prevalence data

Parameter	Prior distribution (mean, 95% CI)	Posterior distribution (mean, 95% CI)
Mean of non-spousal sex age adjustment function	35.0 (25.9-45.5)	38.3 (360.0-40.5)
Std deviation of non-spousal sex age adjustment function	13.0 (7.8, 19.5)	19.1 (17.1-21.2)
Relative rate of partner acquisition in low-risk men	0.50 (0.025-0.975)	0.43 (0.24-0.67)
Relative rate of partner acquisition in low-risk women	0.50 (0.025-0.975)	0.14 (0.11-0.18)
Reduction in unprotected sex after HIV diagnosis	0.68 (0.36-0.93)	0.46 (0.33-0.58)
Female-to-male transmission probability in short-term/ non-spousal partnerships	0.0080 (0.0032-0.0149)	0.0080 (0.0071-0.0090)
Male-to-female transmission probability in short-term/ non-spousal partnerships	0.0120 (0.0043-0.0236)	0.0190 (0.0147-0.0240)
Female-to-male transmission probability in long-term/ spousal partnerships	0.0020 (0.0008-0.0037)	0.0014 (0.0009-0.0022)
Male-to-female transmission probability in long-term/ spousal partnerships	0.002 (0.0008-0.0037)	0.0042 (0.0027-0.0058)
Initial HIV prevalence in high risk women, ages 15-49	0.00100 (0.00005-0.00195)	0.00186 (0.00155-0.00199)

Figure 2.1 shows the calibration of the model to the antenatal survey HIV prevalence data (although the data from the 1990-1996 surveys were not included in the likelihood definition, they are included here as a validation of the model). The posterior mean model estimates of antenatal HIV prevalence are generally consistent with the survey data, although the model slightly over-estimates HIV prevalence in pregnant women aged 20-24. The model also provides a reasonably good fit to the HSRC prevalence survey data (Figure 2.2). The model does not provide a good fit to the HIV prevalence data from sex workers (Figure 2.3), with the early surveys tending to measure a higher prevalence than estimated by the model, and the more recent surveys estimating a lower prevalence than the model. However, none of the sex worker surveys is nationally representative, and some degree of divergence is therefore to be expected.

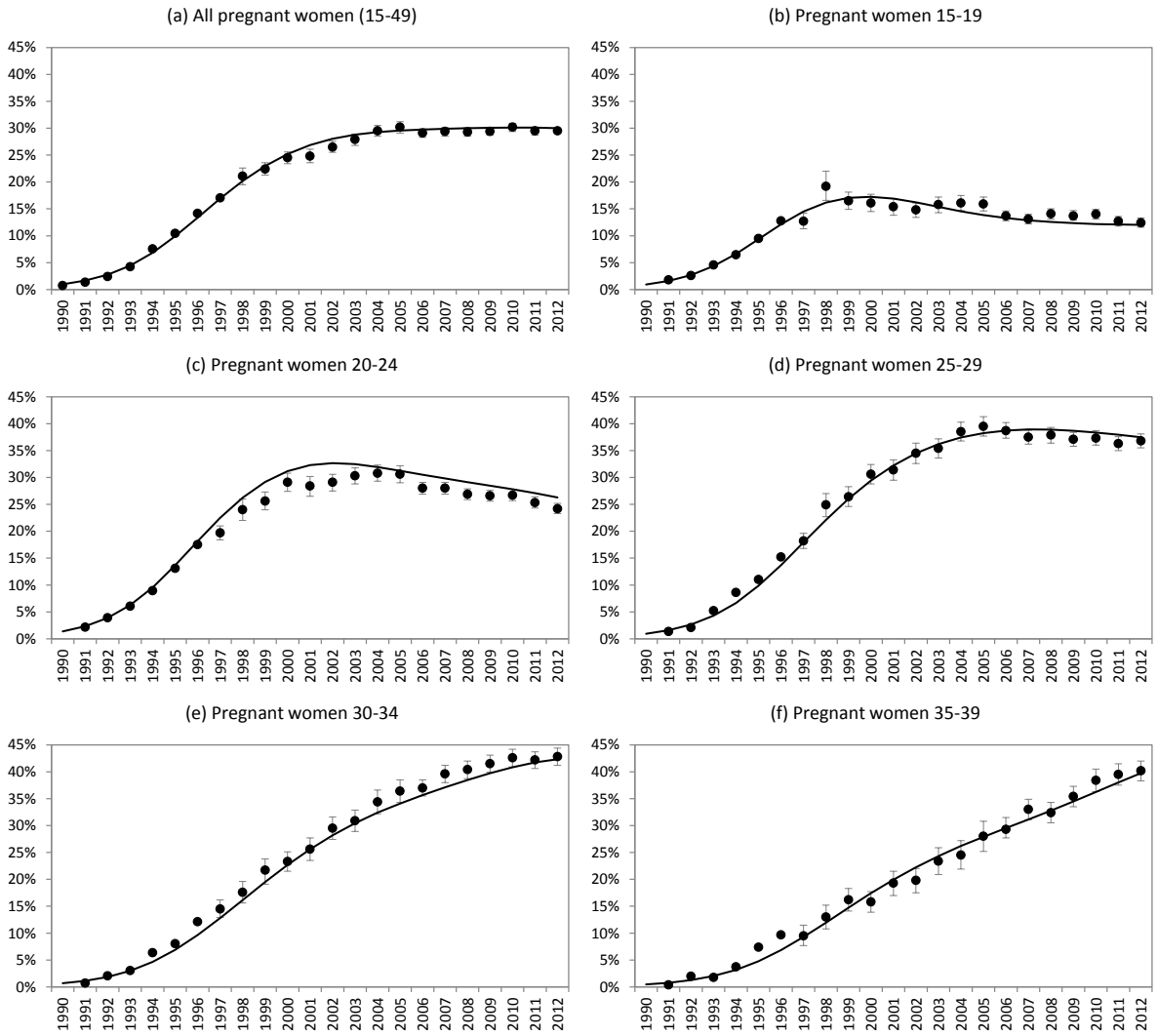

Figure 2.1: HIV prevalence levels in pregnant women attending public antenatal clinics

Dots represent HIV prevalence levels reported in surveys conducted from 1990-2011 (the 1998 data were adjusted to correct an error in the provincial weights in that year). Solid lines represent the posterior mean model estimates of HIV prevalence in pregnant women, after adjusting for antenatal bias.

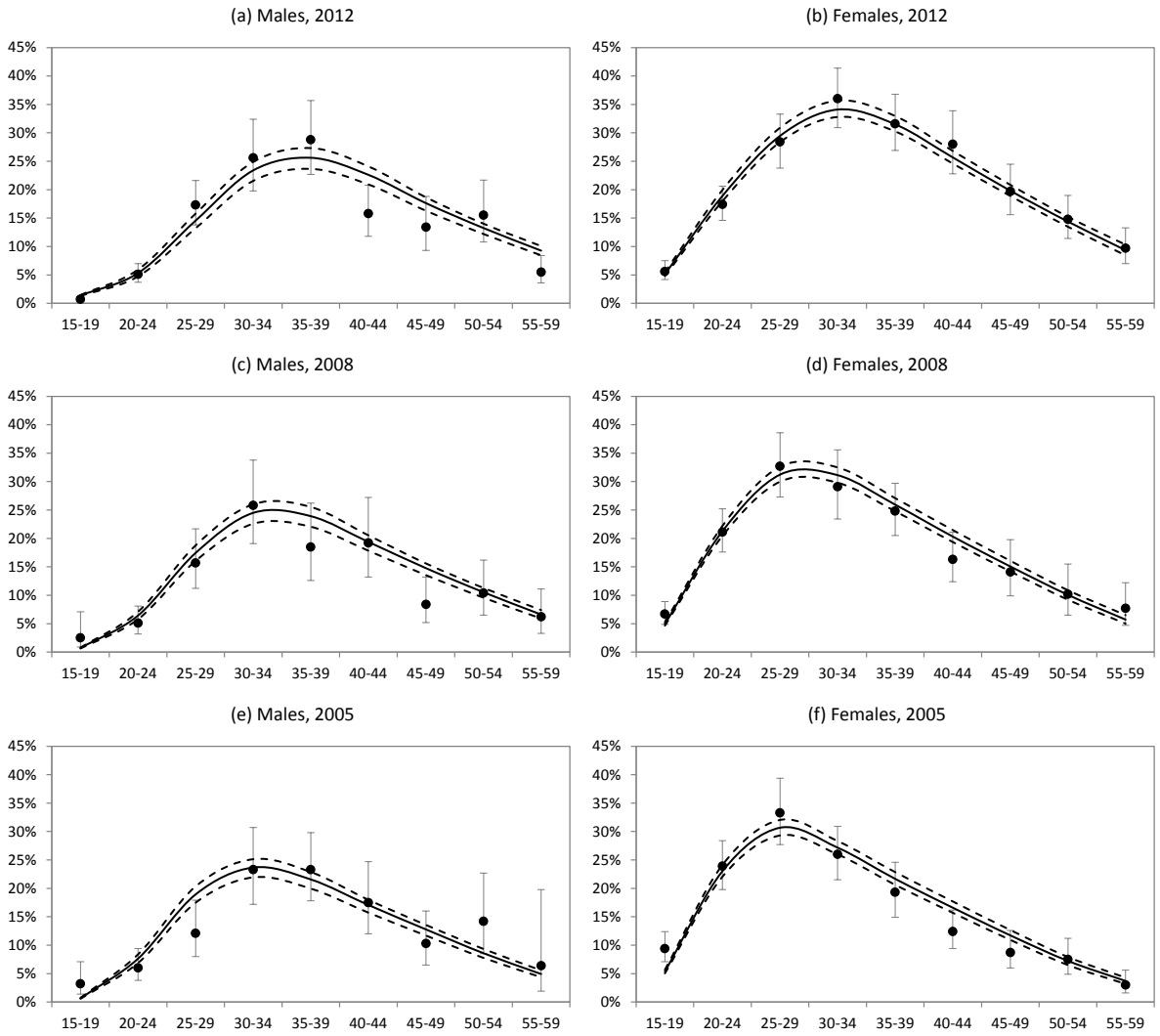

Figure 2.2: HIV prevalence levels in the general population

Dots represent HSRC survey prevalence estimates, together with 95% confidence intervals. Solid lines represent the posterior mean model estimates of HIV prevalence, and dashed lines represent the 95% confidence intervals around these estimates.

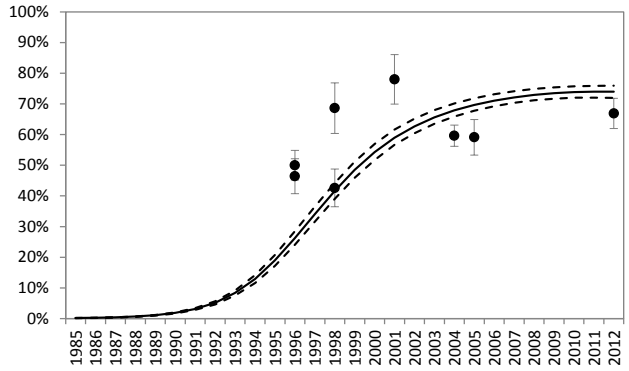

Figure 2.3: HIV prevalence in female sex workers

Dots represent survey prevalence estimates. Solid lines represent the posterior mean model estimates of HIV prevalence, and dashed lines represent the 95% confidence intervals around these estimates.

2.2 Calibration step 2: Model fitting to paediatric HIV prevalence data

2.2.1 Prior distributions

Prior distributions have been specified for 10 of the mother-to-child transmission and paediatric HIV survival parameters. Table 2.4 summarizes the prior distributions; the justification for the choice of prior distributions has been presented in section 1.4 (the sections in which the individual parameters are explained are listed in the last column).

Table 2.4: Prior distributions for parameters considered in calibration to paediatric HIV prevalence data

Parameter	Prior distribution	Prior mean, std deviation	Ref.
Transmission rate at/before birth, from acutely-infected women with no ARV prophylaxis	Beta (12.09, 22.46)	0.35, 0.08	1.4.1
% reduction in perinatal MTCT if mother receives single-dose nevirapine + short-course zidovudine	Beta (42.50, 7.500)	0.85, 0.05	1.4.1
Probability of MTCT from chronically-infected mothers, per year of mixed feeding	Beta (26.83, 164.8)	0.14, 0.025	1.4.2
Probability of MTCT from acutely- infected mothers, per month of mixed feeding	Beta (23.73, 124.6)	0.16, 0.03	1.4.2
Ratio of postnatal transmission risk per month of EBF to postnatal transmission risk per month of mixed feeding	Beta (5.056, 5.056)	0.50, 0.15	1.4.2
Children infected at/before birth			
Annual rate of progression to late disease in older children	Gamma (16.00, 40.00)	0.40, 0.10	1.4.3
Excess annual rate of progression to late disease in neonates	Gamma (64.00, 32.00)	2.00, 0.25	1.4.3
Relative rate of progression to late disease if infected after birth	Beta (3.189, 5.922)	0.35, 0.15	1.4.3
Children in late disease, untreated			
Annual rate of AIDS mortality in older children	Gamma (16.00, 133.3)	0.12, 0.03	1.4.3
Excess annual rate of AIDS mortality in neonates	Gamma (100.0, 28.57)	3.50, 0.35	1.4.3

2.2.2 Likelihood function

The method used to calculate the likelihood in respect of the paediatric HIV prevalence data has been described previously [252], but has been updated to include data from the 2012 national household survey [16]. As with adults, we have relied on data from the 2005, 2008 and 2012 household surveys conducted by the HSRC. For each survey year, sex and age group, the difference between the model estimate of prevalence and survey estimate of prevalence, on the logit scale, is assumed to be normally distributed with zero mean and standard deviation calculated from the reported 95% confidence interval. The likelihood calculation is thus similar to that described in section 2.1.2.1, but with the omission of the bias and model error terms.

2.2.3 Posterior simulation

As for adults, the posterior distribution is simulated numerically using Incremental Mixture Importance Sampling (IMIS) [333]. The procedure is the same as described in section 2.1.3.

2.2.4 Results of calibration to paediatric HIV prevalence data

Table 2.5 compares the prior and posterior means for the 10 parameters that are allowed to vary when fitting the model to the paediatric HIV prevalence data. In most cases the posterior and prior distributions are similar, although the posterior estimate of the annual probability of transmission from breastfeeding mothers (not on ART or in the acute stage of infection) is substantially lower than the prior mean. The posterior estimates of the mortality parameters also tend to be greater than the prior means, although the differences are not substantial.

Table 2.5: Comparison of prior and posterior distributions for parameters considered in calibration to paediatric HIV prevalence data

Parameter	Prior distribution (mean, 95% CI)	Posterior distribution (mean, 95% CI)
Transmission rate at/before birth, from acutely-infected women with no ARV prophylaxis	0.350 (0.203-0.514)	0.326 (0.187-0.479)
% reduction in perinatal MTCT if mother receives single-dose nevirapine + short-course zidovudine	85.0% (74.0-93.4%)	86.3% (75.8-94.4%)
Probability of MTCT from chronically-infected mothers, per year of mixed feeding	0.140 (0.095-0.192)	0.103 (0.072-0.139)
Probability of MTCT from acutely- infected mothers, per month of mixed feeding	0.16 (0.106-0.223)	0.147 (0.099-0.202)
Ratio of postnatal transmission risk per month of EBF to postnatal transmission risk per month of mixed feeding	0.500 (0.213-0.787)	0.503 (0.216-0.780)
Children infected at/before birth		
Annual rate of progression to late disease in older children	0.400 (0.229-0.619)	0.428 (0.255-0.638)
Excess annual rate of progression to late disease in neonates	2.00 (1.54-2.52)	2.11 (1.56-2.62)
Relative rate of progression to late disease if infected after birth	0.350 (0.096-0.666)	0.362 (0.147-0.666)
Children in late disease, untreated		
Annual rate of AIDS mortality in older children	0.120 (0.069-0.186)	0.143 (0.098-0.203)
Excess annual rate of AIDS mortality in neonates	3.50 (2.85-4.22)	3.64 (2.95-4.39)

Figure 2.4(a) shows the calibration of the model to the paediatric HIV prevalence data. Overall, the model over-estimates the prevalence of HIV observed in the 2012 survey, but is roughly consistent with the levels of prevalence in the 2005 and 2008 surveys. The model has also been validated against a number of data sources that have not been considered in the definition of the likelihood. Figure 2.4(b) shows that the model estimates of perinatal transmission rates (at/before birth) from mothers who are diagnosed positive during pregnancy are consistent with PCR-positive rates in infants tested under the age of 2 months, after 2007 [334]. However, in the period up to 2007, PCR testing was less routine and screening tended to occur more frequently in sick infants who were suspected of having HIV, which may explain why the model tends to under-estimate the PCR-positive rates in this period. The model is nevertheless consistent with early studies that achieved more representative PCR screening of infants born to HIV-positive mothers [335, 336].

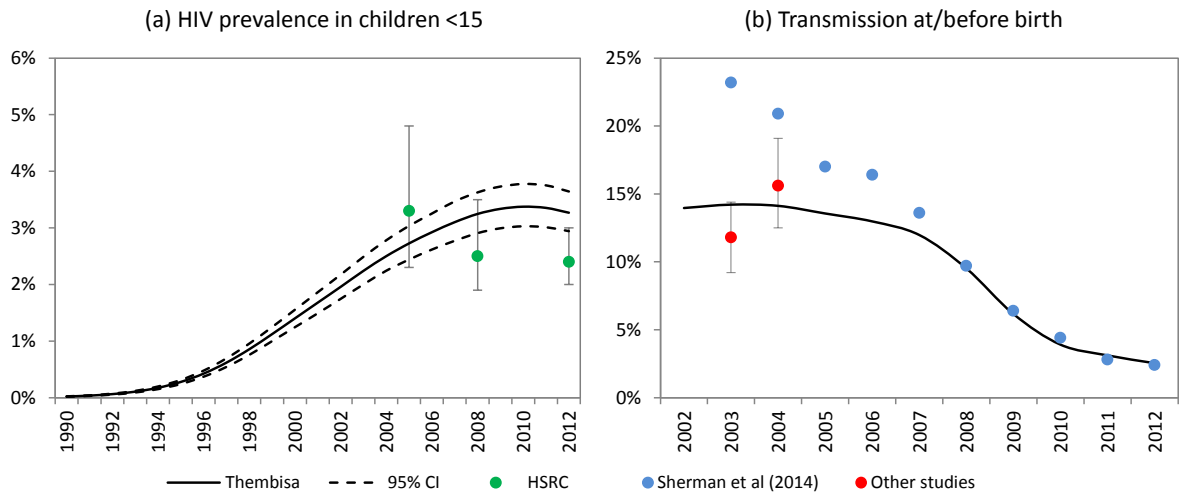

Figure 2.4: Paediatric model calibration and validation
Solid lines represent posterior means and dashed lines represent posterior 95% confidence intervals. Panel b relates to mother-infant pairs in which the mother's HIV status has been diagnosed (i.e. excluding undiagnosed mothers). The data in panel b are from routine reporting of PCR screening in the first 2 months of life [334] and from surveys conducted at the time of single-dose nevirapine prophylaxis [335, 336].

The model has also been validated by comparing the modelled age distribution of children starting ART with the reported age distribution of children starting ART nationally [172] (Figure 2.5). Although these data have not been used in defining the likelihood function, the model is remarkably consistent with the observed age distribution, except in 2012. The discrepancy in 2012 might be due to the extension of ART eligibility to all children under the age of 5 years in 2012 [154], which has not been modelled in Thembisa.

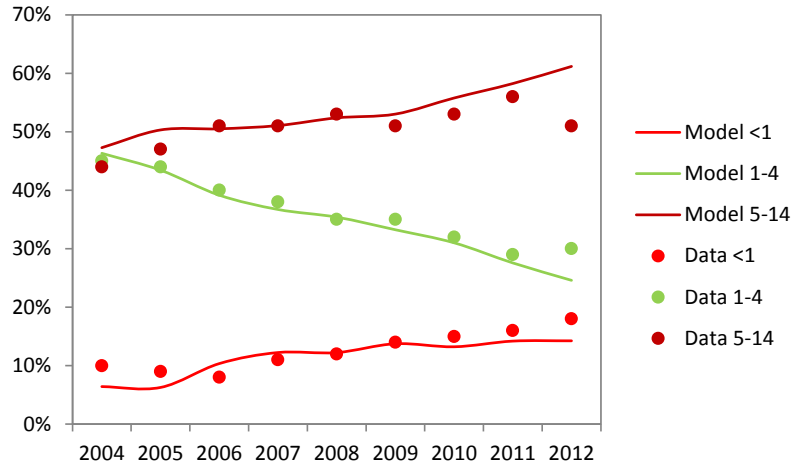

Figure 2.5: Fractions of children starting ART in different age groups
Solid lines represent posterior means. Dots represent data from the national ART monitoring system [172].

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