# Thembisa version 3.2: A model for evaluating the impact of HIV/AIDS in South Africa

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Appendix A: Mathematical approach to modelling sexual behaviour

# 1. Introduction

Thembisa is a mathematical model of the HIV epidemic in South Africa. The purpose of this document is to provide a technical description of the model and the methods used to calibrate the model. The focus of this report is limited to the national model; descriptions of the calibration procedures for the provincial models will be published separately.

This document describes version 3.2 of the Thembisa model, and is similar in structure to the previous report that described version 2.4 of the model [1]. Briefly, the main changes to the previous version of the model are as follows:

- The process of calibrating the model to recorded mortality data has been revised substantially, with four additional years of data, and allowance for differential completeness of vital registration by age and sex.
- The model has been extended to allow for bias in the IeDEA-SA data that were previously used to set the ART mortality parameters, and has also been extended to allow for changes in HIV virulence over time.
- The new model includes men who have sex with men (MSM); the previous model considered only heterosexual transmission and mother-to-child transmission.
- Assumptions about mother-to-child transmission rates have been updated substantially, following a systematic review performed for the UNAIDS Reference Group on Estimates, Models and Projections [2].
- The model of medical male circumcision (MMC) uptake has been revised, with uptake being assumed to depend on age [3] rather than sexual risk behaviour.
- The model has been recalibrated to new HIV prevalence data, including data from surveys conducted in South African MSM.
- The time to sexual debut is modelled using a log-logistic distribution instead of a Weibull distribution, as the former provides a better fit to survey data.

The model is deterministic and compartmental. Due to the large number of parameters in the Thembisa model, it is not possible to retain separate symbols for every parameter in the mathematical descriptions that follow. However, we have attempted to be consistent, as far as possible, in the use of indexing variables. The index variables are listed in Table 1.1, together with an explanation of the possible values for each index variable.

Table 1.1: Index variables in Thembisa

Symbol	Description	Value	Definition
а	ART status	0	ART-naïve
		1	On ART or previously treated
d	Time since	0	ART-naïve
	ART	1	1 <sup>st</sup> 6 months after ART start
	initiation	2	7-18 months after ART start
		3	19-30 months after ART start
		4	31-42 months after ART start
		5	>42 months after ART start
g	Sex	1	Male
		2	Female
<i>i</i> *	Risk group	1	High risk
		2	Low risk
j	Partner	1	High risk
	risk group	2	Low risk
l	Marital	0	Unmarried/short-term relationship
	status or	1	Married/long-term relationship
	relationship	2	Sex worker/sex worker-client relationship
	type	3	MSM/same-sex short-term relationship
r	Circumcision	0	Uncircumcised
	status	1	Circumcised
S	HIV stage	0	Uninfected
	or baseline	1	Acute HIV
	CD4 count	2	HIV-positive, CD4 $\geq$ 500 (after acute infection)
		3	HIV-positive, CD4 350-499
		4	HIV-positive, CD4 200-349
		5	HIV-positive, CD4 <200
t	Year	-	
$v^*$	HIV testing	0	Never tested for HIV
	history	1	Lasted tested HIV-negative
		2	Diagnosed HIV-positive
x	Age	0-90+	Age at last birthday (at start of the year)
У	Partner age	10-90+	Age at last birthday (at start of the year)

\* Note that in section 3.2 we use the symbol i instead of v to refer to the HIV testing history, in order to avoid confusion with the fraction of pregnant women who are tested for HIV.

# 2. 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 unmarried men are further stratified according to whether they engage in samesex activity. There are thus three types of relationship considered in the model: long-term relationships (marital/cohabiting), short-term relationships (non-marital and non-cohabiting) and 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 2.1(a) 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). It is implicitly assumed that women only engage in heterosexual relationships (although this assumption is obviously incorrect, female samesex relationships carry negligible HIV transmission risk and are therefore not considered in the model).

Figure 2.1(b) illustrates the possible transitions for men in the high risk group (the same transitions are defined for men in the low risk group). Unmarried men are divided into those who are heterosexual (having sex only with women) and those who are bisexual (having sex with both men and women). For the sake of simplicity, we do not distinguish 'gay' and 'bisexual' men, as the vast majority of South African men who have sex with men (MSM) report having had sex with women [4-7]. It is also assumed, in the interests of simplicity, that bisexual men only enter into long-term relationships with female partners, as surveys of South African MSM show that only about 20% report being in marital/cohabiting relationships [5, 8]. Once bisexual men enter into long-term relationships with female partners, they are assumed to cease sexual activity with other men. Although this assumption is unrealistic, it has the advantage of ensuring that the age profile of MSM matches the very young age profile observed in various surveys of MSM [5-9].

#### (a) High risk females



(b) High risk males



Figure 2.1: Transitions between relationship states

Table 2.1 summarizes the major sexual behaviour parameters. These parameters are explained in more detail in subsequent sections. 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 [10-12].

Table 2.1: Sexual behaviour assumptions

Parameter	Men*	Women	Reference
Initial % of population in high risk group	35%	25%	[10-12]
Median age at sexual debut: high risk	17.5	16.5	Calibrated
Log-logistic shape parameter for time to sexual debut	6.0	7.0	f Canorated
Relative rate of short-term partnership formation in married high	0.33	0.14	Calibrated
risk adults (compared to unmarried high risk)			(see [13])
Relative rate of short-term partnership formation in unmarried low	0.37	0.16	Calibrated
risk adults (compared to unmarried high risk)			(Thembisa v2.5)
Mean age difference between partners in short-term relationships	-	3	L [14-18]
Standard deviation of age difference in short-term relationships	-	3	$\int \left[ 1 + 10 \right]$
Mean age difference between partners in long-term relationships	-	6	ر ا
Standard deviation of age difference in long-term relationships	-	5	$\int [1]$
Assortativeness of sexual mixing	-	0.47	Calibrated, [13]

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

## 2.1 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 follows a log-logistic distribution in high risk individuals. Separate log-logistic parameters are specified for males and females (Table 2.1). We assume that at each age the rate of starting sexual activity in the low risk group is 0.58 times that in the high risk group [20-25]. 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 [16, 26, 27], as demonstrated in Figure 2.2. Rates of sexual debut are assumed to be the same for heterosexual and bisexual men [28, 29].



Figure 2.2: 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).

### 2.2 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

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

where the  $\lambda$  and  $\alpha$  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 [30]. The mean and standard deviation of the gamma density have been set to 38.71 and 19.38 respectively, and  $\lambda$ and  $\alpha$  parameters are calculated to be consistent with these values (values are set at 0.0764 and 2.195 respectively). These values were chosen to yield the best model fit to the age pattern of HIV infection and HIV mortality in previous model simulations. For unmarried individuals in the low risk group, the rate of non-marital partnership is assumed to be

$$c_{g,2,0}(x) = L_g c_{g,1,0}(x), \qquad (2.2)$$

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.  $L_1$  and  $L_2$  values have been set to 0.3719 and 0.1621, the values previously estimated in the calibration of Thembisa version 2.5 (Table 2.1\_.

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

$$c_{g,1,1}(x) = R_g c_{g,1,0}(x), \qquad (2.3)$$

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 2.1), based on values previously fitted using the STI-HIV Interaction model [13]. 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 in Appendix A. Rates of non-marital relationship formation are assumed to be the same in heterosexual and bisexual men, in the absence of reliable data comparing the two. Although this is probably not realistic, it ensures that overall coital frequencies are the same in heterosexual and bisexual men, which is consistent with studies that have found coital frequencies in MSM [31] similar to the coital frequencies we have assumed for heterosexual men.

# 2.3 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 [30], 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 [32], applying a multiple of 2 to the crude rates to reflect known biases in divorce statistics [33]. Age-specific rates of marriage and divorce are shown in Table 2.3.

					Annual rate	
	Annua	l rate of	Annua	l rate of	of sex worker	Proportion
Age	mar	riage	div	orce	contact in	of sex workers
U		e			unmarried	at each age
	Males	Females	Males	Females	high risk males	U
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%
22	0.0475	0.0807	0.0188	0.0201	8.44	4 7%
23	0.0674	0.0879	0.0211	0.0215	12.01	4.8%
25	0.0074	0.0073	0.0211	0.0220	16.27	4.070
25	0.0000	0.0943	0.0230	0.0233	21.14	4.9%
20	0.1000	0.0775	0.0240	0.0237	21.14	4.970
27	0.1202	0.1022	0.0257	0.0241	20.40	4.870
20	0.1302	0.1023	0.0202	0.0244	32.03	4.770
29	0.1309	0.1008	0.0202	0.0245	37.00	4.5%
21	0.1297	0.0980	0.0239	0.0240	45.14	4.2%
22	0.1290	0.0949	0.0255	0.0244	48.21	4.0%
32 22	0.1278	0.0918	0.0230	0.0239	52.12	5.7% 2.4%
33 24	0.1268	0.0891	0.0245	0.0230	50.50	5.4%
34 25	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	0.118/	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%

Table 2.3: Age-specific behavioural parameters

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

# 2.4 Commercial sex

Sexually experienced heterosexual 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) [34] and that the effect of age is determined by a gamma scaling function with parameters  $\lambda_1$  and  $\alpha_1$ . The formula used to determine the rate of male contact with sex workers is thus

$$w_{l}(x) = K \frac{\lambda_{1}^{\alpha_{1}}(x-10)^{\alpha_{1}-1} \exp(-\lambda_{1}(x-10))}{\lambda_{1}^{\alpha_{1}}(21.5-10)^{\alpha_{1}-1} \exp(-\lambda_{1}(21.5-10))} 0.25^{l}$$
  
=  $K \times \left(\frac{x-10}{11.5}\right)^{\alpha_{1}-1} \exp(-\lambda_{1}(x-21.5)) \times 0.25^{l}$ , (2.4)

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 [35].) The parameters  $\lambda_1$  and  $\alpha_1$  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 [36, 37] as well as a more recent survey (Tim Lane, personal communication [38]). 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 [39], assuming that the average sex worker has 750 client contacts per annum [40-47]. (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 2.3). Bisexual men and 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 2.1), 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 2.3), based on surveys of South African sex workers [14, 42, 44-51]. Women are assumed to retire from commercial sex at a rate of 0.33 per annum [42, 43, 45].

## 2.5 Preferences regarding partner risk group

Mixing between the high and low risk groups is determined by a 'degree of assortative mixing' parameter,  $\varepsilon$ . 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) [52]. The  $\varepsilon$  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 [13]. The same mixing parameter is assumed to apply in the selection of heterosexual and same-sex partners.

#### 2.6 Preferences regarding partner age

The symbol  $f_{g,l}(y | x)$  represents the probability that, for an individual of sex g and age x, in a relationship of type l, the partner's age is y. We model female age preferences regarding married partner ages using 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

$$f_{2,1}(y \mid x) \equiv \int_{y}^{y+1} \frac{(\lambda_{2}(x) + \xi(x))^{\alpha_{2}(x)} (t - \min(x))^{\alpha_{2}(x) - 1}}{\Gamma(\alpha_{2}(x)) \exp((\lambda_{2}(x) + \xi(x))(t - \min(x)))} dt, \qquad (2.5)$$

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  $x \ge 17$  (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 nonmarital 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 [14-18]. 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 female partners from different ages  $(f_{1,l}(y | x))$  are calculated to be consistent with the distributions specified for women, taking into account the relative rates of partnership formation at different ages, and relative numbers of men and women at different ages. Further mathematical detail is provided in Appendix A. Appendix A also describes the approach to modelling age mixing patterns in MSM  $(f_{1,4}(y | x))$ .

# 2.7 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 [16, 18, 53, 54] and an average non-marital relationship duration of 6 months [30]. 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 [30].

#### 2.8 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 [55]. 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,  $\gamma^*$ , 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  $\gamma_{2,l}(x,t)$ :

$$\ln\left(\frac{\gamma_{2,l}(x,t)}{1-\gamma_{2,l}(x,t)}\right) = \ln\left(\frac{\gamma^{*}}{1-\gamma^{*}}\right) + \chi_{l} + \nu_{l}(x-20) + \varsigma_{l}(t)$$
(2.6)

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;

 $\exp(v_l)$  = 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*.

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. In mathematical terms,

$$\varsigma_{l}(t) = \kappa_{l}^{1} + \left(\kappa_{l}^{2} - \kappa_{l}^{1}\right) \left(1 - 0.5^{\left(t/M_{l}^{1}\right)^{Q_{l}}}\right) - \left(\kappa_{l}^{2} - \kappa_{l}^{3}\right) \left(1 - 0.5^{\left(t/M_{l}^{2}\right)^{2Q_{l}}}\right)$$
(2.7)

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

 $\kappa_l^1$  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;

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

 $M_1^2$  = 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 2.4. 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 [13], 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.

8			
Parameter	Symbol	Value	Source
'Baseline' condom usage	$\gamma^{*}$	0.104	[19], calibrated
OR for condom use in marital relationships (1998)	$\exp(\chi_1)$	0.46	[19]
OR for condom use in commercial sex (1998)	$\exp(\chi_2)$	6.0	[14, 48]
OR for condom use per year increase in age	$\exp(v_l)$	0.975†	[19, 56]
OR for condom use in 1985 (relative to 1998) Marital and non-marital relationships	$\exp(\kappa_1^1)$	0.07	[57]
Commercial sex	$\exp(\kappa_2^1)$	0.17	[37]
Maximum OR for condom use (relative to 1998)	I ( 2)		
Non-marital relationships	$\exp(\kappa_0^2)$	4.6	] [16, 17, 27],
Marital relationships	$\exp(\kappa_1^2)$	2.16	∫ calibrated
Commercial sex	$\exp(\kappa_2^2)$	3.8	[51, 58], 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
Marital relationships	$\exp(\kappa_1^3)$	1.47	$\int \operatorname{root} \operatorname{of} \exp(\kappa_l^2)$
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

 Table 2.4: Condom usage assumptions in period up to 2012

 $\dagger$  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:

$$M_{l}^{1} = 13 \left\{ \left( \ln \left[ \kappa_{l}^{3} + \left( \kappa_{l}^{2} - \kappa_{l}^{3} \right) 0.5^{\left( 13/M_{l}^{2} \right)^{2Q_{l}}} \right] - \ln \left( \kappa_{l}^{2} - \kappa_{l}^{1} \right) \right) / \ln (0.5) \right\}^{-1/Q_{l}}$$
(2.8)

The resulting trends in women's condom use, by relationship type, are shown in Figure 2.3. 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

$$\gamma_{1,l}(x,t) = \sum_{y} f_{1,l}(y \mid x) \gamma_{2,l}(y,t), \qquad (2.9)$$

where  $f_{1,l}(y | x)$  is the probability that a female partner is aged y, if the male partner is aged x. The rate of condom use among clients of sex workers is the same as that estimated for sex workers, with no age dependency. It is also assumed that the rate of condom use in same-sex relationships is the same as that in heterosexual relationships [28, 29, 59].



Figure 2.3: Trends in proportion of sex acts that are protected among 20-year old HIVnegative 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 2.10 and 2.11).

### 2.9 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  $\geq$ 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  $\geq$ 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 [60-66]; results of the individual studies are shown in Figure 2.4.



Figure 2.4: 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/ $\mu$ l category is taken as the average of that in the 350-499/ $\mu$ l and 200-349/ $\mu$ l 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 [67], who were found to be significantly more likely to abstain from sex at lower CD4 counts (OR 1.70 for CD4 counts of 200-499 and 2.39 for CD4 counts of <200). It is also assumed that the frequency at which men visit sex workers is reduced by the same factors as those used to reduce coital frequencies in short-term and long-term relationships.

## 2.10 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 [68-71], 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 61%, based on a random effects meta-analysis of the estimates in Table 2.5). We have set the assumed reduction in the fraction of sex acts that are unprotected to 58%, based on the average value estimated in the calibration of Thembisa version 2.5, and roughly consistent with the 61% estimated from the studies summarized in Table 2.5.

developing countri	165			
Study	Location	Definition of risk behaviour	Controls	Effect on risk behaviour in HIV-diagnosed (OR, 95% CI)
Marlow et al	South	No condom use at 14	HIV-negative	0.59 (0.48-0.72)
[72]	Africa	weeks postpartum	women	
Ngubane et al	South	No condom use	HIV-negative	
[73]	Africa	0-12 mo postpartum	women	0.58 (0.47-0.72)
		13-24 mo postpartum		0.62 (0.44-0.87)
Morroni <i>et al</i>	South	No condom use at	Women at FP/	0.28 (0.16-0.51)
[/4] Maagaci et al	Africa	last sex	S I I Clinics	0.05 (0.02 0.12)
Mwangi <i>et al</i>	Kenya	Any unprotected sex		0.05 (0.02-0.12)
[73]		With a partiel who was	wele niv-	
		unknown UIV status	undiagnosod	
Voluntary HIV 1	Konya	Any upprotected sex	Individuals who	0 60 (0 40 0 80)
Counselling and	Kenya, Tanzania	with primary partner	tested HIV-	0.00 (0.40-0.07)
Testing Efficacy	Trinidad	Any unprotected sex	negative	
Study Group	Timudud	with non-primary	negative	
[76]		partner: Women		0.90 (0.49-1.66)
[,0]		Men		0.19 (0.05-0.81)
Müller <i>et al</i>	Thailand	<100% condom use in	Individuals who	0.15 (0.09-0.24)
[77]		last 3 sex acts	were HIV-	0.12 (0.03 0.2.)
[]			positive but	
			undiagnosed	
Cremin et al	Zimbabwe	Inconsistent condom	Individuals who	
[70]		use with regular	were HIV-	
		partners: Women	positive but	0.53 (0.24-1.16)
		Men	undiagnosed	0.61 (0.25-1.47)
Pooled OR				0.39 (0.28-0.56)

Table 2.5: Studies evaluating the effect of HIV diagnosis on sexual risk behaviour in developing countries

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

### 2.11 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 [78], 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 2.9, 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 [79-81].

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

$$1 - \left(1 - \gamma_{g,l}(x,t)\right) \left(1 - \delta(t)\right) \left(1 - h\right), \qquad (2.11)$$

where  $\gamma_{g,l}(x,t)$  is the corresponding rate of condom use in HIV-negative individuals (discussed in section 2.8),  $\delta(t)$  represents the reduction in unprotected sex following diagnosis (discussed in section 2.10), 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 metaanalysis [82], 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.

#### 2.12 Same-sex relationships

It is assumed that at the time of beginning sexual activity, 5% of men enter the 'bisexual, unmarried' group and the remainder enter the 'heterosexual, unmarried' group. This 5% assumption is based on the results of a household survey conducted in two South African provinces, which used computer-assisted interview techniques to obtain sensitive estimates of the fraction of men who had ever engaged in sex with other men [4]. Bisexual men are assumed to form 70% of their short-term relationships with other men and the remaining 30% with women. 69% is the average fraction of MSM who report *only* engaging in sex with men in the last 6 months, across three South African studies [5-7]. Although this may be an underestimate of the fraction of partners who are male (since those who reported having sex with women were also having sex with men), it could also be an over-estimate if MSM who have less frequent sex with men are less likely to be included in the sample (recent sex with other men was a condition for inclusion in the three cited studies).

# 3. 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  $\geq$ 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 [83]. 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 3.1.



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

# 3.1 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

$$\lambda_{g,s}(x) = \lambda_s \sigma^{g-1} (1+k)^{(x-30)/10} E^{t-1999}, \qquad (3.1)$$

where  $\lambda_s$  is the rate that applies in men aged 30,  $\varpi$  is the factor by which HIV disease progression is adjusted in women, k is the proportional increase in the rate of disease progression per 10-year increase in age, and E is the factor by which the rate is adjusted per year as a result of changes in HIV virulence. 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

$$\mu_{g,s}(x) = \mu_s \overline{\omega}^{g-1} (1+k)^{(x-30)/10}, \qquad (3.2)$$

where  $\mu_s$  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 (except in respect of the HIV evolution parameter). HIV-positive women tend to have lower viral loads [84-86] and lower rates of CD4 decline [87] than HIV-positive men, and studies suggest a lower mortality rate in HIV-positive women than in HIV-positive men in the pre-ART era [86, 88-90]. To represent the uncertainty regarding the  $\varpi$  parameter, a gamma prior distribution has been assigned, with a mean of 0.96 and standard deviation of 0.05 [91].

Evidence suggests that increasing age is associated with both increasing rates of CD4 decline [92, 93] and increasing mortality in HIV-positive adults [94-97]. To represent the uncertainty around the *k* parameter, a gamma prior with a mean of 0.18 and standard deviation of 0.06 has been assigned [91]. A gamma prior has also been assigned to represent the uncertainty regarding the overall mean HIV survival time (mean 12 years, standard deviation 1 year), and this is used to determine  $\lambda_s$  and  $\mu_s$  parameters (corresponding prior means are shown in Table 3.1) [91]. Assumptions about the relative lengths of time spent in different CD4 stages were determined by calibrating the model to cross-sectional surveys of CD4 distributions in HIV-positive adults [98-104], 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 [83].

HIV virulence may be changing as a result of HIV evolution; recent studies from Uganda and Botswana suggest that there have been substantial reductions in HIV virulence over time [105, 106]. It is also possible that HIV virulence may have changed as a result of improvements in tuberculosis prevention, screening and treatment (for example, isoniazid preventive therapy for HIV-positive individuals and tuberculosis case finding in HIV-positive individuals [107]). However, evidence from high-income countries generally suggests a shift towards *increased* HIV virulence over time [108, 109]. Given the inconsistent estimates from the literature, a gamma prior has been assigned to represent the uncertainty in the *E* parameter, with a mean of 1 and a standard deviation of 0.0065 [91].

Table J.I. I diameters by III v disease sta	Table 3.1:	Parameters	by HIV	disease	stage
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· · · ·	A		CD4	range		
Parameter	Acute	500	350-	200-	<200	Source
	ΠIV	300+	499	349	<200	
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* ( $\mu_s$ )	0.00	0.00	0.00	0.033†	0.254†	Calibrated
Annual incidence of OIs, in absence of ART						[110, 111]
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	[112-114]
Annual male HIV mortality after ART initiation,						
by baseline CD4‡						
1 <sup>st</sup> 6 months of ART	-	0.0002	0.0016	0.0146	0.2554	[115]
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‡						
1 <sup>st</sup> 6 months of ART	-	0.0001	0.0016	0.0159	0.2072	[115]
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 in 1999, and adjustments for age sex and year are made in the process of calibrating the model to reported death data. † Prior means corresponding to average untreated survival of 12 years. ‡ Parameters are adjusted to take into account age effects, effects of increasing baseline CD4 counts over time and effects of bias in the data source (the IeDEA-SA data are likely to under-estimate the true mortality rate at early ART durations [91]). OI = opportunistic infection.

#### 3.2 HIV testing and diagnosis

As shown in Figure 3.1, 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*):

$$\tau_{g,i,s}(x,t) = b(t)A_g(x,t)r_i + \Omega_s d_i(t) + F_{g,s}(x,t)v_i(t)$$
(3.3)

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;  $\Omega_s$  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  $v_i(t)$  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

$$A_{g}(x,t) = B_{g}(t) \left(\frac{x}{25}\right)^{\alpha_{g}-1} \exp\left(-\sigma_{g}(x-25)\right),$$
(3.4)

where  $B_g(t)$  is a time-dependent sex adjustment factor, and  $\alpha_g$  and  $\sigma_g$  are coefficients for the effect of age on the rate of HIV test uptake. The parameterization of the model is described in detail elsewhere [116]. 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 [16, 17, 117], 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 [118, 119] and observed increases in rates of testing in previously-tested individuals [49, 120, 121]. The assumed incidence of OIs by HIV stage ( $\Omega_s$ ) is shown in Table 3.1, and the assumed proportions of OIs tested for HIV are shown in Table 3.2.

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%         [122]         5%         2.5%           2002-03         15.6%         [123, 124]         5%         2.5%           2003-04         31.3%         5%         3.6%           2004-05         42.0%         [125]         8%         [126]         12.6%           2005-06         54.5%         [127]         20%         [128]         29.1%           2007-08         84.0%         [131]         40%         [128, 132]         35.5%         [133]‡           2008-09         89.0%         [134]         45%         [128, 132]         44.5%         [135]‡           2009-10         93.0%         50%         [137]         64.1%         [138]           2011-12         98.0%         [139]         60%         75.4%         [138]           2012-13         98.0%         65%         75.9%         75.9%	Voor	Antenatal testing $(v_i(t))$		Testing of (	OI patients $(d_i(t))$	Linkage to ART in pregnancy $(l_2(s,t))$		
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Teal	Rate	Sources	Rate	Sources	Rate	Sources	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Pre-1999	0.0%		5%		0.0%		
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	1999-00	0.9%		5%		0.0%		
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	2000-01	2.9%		5%		1.9%		
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	2001-02	7.5%	[122]	5%		2.5%		
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	2002-03	15.6%	[123, 124]	5%		2.5%		
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	2003-04	31.3%		5%		3.6%		
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	2004-05	42.0%	[125]	8%	[126]	12.6%		
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	2005-06	54.5%	[127]	20%	[128]	22.6%	[129]‡	
2007-08       84.0%       [131]       40%       [128, 132]       35.5%       [133]‡         2008-09       89.0%       [134]       45%       [128, 132]       44.5%       [135]‡         2009-10       93.0%       50%       [128]       55.0%         2010-11       97.0%       [136]       55%       [137]       64.1%       [138]         2011-12       98.0%       [139]       60%       75.4%       [138]         2012-13       98.0%       65%       75.9%       1100	2006-07	72.2%	[130]	31%	[128]	29.1%		
2008-09       89.0%       [134]       45%       [128, 132]       44.5%       [135]‡         2009-10       93.0%       50%       [128]       55.0%       [138]         2010-11       97.0%       [136]       55%       [137]       64.1%       [138]         2011-12       98.0%       [139]       60%       75.4%       [138]         2012-13       98.0%       65%       75.9%       1100	2007-08	84.0%	[131]	40%	[128, 132]	35.5%	[133]‡	
2009-10       93.0%       50%       [128]       55.0%         2010-11       97.0%       [136]       55%       [137]       64.1%       [138]         2011-12       98.0%       [139]       60%       75.4%       [138]         2012-13       98.0%       65%       75.9%       110]	2008-09	89.0%	[134]	45%	[128, 132]	44.5%	[135]‡	
2010-11       97.0%       [136]       55%       [137]       64.1%       [138]         2011-12       98.0%       [139]       60%       75.4%       [138]         2012-13       98.0%       65%       75.9%       110]	2009-10	93.0%		50%	[128]	55.0%		
2011-12       98.0%       [139]       60%       75.4%       [138]         2012-13       98.0%       65%       75.9%	2010-11	97.0%	[136]	55%	[137]	64.1%	[138]	
2012-13 98.0% 65% 75.9%	2011-12	98.0%	[139]	60%		75.4%	[138]	
	2012-13	98.0%		65%		75.9%		
2013-14 98.0% 70% 76.3% [140]	2013-14	98.0%		70%		76.3%	[140]	
2014-15 98.0% 75% 91.2% [140]	2014-15	98.0%		75%		91.2%	[140]	
2015-16 98.0%* 80%† 93.0% [140]	2015-16	98.0%*		80%†		93.0%	[140]	

Table 3.2: Assumed proportions of patients tested for HIV and linked to ART

\* Rates are assumed to remain constant at 98% after 2015. † 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), over the four-year period from mid-2012 to mid-2016, is 0.287. 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. This rate is assumed to apply in each future year from mid-2016 onward.

#### **3.3 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 3.3 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 [141-144] – 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 [145-147], and these adjustments are necessary to bring the model estimates in line with reported fractions of ART initiators in the CD4 200-349 category [148].

Table 3.3: Proportions of adult patients assumed to be eligible to receive lifelong ART

	2000-	2003-	2009-	2010-	2011-	2012-	2014-	2015-	Post-
	$2003^{*}$	2009	2010	2011	2012	2014	2015	2016	2016
WHO stage IV or CD4 <200	100%	100%	100%	100%	100%	100%	100%	100%	100%
Pulmonary TB, CD4 200-349	10%	10%	50%	100%	100%	100%	100%	100%	100%
WHO stage III, CD4 350+	0%	0%	0%	0%	0%	100%	100%	100%	100%
Pregnant women, CD4 200-349	10%	10%	50%	100%	100%	100%	100%	100%	100%
Pregnant women, CD4 350+	0%	0%	0%	0%	0%	0%	50%	100%	100%
Other patients, CD4 200-349	10%	10%	10%	20%	80%	100%	100%	100%	100%
Other patients, CD4 350-499	0%	0%	0%	0%	0%	0%	50%	100%	100%
Other patients, CD4 500+	0%	0%	0%	0%	0%	0%	0%	0%	100%†

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. † Except in 2016/17 (80%).

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

$$S_{g}^{0}(t) = \sum_{i=0}^{1} \sum_{s=2}^{5} \sum_{x=15}^{90} N_{g,i,s}(x,t) \left\{ b(t)A_{g}(x,t)r_{i}l_{0}(s,t) + \Omega_{s}d_{i}(t)l_{1}(s,t) \right\} + \sum_{i=0}^{2} \sum_{s=2}^{5} \sum_{x=15}^{49} N_{g,i,s}(x,t)F_{g,s}(x,t)v_{i}(t)l_{2}(s,t)$$
(3.5)

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 (3.3)). Although the calculation is presented as an annual total for ease of comparison with equation (3.3), 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.

#### 3.3.1 Linkage to ART after diagnosis during pregnancy

The assumed fractions of ART-eligible pregnant women who start ART during pregnancy are shown in Table 3.2. Assumptions for the early years are based on studies in the Western Cape [129, 133, 135], 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 [138]. 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. Based on data from the DHIS [140], it is assumed that coverage increased to 93% in 2015/16 and remains at this level in subsequent years.

#### 3.3.2 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 [149-151]. In one Cape Town study the rate of linkage in OI patients was found to be similar to that in pregnant patients [135]. 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 ( $l_2(s,t)$ ) (Table 3.2).

# 3.3.3 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 [152]. Restricting attention to those studies conducted in South Africa, the median proportion of patients who received CD4 testing following HIV diagnosis was around 75% and the median proportion of those receiving CD4 testing who collected their test results was around 80%. Of those who were determined to be ART-eligible, the average proportion who started ART was around 67%. This suggests that of all individuals who are newly diagnosed and ART-eligible, the proportion who actually start ART within a few months of diagnosis is only about 40% (0.75  $\times$  0.80  $\times$  0.67). 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 [135]. We have therefore set the  $l_0(s,t)$  parameters for all years to be half of the corresponding rates assumed for OI patients.

# 3.3.4 ART initiation in previously-diagnosed adults who did not link to ART soon after diagnosis, up to mid-2017

In the period up to mid-2017, 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-2017,  $S_g(t)$  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 (3.5) 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  $<200/\mu$ l 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. When 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 [153], and are consistent with the relative rates at which individuals enrolled in pre-ART care return for regular CD4 testing [87, 145].) We wish to estimate the monthly rate at which previously-diagnosed individuals in the CD4 <200/µl category initiate ART,  $\rho_{e}(t)$ . We estimate this by noting that

00.5

$$S_{g}(t) - S_{g}^{0}(t) = \sum_{x=15}^{90} \sum_{s=1}^{5} N_{g,s}(x,t) \int_{0}^{1} \rho_{g}(t) J_{s}(t) \exp\left(-\left(\mu_{g,s}(x,t) + \rho_{g}(t) J_{s}(t)\right)u\right) du$$
  
$$\approx \sum_{x=15}^{90} \sum_{s=1}^{5} N_{g,s}(x,t) \rho_{g}(t) J_{s}(t) \left(1 - 0.5\left(\mu_{g,s}(x,t) + \rho_{g}(t) J_{s}(t)\right)\right)$$
(3.6)

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 3.4. 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 [154]. 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 [138, 155]. To estimate the number of new initiates in each period from the reported numbers of current patients, we have modelled the change over time in the number of new ART initiates using Bayesian B-splines, with the model being fitted to the reported totals; a more detailed description is provided elsewhere [156]. The model has been fitted separately for each province, and the results presented in Table 3.4 are the aggregated totals for the whole country.

	$M_{op}(15)$	Woman $(15)$	Children (<15)	Implied ART delay $(1/\rho(t))$	
	Men (13+)	women (13+)	Children (<13)	Men (15+)	Women (15+)
Pre-2000	0	0	0	-	-
2000-01	3309	4187	457	167.5	211.7
2001-02	3885	4916	547	189.3	249.2
2002-03	4569	5782	657	203.8	280.2
2003-04	10486	14481	1961	100.5	134.0
2004-05	21408	41440	6183	59.2	55.5
2005-06	35717	69521	10185	53.5	45.2
2006-07	61410	117959	17758	35.8	28.9
2007-08	79263	154150	23233	32.1	23.4
2008-09	106103	199404	30789	23.4	16.6
2009-10	142921	255630	34546	15.7	11.6
2010-11	178639	341503	39215	11.8	7.5
2011-12	176543	344911	32728	21.6	13.3
2012-13	184419	339526	27647	24.7	12.7
2013-14	165661	305706	21992	25.5	10.7
2014-15	151133	280209	18011	40.0	29.2
2015-16	130440	243881	13779	-	-
2016-17	117862	222093	11246	-	-

Table 3.4: Assumed annual numbers of patients starting ART in South Africa, and implied average treatment delays in previously-diagnosed patients with CD4 counts  $<200 \text{ cells}/\mu l$ 

# 3.3.5 ART initiation in previously-diagnosed adults who did not link to ART soon after diagnosis, after mid-2017

Because we do not yet have data on the absolute numbers starting ART after mid-2017, we specify the  $\rho_{e}(t)$  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  $(1/\rho_{p}(t))$ . The average delays implied by our assumed absolute numbers are shown in the last two columns of Table 3.4. Our simulations suggest that in both men and women with CD4 counts of <200 cells/µl, this average delay increased roughly four-fold between 2010/11 and 2014/15, 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 3.3.1-3.3.3), which are difficult to determine precisely. (Results for the 2015-17 period are not shown because they are highly uncertain.) For the period after 2021, we assume an average treatment delay of 18 months and 36 months in women and men respectively who have CD4 counts <200 cells/µl, roughly consistent with the average delay over the period from mid-2012 to mid-2015. In the period up to 2021, the delays are interpolated between the rates shown in Table 3.4 and these ultimate rates.

# 3.4 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 3.1 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 [115]. 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 HIVrelated 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 [157]. 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 3.1 and the theoretical minimum is reduced by a factor of  $\exp(-m\rho_{g}(t^{-}))$  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/ $\mu$ l, 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. To represent the uncertainty regarding the *m* scaling parameter, a gamma prior has been assigned, with a mean of 7.5 and standard deviation of 3.5 [91]. 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.

In addition, the mortality assumptions are adjusted to take into account likely bias in the IeDEA-SA data. This bias arises mainly because the IeDEA-SA cohorts do not constitute a representative sample of all ART services in South Africa; IeDEA-SA cohorts are almost all located in urban areas, and most have support from academic partners and NGOs. This means that the mortality rates in those cohorts are likely to be lower than the national average. However, the bias may become less substantial at longer treatment durations, as patients frequently discontinue ART or move to different services, though their vital status can still be tracked through the South African vital registration system. In addition, the IeDEA-SA data

may *over-state* the true mortality rate in the longest duration category, i.e. durations >42 months (Table 3.1). This is because the average follow-up duration in the IeDEA-SA cohorts is short, which means that follow-up times in the >42 month category are likely to be biased towards those individuals with relatively short follow-up, who are likely to have higher mortality. We therefore specify parameter  $I_d$  to represent the ratio of the true mortality rate to the IeDEA-SA mortality estimate at duration d after ART initiation. Gamma prior distributions are assigned to represent the uncertainty around  $I_0$  and the ratio  $I_4/I_0$ . The mean and standard deviation for the first prior are 1.85 and 0.50 respectively, while those for the second prior are 0.80 and 0.10 respectively [91]. The  $I_d$  values at other durations are calculated by interpolating between the  $I_0$  and  $I_4$  values.

# 4. Model of sexual transmission of HIV

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.

# 4.1 The effect of sex and relationship type

The symbol  $\beta_{e,l}$  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 of the opposite sex in relationship type l. Table 4.1 summarizes the assumed prior distributions for these parameter values. Although empirical estimates suggest high femaleto-male transmission probabilities per act of unprotected sex in unmarried men [158, 159], 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 [160]. The prior distribution for the  $\beta_{1,0}$  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. In the case of male-to-male transmission probabilities, the only published estimates are from high-income settings [161-163], and as heterosexual transmission probabilities in developing countries tend to be higher than those in high-income settings [114], we have chosen a parameter value substantially higher than that observed (0.0268), this parameter having been chosen so that the model matched the levels of HIV prevalence observed in South African studies of MSM. The model does not distinguish transmission probabilities in MSM relationships according to the type of sex act.

Tuble 1.1. Tisbumed probabilities of The transmission per det of sex							
Polationship type	Symbol	Susceptible female			Susceptible male <sup>c</sup>		
Kelationship type		Mean	Std dev.	Ref.	Mean	Std dev.	Ref.
CSW-client relationships	$eta_{g,2}$	0.001ª	-	[164, 165]	$0.008^{b}$	-	-
Short-term relationships	$eta_{_{g,0}}$	0.012	0.005	[166, 167]	0.008	0.003	[158, 159]
Long-term relationships	${m eta}_{g,1}$	0.0043ª	-	[85, 168, 169]	0.0010 <sup>a</sup>	-	[85, 168, 169]
MSM relationships	$eta_{\scriptscriptstyle 1,4}$	-	-		0.0268 <sup>a</sup>	-	[161-163]

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

CSW = commercial sex worker.

<sup>a</sup> Fixed parameter, not included in Bayesian analysis, based on previous model calibrations. <sup>b</sup> Parameter value is assumed to be the same as in short-term relationships. <sup>c</sup> For a male partner who is uncircumcised.

# 4.2 The effect of risk group

Sexually transmitted infections (STIs) have been shown to have a significant effect on HIV transmission probabilities, both when present in the HIV-susceptible partner [170, 171] and

when present in the HIV-infected partner [172]. 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 4.1 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 [173], and are shown in Table 4.2.

Table 4.2: Assumed multiples by which HIV transmission probabilities are increased depending on partner risk groups

	Short-ter	m contacts	Marital contacts	
	HIV+ male	HIV+ female	HIV+ male	HIV+ female
	partner	partner	partner	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

# 4.3 The effect of HIV stage and antiretroviral treatment

Table 3.1 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<sub>10</sub> 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  $\phi$ . The probability of viral suppression (a viral load of less than 400 copies/ml) in treated individuals is thus

$$\exp\left(-\omega_{1,s}\left(6 - \log 400\right)^{\phi}\right),\tag{4.1}$$

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

$$\omega_{1,s} = \frac{-\ln(V_s(t))}{(6 - \log 400)^{\phi}}.$$
(4.2)

In fitting Weibull distributions to viral load data from both treated [101, 104] and ART-naïve South Africans [174], we have found that a  $\phi$  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 [155] (a similar estimate of 0.74 was estimated for 2012 in a recent analysis of data from the National Health Laboratory Service [175]). 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 [174], 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

$$c \exp(-\theta x^{\phi}),$$
 (4.3)

where *c* is the maximum HIV transmission risk (when x = 0) and parameter  $\theta$  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 [176]. 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  $\theta$  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 [85, 177, 178], this implies that

$$\frac{-\frac{d}{dx}\left[c\exp\left(-\theta x^{\phi}\right)\right]}{c\exp\left(-\theta x^{\phi}\right)} = \ln(2.5).$$
(4.4)

From this it follows that  $\theta \phi x^{\phi-1} = \ln(2.5)$ . Substituting  $\phi = 1.5$  and x = 2 [85, 177] yields  $\theta = 0.432$ . The average HIV transmission probability, for patients with ART status *a* and CD4 stage *s*, is then

$$\int_{0}^{\infty} \omega_{a,s} \phi x^{\phi-1} \exp\left(-\omega_{a,s} x^{\phi}\right) c \exp\left(-\theta x^{\phi}\right) dx = c \int_{0}^{\infty} \omega_{a,s} \phi x^{\phi-1} \exp\left(-\left(\theta + \omega_{a,s}\right) x^{\phi}\right) dx$$
$$= \frac{c \omega_{a,s}}{\omega_{a,s} + \theta}.$$
(4.5)

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 (4.5), the ratio of the infectiousness after ART initiation to that prior to ART initiation is

$$R_{s} = \frac{\omega_{1,s}}{\omega_{1,s} + \theta} \bigg/ \frac{\omega_{0,s}}{\omega_{0,s} + \theta} \,. \tag{4.6}$$

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 [113, 179], but lower than the relative risk of 0.36 estimated in a recent meta-analysis of observational studies [180]. For patients who start ART at higher CD4 counts, data show that although they have lower baseline viral loads [98], they also have lower rates of virological failure after ART initiation [181], 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 (4.6), assuming that average viral load levels in untreated patients decrease by 0.18 for each 100-cell increase in the CD4 cell count [98] (which determines the  $\omega_{0,s}$  values).

## 4.4 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 in the context of heterosexual intercourse [85, 182], it is likely that empirical estimates are biased downward due to over-reporting of condom usage [183, 184]. Levels of condom efficacy close to 90% have also been estimated in MSM [162].

## 4.5 Age and year effects

Young women are at a biologically increased risk of HIV acquisition due to the high prevalence of cervical ectopy in adolescence and young adulthood [185-187], and their relatively low levels of protective lactobacilli [188]. 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

$$Z_{g}(x) = \begin{cases} \left(1 + Z_{g}\right)^{25-x} \text{ for } x < 25\\ 1 & \text{ for } x \ge 25 \end{cases}.$$
(4.7)

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 [189-191]. For males, there does not appear to be strong evidence of age variation in the risk of HIV acquisition per sex act [85, 190], and the  $Z_1$  parameter has therefore been set to zero.

As described in section 3.1, the model allows or changes in HIV virulence over time through the parameter E, which represents the factor by which the rate of CD4 decline reduces per year, in untreated adults. These reductions in virulence are likely to be associated with reductions in set point viral load (SPVL), which in turn are likely to cause reductions in HIV transmission probabilities. The model therefore allows for an annual reduction in the

transmission probability, which depends on the annual reduction in the rate of CD4 decline. We define the transmission probability in year t to be

$$\beta_{g,l}(t) = \beta_{g,l} E^{(t-1999) \times 2.5\alpha}, \qquad (4.8)$$

where  $2.5\alpha$  is the scaling factor for the relationship between HIV virulence and HIV transmissibility. As explained in more detail elsewhere [91], the  $\alpha$  parameter can be interpreted as the ratio of the increase in infectivity to the increase in HIV disease progression (on a natural log scale), for a given change in SPVL. A gamma prior distribution with a mean of 1 and a standard deviation of 0.8 has been assigned to represent the uncertainty around this parameter.

#### 4.6 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 2.9). 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  $\geq 500$  cells/µl (*s* = 2), then

$$\beta_{g,l} = \beta_{g,l}^{*} \frac{\sum_{s=1}^{3} \frac{I_{s} \Gamma(s)}{\lambda_{s}} + \frac{I_{4} \Gamma(4)}{\lambda_{4} + \mu_{4}} + \frac{\lambda_{4}}{\lambda_{4} + \mu_{4}} \times \frac{I_{5} \Gamma(5)}{\mu_{5}}}{\sum_{s=1}^{3} \frac{\Gamma(s)}{\lambda_{s}} + \frac{\Gamma(4)}{\lambda_{4} + \mu_{4}} + \frac{\lambda_{4} \Gamma(5)}{(\lambda_{4} + \mu_{4})\mu_{5}}},$$
(4.9)

where the  $I_s$  factors are the relative levels of infectiousness (Table 3.1), and the CD4 decline parameters ( $\lambda_s$ ) and mortality parameters ( $\mu_s$ ) are those specified in section 3.1. We define  $I_s^*$  to be the ratio of infectiousness in stage *s* to average infectiousness, from which it follows that  $I_2^* = \beta_{g,l}^* / \beta_{g,l}$ , and hence

$$I_{2}^{*} = \frac{\sum_{s=1}^{3} \frac{\Gamma(s)}{\lambda_{s}} + \frac{\Gamma(4)}{\lambda_{4} + \mu_{4}} + \frac{\lambda_{4}\Gamma(5)}{(\lambda_{4} + \mu_{4})\mu_{5}}}{\sum_{s=1}^{3} \frac{I_{s}\Gamma(s)}{\lambda_{s}} + \frac{I_{4}\Gamma(4)}{\lambda_{4} + \mu_{4}} + \frac{\lambda_{4}}{\lambda_{4} + \mu_{4}} \times \frac{I_{5}\Gamma(5)}{\mu_{5}}}{\lambda_{5}}.$$
(4.10)

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  $I_s^*(1) = I_s^*(t_d + (1 - t_d)R_s)$ , where  $t_d$  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 (4.6)). The  $t_d$  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 [192].

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 3.2, 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

$$G(v,a) = (1 - \delta(t))(1 - h)^{a}, \qquad (4.11)$$

where the  $\delta(t)$  and *h* parameters represent the reductions in unprotected sex due to HIV diagnosis and ART initiation respectively (see sections 2.10 and 2.11).

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 HIVnegative 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

$$Y(1, s, d) = \iota_d \Gamma(s) + (1 - \iota_d) \sum_{s'=2}^{5} \psi_d(s' \mid s) \Gamma(s'), \qquad (4.12)$$

where  $\psi_d(s'|s)$  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 [84], and the frequency of sex is thus assumed to be a function only of the *current* CD4 count. The  $\psi_d(s'|s)$  values are estimated from studies of CD4 distributions after ART initiation [193-195], and the assumed values are shown in Table 4.3.
		υ			
		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

Table 4.3: Proportions of treated patients in different CD4 categories

For the purpose of calculating average transmission probabilities, we define  $N_{g,i,l,j}^r(x)$  to be the total number of individuals aged x and of sex g, who are in risk group i, in relationship state l (0 for unmarried heterosexual, 1 for married/cohabiting, 2 for sex workers and 3 for MSM) with a partner in risk group j (the j subscript is omitted in the case of unmarried individuals, i.e. for l = 0, 2 or 3) and circumcision status r (1 for circumcised males, 0 otherwise). Within this group we define  $X_{g,i,l,j}^r(x,a,s,v,d)$  to be the proportion who are in HIV stage s, with ART status a, HIV testing history v and ART duration d. In total there are 35 possible HIV-positive states, summarized in Table 4.4.

ART	HIV	Testing	ART	
status	stage	history	duration	Description
<i>(a)</i>	<i>(s)</i>	<i>(v)</i>	(d)	
0	1	0	0	Acutely infected, never tested
0	2	0	0	$CD4 \ge 500$ , 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	$CD4 \ge 500$ , 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 $\geq$ 500 in current year
1	2	2	1	Started ART with CD4 ≥500 in previous year
1	2	2	2	Started ART with CD4 $\geq$ 500 2 years previously
1	2	2	3	Started ART with CD4 $\geq$ 500 3 years previously
1	2	2	4	Started ART with CD4 $\geq$ 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

Table 4.4: Definitions of HIV-positive states

\* 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 [196], 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

$$n_{g,0}(x)Y(a,s,d)\beta_{g,0}(t)I_{s}^{*}(a)\Theta_{g,i,0,j}\left(1-\left[1-\left(1-\gamma_{g,0}(x,t)\right)G(v,a)\right]E\right)$$
  
=  $n_{g,0}(x)Y(a,s,d)\beta_{g,0}(t)I_{s}^{*}(a)\Theta_{g,i,0,j}\left\{\left(1-\gamma_{g,0}(x,t)\right)G(v,a)E+\left(1-E\right)\right\}$  (4.13)

where  $n_{g,0}(x)$  is the average number of sex acts per short-term relationship,  $\gamma_{g,0}(x,t)$  is the probability of condom use by HIV-negative individuals (as defined in section 2.8), and *E* is

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

$$1 - \exp\left(-n_{g,0}(x)Y(a,s,d)\beta_{g,0}(t)I_s^*(a)\Theta_{g,i,0,j}\left(\left(1 - \gamma_{g,0}(x,t)\right)G(v,a)E + \left(1 - E\right)\right)\right). \quad (4.14)$$

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 4.4, is defined as

$$T_{g,i,l,k}^{0,r}(j,x) = \sum_{a,s,v,d} X_{g,i,l,k}^{r}(x,a,s,v,d) n_{g,0}(x) Y(a,s,d) \beta_{g,0}(t) I_{s}^{*}(a) \Theta_{g,i,0,j} \times \left\{ \left(1 - \gamma_{g,0}(x,t)\right) G(v,a) E + \left(1 - E\right) \right\}$$
(4.15)

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  $T_{g,l,k}^{2,r}(j,x)$ represents the average transmission probability per sex act. The same approach is again followed in MSM relationships (replacing 0 with 3 in the above equations). Finally, it should be noted that the relationship type in the superscript is not necessarily the same as the marital status indicator (1) 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

$$1 - \exp\left(-T_{g,i,l,k}^{0,r}(j,x)\right),\tag{4.16}$$

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

$$U_{g,i}^{0}(j,x) = 1 - \frac{\sum_{r,l,k} N_{g,l,k}^{r}(x) c_{g,l,l}(x) \exp\left(-T_{g,l,k}^{0,r}(j,x)\right)}{\sum_{r,l,k} N_{g,l,k}^{r}(x) c_{g,l,l}(x)},$$
(4.17)

where  $c_{g,i,l}(x)$  is the annual rate at which new non-spousal relationships are formed (as defined in section 2.2). Although MSM are included in the above equation (l = 3), their rate of partner acquisition is scaled down in proportion to the fraction of their partners who are female (see Appendix A).

Following the same approach, 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

$$U_{g,i}^{1}(j,x) = 1 - \frac{\sum_{r} N_{g,i,1,j}^{r}(x) \exp\left(-T_{g,i,1,j}^{1,r}(j,x)\right)}{\sum_{r} N_{g,i,1,j}^{r}(x)},$$
(4.18)

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

$$U_{1,1}^{2} = \frac{\sum_{r,l,k,x} N_{1,l,k}^{r}(x) w_{l}(x) T_{1,l,k}^{2,r}(1)}{\sum_{r,l,k,x} N_{1,l,k}^{r}(x) w_{l}(x)},$$
(4.19)

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*. Note that MSM are excluded from this equation, i.e. MSM are assumed not to have sex with female sex workers.

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 heterosexual partner in the next month is

$$P_{g,i,l}^{0}(x) = 1 - \exp\left(-\frac{c_{g,i,l}(x)}{12}Z_{g}(x)\sum_{y=10}^{90}f_{g,0}(y \mid x) \times \left[\rho_{g,i,0}(1,t)U_{3-g,1}^{0}(i,y) + \rho_{g,i,0}(2,t)U_{3-g,2}^{0}(i,y)\right]\right)$$
(4.20)

where  $f_{g,0}(y | x)$  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.

For a man who has sex with other men, a similar approach is adopted in calculating their probability of HIV acquisition through a same-sex relationship, with the inclusion of a factor  $\Omega(x)$  to represent the fraction of partners who are of the same sex:

$$P_{1,i,3}^{0}(x) = 1 - \exp\left(-\frac{c_{1,i,3}(x)\Omega(x)}{12}Z_{1}(x)\sum_{y=10}^{90}f_{1,3}(y \mid x) \times \left[\rho_{1,i,3}(1,t)U_{1,1}^{0}(i,y) + \rho_{1,i,3}(2,t)U_{1,2}^{0}(i,y)\right]\right)$$
(4.21)

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

$$P_{g,i,1,j}^{1}(x) = 1 - \exp\left(-Z_{g}(x)\sum_{y=10}^{90} f_{g,1}(y \mid x)U_{3-g,j}^{1}(i, y)\right).$$
(4.22)

If the individual is a high-risk man who has sex only with women, then the probability that they acquire HIV from a sex worker in the next month is

$$P_{1,1,l}^{2}(x) = 1 - \exp\left(-\frac{w_{l}(x)}{12}Z_{1}(x)\sum_{y=10}^{90}N_{2,1,2}^{0}(y)T_{2,1,2}^{2,0}(1,y) \middle/ \sum_{y=10}^{90}N_{2,1,2}^{0}(y) \right), \quad (4.23)$$

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

$$P_{2,1,2}^{2}(x) = 1 - \exp\left(-\frac{C}{12}Z_{2}(x)U_{1,1}^{2}\right), \qquad (4.24)$$

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

#### 4.7 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 4.1 relate to uncircumcised men) [197-200]. Male circumcision is assumed to have no effect on male-to-female rates of HIV transmission [201] or male-to-male transmission [202, 203].

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

$$p(x) = a + (b - a) \left( 1 - 0.5^{(x/m_1)^{\phi}} \right), \tag{4.25}$$

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  $\phi$  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

$$m_1 = m_2 \left(\frac{\ln(b/(2(b-a)))}{\ln(0.5)}\right)^{-\frac{1}{\phi}} \qquad \text{for } \frac{b}{2} > a \,. \tag{4.26}$$

Parameters *a* and *b* are set at 0.105 and 0.42 respectively. The shape parameter  $\phi$  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 [204]. Most of these parameters have been set so that the model is consistent with reported rates of male circumcision by age in national surveys [56, 204, 205], after correcting the self-reported data to take into account known biases in the reporting of male circumcision [206-211]. 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 4.1 shows the model calibration.



Figure 4.1: Fraction of men who are circumcised, by age, prior to MMC campaigns Unadjusted data represent the average of the results from national surveys in 2002 and 2003 [56, 204, 205]. 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

$$\psi(x) = 1 - \frac{1 - p(x+1)}{1 - p(x)}.$$
(4.27)

Men are assumed to undergo MMC only if they are HIV-negative, as HIV testing is conducted prior to most MMC operations [212, 213], and although men who are HIV-positive are not excluded from getting circumcised, there would be little incentive to undergo the procedure if they were already HIV-positive. 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

$$\eta_{i,l}(x,t) = R(t)\mathcal{G}(x), \qquad (4.28)$$

where R(t) is the maximum probability in year t and  $\mathcal{G}(x)$  is the relative rate of MMC uptake in men aged x, compared to boys aged 10-14. Although some South African evidence suggests that uptake is increased in high-risk groups [214], other South African studies refute this [206], and the high proportion of MMC operations occurring in the 10-14 age group [3] suggests that uptake is determined principally by age rather than level of HIV risk behaviour. The relative rates of MMC uptake in the 15-19, 20-24, 25-49 and 50+ age groups have been set to 0.60, 0.35, 0.20 and 0.02 respectively; these rates were chosen to ensure the model matched the age profile of MMC operations reported in South Africa over the 2010-14 period [3]. In the period up to 2015/16, the R(t) values are calculated from the annual total numbers of MMC operations performed through MMC campaigns, as reported by the Department of Health (summarized in Table 4.5). 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

$$\Lambda(t) \approx \sum_{i} \sum_{l} \sum_{x} N_{i,l}(x,t) \times \eta_{i,l}(x,t) \left(1 - 0.5 \times \psi(x)\right), \tag{4.29}$$

from which it follows that

$$R(t) \approx \frac{\Lambda(t)}{\sum_{i} \sum_{l} \sum_{x} N_{i,l}(x,t) \mathcal{G}(x) (1 - 0.5 \times \psi(x))}.$$
(4.30)

Table 4.5: Annual numbers of MMC operations performed through MMC campaigns Year Pre-2008 2008/09 2009/10 2010/11 2011/12 2012/13 2013/14 2014/15 2015/16 5 190 9 1 6 8 131 117 347 973 422 262 331 668 508 404 Operations 0 518 130

Source: World Health Organization [215], Department of Health [216-219]

Based on equation (4.30), the model estimates the annual probability of MMC in 2015/16, for boys aged 10-14, to be 0.15. This value is assumed to continue to apply in future years.

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

#### 4.8.1 Effectiveness of PrEP

Randomized controlled trials published to date have yielded conflicting estimates of the effectiveness of PrEP. As in our previous work [220], we set the average PrEP effectiveness at 40%. This corresponds to the average efficacy level in the studies of PrEP in heterosexual adults that have been published to date [221-225], and is close to the average heterosexual efficacy of 46% estimated in a recent meta-analysis [226].

#### 4.8.2 Risk compensation

Although data from randomized trials generally do not show evidence of risk compensation in PrEP recipients [221, 222, 224], 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 [227]. Another microbicide acceptability study found that women were resistant to the idea of using both condoms and microbicides simultaneously [228]. This suggests that some reduction in condom use could occur. However, in a study of 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 [229]. Based on the Partners PrEP trial data, we assume a 10% reduction in condom use among PrEP users.

#### 4.8.3 PrEP discontinuation

Rates at which individuals discontinue PrEP are highly variable between studies, ranging from rates of 0.23 per annum in American MSM [230] 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 [227, 229]. 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.

#### 4.8.4 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 [231] 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 [232]. 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 [230]. 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 assume that from mid-2016 (around the time when South Africa's PrEP for sex worker programme was announced) the mean annual rate at which sex workers adopt PrEP is 0.3. 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).

# 5. 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.

## **5.1 Perinatal transmission**

The model of mother-to-child transmission has been described elsewhere [233], and key parameters are summarized in Table 5.1. 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 3.2.

#### 5.1.1 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 [234]). The D(t) parameters are assumed to increase from zero in 2002/3 up to 90% in the 2010-2012 period [234, 235]. However, D(t) parameters are assumed to decline to zero in 2014, following the introduction of WHO option B, which recommended triple-drug prophylaxis for all HIV-positive women, regardless of CD4 count. It is nevertheless assumed that even after the introduction of WHO option B, 71% of HIV-diagnosed mothers who do not start triple-drug therapy prior to ART initiation would receive sd NVP as an emergency prophylaxis (typically in situations where HIV is diagnosed only in labour).

Table 5.1: Mother-to-child transmission assumptions

Parameter	Value	Source
Transmission rate at/before birth, from chronically-		
infected women with no ARV prophylaxis, with		
CD4 >500	13.4%	Meta-analysis of
CD4 350-500	15.2%	published studies [236]
CD4 200-349	25.8%	-
CD4 <200	35.0%	
Transmission rate at/before birth, from acutely-	26.0%	[237-242]
infected women with no ARV prophylaxis		
% of HIV-diagnosed women who receive	71.0%	Kate Kerber (pers. comm.), based
single-dose nevirapine, if not starting ART		on national survey data [234]
% reduction in perinatal MTCT if mother	40.0%	[243]
receives single-dose nevirapine only		
% reduction in perinatal MTCT if mother	65.0%	[244]
receives short-course zidovudine only		
% reduction in perinatal MTCT if mother receives	86.3%*	[245, 246]*
single-dose nevirapine + short-course zidovudine		
Transmission rate at/before birth, from	0.3%	[247-252]
women on long-term ART pre-conception		
Probability of MTCT from chronically-	9.8%*	Meta-analysis [253], adjusted to
infected mothers, per year of mixed feeding		reflect effect of excluding EBF*
Probability of MTCT from acutely-	14.7%*	Derived from meta-analysis [233]*
infected mothers, per month of mixed feeding		
Ratio of postnatal transmission risk per month	0.362*	[254, 255]
of EBF to postnatal transmission risk per month		
of mixed feeding		
% reduction in monthly postnatal MTCT risk	60.0%	[256-258]
if child receives extended nevirapine prophylaxis		
% reduction in monthly postnatal MTCT risk		1 - average MTCT rate per month
if mother receives long-term ART		of BF divided by the rate in
		women not on ART [253]
ART initiated during pregnancy	78%	[259-268]
ART initiated before conception	96%	[249, 252, 269]

\* Posterior means estimated from a previous analysis [1]; cited data sources determined the corresponding prior distributions. EBF = exclusive breastfeeding; MTCT = mother-to-child transmission.

#### 5.1.2 Effectiveness of long-term maternal ART

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

 $a+b_s R^x, (5.1)$ 

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

$$\int_{0}^{\infty} g(x) \left( a + b_{s} R^{x} \right) dx = a + b_{s} \int_{0}^{\infty} \frac{\lambda(t)^{\alpha} x^{\alpha - 1} \exp\left(-\lambda(t)x\right)}{\Gamma(\alpha)} R^{x} dx$$
$$= a + b_{s} \left(\frac{\lambda(t)}{\lambda(t) - \ln(R)}\right)^{\alpha}.$$
(5.2)

where  $\alpha$  and  $\lambda(t)$  are the parameters of the gamma distribution. Based on South African data sources [247, 248, 270, 271], the mean and standard deviation of the gamma distribution in the baseline scenario have been set to 10.6 weeks and 8 weeks respectively ( $\alpha = 1.7556$  and  $\lambda(t) = 0.1656$  for t < 2010), and the *R* parameter has been set to 0.9. Parameter *a* has been set to 0.003, the average transmission risk from studies that evaluated the perinatal transmission rate from mothers who started ART prior to conception [247-252] (Table 5.1).

The remaining  $b_s$  parameter is estimated by equating expression (5.2) 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 0.036 and 0.013 respectively [247, 248, 250, 259-261, 263, 264, 267, 268, 270, 272, 273]. The resulting estimates of the  $b_s$  parameter are 0.078 and 0.024 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 [274], which led to more rapid initiation of ART during pregnancy. For example, Van Schalkwyk et al [271] 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 [275]. Stinson et al [276] 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 [216] 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. We assume that after 2013, the average ART duration before delivery increases by 70% (relative to baseline), which is roughly consistent with what would be expected if all pregnant women starting ART during pregnancy did so soon after their first antenatal visit.

#### 5.1.3 HIV incidence in pregnancy and retesting in late pregnancy

The first antenatal visit is assumed to occur at 23 weeks gestation [19, 277, 278] and delivery at 39 weeks [278], 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 [279]. 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 value of 26% has been assumed (Table 5.1). 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 [280, 281], with the most recent DHIS data suggesting a proportion close to 100% in 2016/17. A retesting frequency of 95% is therefore assumed from 2016 onward. 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.

## 5.2 Postnatal HIV transmission

#### 5.2.1 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 [19]. All of these women are assumed to practise mixed feeding, as exclusive breastfeeding (EBF) was rare prior to the introduction of PMTCT programmes [19, 282]. Of women who were diagnosed HIV-positive antenatally in the period up to 2011, it is assumed 56% avoided breastfeeding completely [136], 30% practised EBF and 14% practised mixed feeding [283]. 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 [283-285]. 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.

#### 5.2.2 Infant feeding practices after 2011

The benefits of EBF have been increasingly emphasized following the Tshwane declaration [286], 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 [287].

#### 5.2.3 Postnatal transmission probabilities

Table 5.1 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 the same as the duration of acute infection.

Following the revision to the South African PMTCT guidelines in 2010 [274], HIV-positive mothers who breastfed but did not 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 3.3. 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.

For women who are on ART while breastfeeding, the monthly HIV transmission risk is assumed to depend on whether they started ART before conception or during pregnancy (Table 5.1). The assumption of an 78% reduction in postnatal transmission rates in women who started ART during pregnancy, relative to breastfeeding mothers who are untreated, is calculated as one less the ratio of the average monthly postnatal transmission risk in various studies (0.0017) to the average monthly transmission risk of 0.0077 for untreated mothers in a meta-analysis [253]. Similarly, the 96% reduction in postnatal transmission risk from mothers who started ART prior to their pregnancy is calculated as one less the ratio of the average monthly transmission risk from these mothers (0.0003) to that in untreated mothers (0.0077).

## 5.3 Paediatric HIV survival

The structure of the paediatric HIV survival model is illustrated in Figure 5.1, and a detailed description of the model of paediatric HIV survival has been published previously [288]. 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 [289]). 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 5.1: Multi-state model of HIV survival in HIV-positive children

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

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

$$\eta(x) = G_p + \left(H_p \times c^x\right),\tag{5.3}$$

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  $\theta$  is a constant scaling factor. The assumed parameter values and the data sources on which they are based are summarized in Table 5.2.

Parameter	Symbol	Value	Source
Children infected at/before birth	-		
Annual rate of progression to late disease in older children	$G_p$	0.428*	$\theta G_p = 0.14$ is consistent with rates of progression observed by Charlebois <i>et al</i> [290] in children aged $\geq 1$ year*
Excess annual rate of progression to late disease in neonates	$H_p$	2.11*	[291, 292]*
Excess progression reduction factor, per year of age	С	0.25	[291-294]
Relative rate of progression to late	$\theta$	0.362*	[295-298]*
Children in late disease untreated			
Annual rate of AIDS mortality in older children	$G_m$	0.143*	[299, 300]*
Excess annual rate of AIDS mortality in neonates	$H_m$	3.64*	Based on fitting model to mortality data from children diagnosed with
Excess mortality reduction factor, per year of age	d	0.05	HIV-related symptoms at different ages [300]*
Relative rate of AIDS mortality in children who started APT after			
progression to late disease			Based on fitting model to mortality
'High risk' phase	$\Phi_0$	0.95	data from IeDEA Southern Africa
'Stabilized' phase	$\Phi_1$	0.10	Collaboration [301]
Children who started ART while in			
early disease			
Relative rate of excess early AIDS mortality	Р	0.40	Based on fitting model to data from early ART trial [291]

Table 5.2: Paediatric HIV survival assumptions (ages <10)

\* Posterior means estimated from a previous analysis [1]; cited data sources determined the corresponding prior distributions.

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 [299, 300], 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

$$\mu(x) = G_m + \left(H_m \times d^x\right),\tag{5.4}$$

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. Assumed parameter values are summarized in Table 5.2.

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

$$\psi(x) = \Phi_1 \Big( G_m + \Big( P \times H_m \times d^x \Big) \Big), \tag{5.5}$$

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 5.1), 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 soon after birth (until 2015, guidelines recommended PCR screening at 6 weeks and since then screening has been done both at birth and at 10 weeks). Of these screened infants, a proportion of those eligible for ART are assumed to start ART, which is assumed to occur either at birth or at 2 months of age (the latter being a crude approximation to the timing that might be expected if screening occurs at 6 weeks or 10 weeks). Mathematically, the number of perinatally-infected infants who start ART at birth or at 2 months, following PCR screening, is assumed to be

$$S^{0}(t) = \sum_{s=0}^{2} \left( N_{s}(0,t) V(0,t) \pi_{s}(0) + N_{s}(2,t) V(2,t) \pi_{s}(2) \right) E_{s}(t) l, \qquad (5.6)$$

where  $N_s(x, t)$  is the number of perinatally-infected infants at the age of x months, in stage s of infection; V(x, t) is the fraction of children born to HIV-positive mothers who receive PCR testing at age x in year t;  $\pi_s(x)$  is the sensitivity of the PCR in infants in stage s aged x;  $E_s(t)$  is the fraction of infants who are eligible to receive ART in year t, in stage s of infection; and lis 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 PMTCTunexposed 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 5.3. Rates of PCR testing at 6 weeks are based on public sector statistics [138, 302], adjusted to reflect under-count due to late immunization [303, 304] and over-count due to non-return of test results to caregivers [305-307]. Although recent data suggest a birth screening rate of 68.7% [140], no information is available on the rate of screening at 10 weeks since the introduction of the new screening policy. Preliminary data suggest that screening coverage at 10 weeks may be lower than has historically been observed at 6 weeks [308], but we have optimistically assumed 92% coverage from 2015 onward. PCR sensitivity levels at 2 months have been set at 76%, 81% and 100% for stages 0, 1 and 2 respectively, based on a previous model of perinatal transmission [309], assuming that all infants who are tested for HIV would at least have received NVP prophylaxis postnatally [274]. Sensitivity levels at birth have been set to 38% and 75% for stages 0 and 1 respectively (no infants are assumed to be already in advanced disease at birth). Although children in late disease have been eligible for ART since 2004 [141], ART eligibility for infants in early disease only became official policy in 2010 [310], with some earlier provision following the 2008 WHO guideline revision [311]. The fraction of eligible, diagnosed infants who link to care has been set to 80% [307, 312].

1 dole 5.5. midi	t diagnosis and mitter of	igiointy in permatany	micetea mants	
	Fraction tested	Fraction tested	Early ART	Late ART
	at 6 or 10 weeks	at birth	eligibility	eligibility
	(V(2,t))	(V(0,t))	$(E_0(t), E_1(t))$	$(E_2(t))$
Pre-2004	0.0%	0.0%	0.0%	0.0%
2004-2006	0.0%	0.0%	0.0%	100.0%
2006-2007	8.5%	0.0%	0.0%	100.0%
2007-2008	19.1%	0.0%	0.0%	100.0%
2008-2009	29.5%	0.0%	20.0%	100.0%
2009-2010	40.1%	0.0%	60.0%	100.0%
2010-2011	53.0%	0.0%	100.0%	100.0%
2011-2012	60.8%	0.0%	100.0%	100.0%
2012-2013	68.9%	0.0%	100.0%	100.0%
2013-2014	84.8%	0.0%	100.0%	100.0%
2014-2015	92.0%	0.0%	100.0%	100.0%
Post-2015	92.0%	68.7%	100.0%	100.0%

Table 5.3: Infant diagnosis and ART eligibility in perinatally-infected infants

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 (3.6),

$$S(t) - S^{0}(t) = \sum_{x=0}^{179} \sum_{s=2,4} N_{s}(x,t) \int_{0}^{1} \rho(t) \exp\left(-\left(\mu(x) + \delta(x,t) + \rho(t)\right)u\right) du$$
  
$$\approx \sum_{x=0}^{179} \sum_{s=2,4} N_{s}(x,t)\rho(t) \left(1 - 0.5\left(\mu(x) + \delta(x,t) + \rho(t)\right)\right)$$
(5.7)

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 (5.7) 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 3.5 for each year up to mid-2017 (monthly numbers are calculated by dividing these annual totals by 12).

In the period after mid-2017, 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-2017 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 [289]. This means that on reaching age 10, children who are in the late HIV stage and ART-naïve get moved into the

 $CD4 < 200/\mu l$  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.

# 6. Demographic assumptions

## 6.1 Base population

The initial population numbers in 1985, by sex and individual age from 0 to 89 and open interval 90+, were set the same as those from the ASSA2008 provincial models [313].

## 6.2 Fertility

Total fertility rates (TFRs) for the 12 months prior to each census and the Community Survey (CS) were estimated by rescaling the age-group specific fertility rates (ASFRs) derived from the number of births in the 12 months prior to each census/survey and children ever born reported by women in the censuses [314] so that the number of births in a particular year was equal to the number estimated by projecting the number of survivors at the time of the 2011 census who were born in the province/country, backward to the time of birth. TFRs for the years between the censuses/survey were produced in a similar way, assuming that the proportion of births to each 5-year age group of women changed linearly over time between the censuses/survey.

TFRs for the projection years (from the middle of one year to the middle of the next) were linearly interpolated from the estimates by census year (i.e. from census anniversary in one year to the census anniversary in the next).

TFRs for the period from the middle of 1985 to middle of 1996 were estimated to be the linear trend from the ASSA2008 estimate for 1985 to the estimate for the year starting at the middle of 1996, produced above. Kinks in the estimates in the period 1998 to 2003 were smoothed to produce a smooth trend over time.

The age-specific fertility rates were set by applying proportions of the TFR at each individual age to TFRs for each year from 1985 to 2011.

The proportions of the TFR attributable to single ages for 1996, 2001, 2006 and 2011 were derived from the proportions attributable to five year age groups reported by women in each census and the 2007 Community Survey using Beers subdivision. The proportions for individual years between the census/survey years were derived by linear interpolation. For the projection years 1985-1995 the ASSA2008 ASFRs were rescaled to the TFRs estimated above.

Beyond 2011, age-specific fertility rates are assumed to decline to a common set of ultimate fertility rates at annual rates of decline. The assumed ultimate rates and annual rates of decline are both the same as assumed in the ASSA2008 models.

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

$$F(x,t)\Gamma(s)^q,\tag{6.1}$$

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  $\geq$ 500, 350-499, 200-349 and <200 are 1, 0.92, 0.76 and 0.55 respectively (the same as the assumed relative frequencies of sex in different stages, as discussed in section 2.9). 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 [315, 316]. 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

$$F(x,t)Y(1,s,d)^{q}$$
 (6.2)

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 (4.12)). 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 [64, 249, 317, 318].

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

$$\overline{F}(x,t) = \frac{F(x,t) \left[ N_{0,0,0}^{1}(x,t) + \sum_{s=1}^{5} N_{0,s,0}^{1}(x,t) \Gamma(s)^{q} + \sum_{s,d} N_{1,s,d}^{1}(x,t) Y(1,s,d)^{q} \right]}{\sum_{i,a,s,d} N_{a,s,d}^{i}(x,t)}$$
(6.3)

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.

## **6.3 Non-HIV mortality**

The age-specific probabilities ( $q_x$ ) of non-HIV/AIDS mortality for 1997-2010 were derived from the central mortality rates ( $_nm_x$ ) for all-cause and HIV-specific mortality from the 2010 National Burden of Disease (NBD) study [319]. First  $m_0$ ,  $4m_1$ ,  $5m_5$ , ...  $5m_{80}$ , and  $m_{85+}$  were derived by subtracting the HIV/AIDS-specific rates from the all-cause rates. Next, because of the erratic nature of the rates at the older ages, the rates above age 65 were smoothed to follow the curve of the average rates by age over the period, scaled to the level of the rates in each year. Then Beers interpolation was applied to the rates from  $4m_1$  to  $m_{85+}$  to produce rates at individual ages from 2 to 87. These rates were then converted to probabilities of death for ages 2 to 80. Probabilities above age 80 were derived from extrapolated central mortality rates assuming that rates followed a Gompertz curve, increasing by 9% per year of age, to further reduce fluctuation over time and age. Finally  $q_0$  was set equal to  $1-\exp(-0.983m_0)$  and  $q_1$  was set equal to  $1-\exp(-3.9854m_1)/[(1-q_2)(1-q_3)(1-q_4)]$ , where  $m_0$  and  $4m_1$  were the rates derived from the NBD estimates.

Probabilities of death for 1985 were set to those from the ASSA2008 model and for 1986 to 1996, probabilities of death were determined by linear interpolation between the estimates for 1985 and 1997. Beyond 2010, non-HIV/AIDS mortality rates are assumed to decline to a common set of ultimate rates at age-specific rates of decline. The ultimate rates and annual rates of decline are the same as assumed in the ASSA2008 models.

## **6.4 Migration**

For each year from 1985 to 2015, we specify a number of net in-migrants (immigrants less emigrants) for each age and sex. The numbers of migrants were set in two stages. Initially the numbers of migrants by sex and single age for each year 1985 to 2000 were set equal those from the ASSA2008 models. The numbers for 2001-2010 were set as per those used to produce the alternative mid-year estimates. These numbers were derived from the change in the numbers of people by place of birth (province or outside South Africa) between censuses, deducting an estimate of the number of South African-born emigrants as captured by censuses in the main countries of destination (UK, Australia, New Zealand, USA and Canada), scaled to match the total numbers recorded in the official mid-year estimates [320].

After this, these numbers were adjusted by an age-specific number (fixed over time) so that the projection of the population to the middle of 1996, 2001 and 2011 matched the census counts (approximately, for example, allowing for differences that might be expected due to errors in the census, such as undercounting of children or age exaggeration at the old ages). Although adjustment of migration of those born in the intercensal period was avoided as far as possible, there are probably some instances where the adjustment of migration compensated for errors in fertility. These adjustments were made at a provincial level, with national net immigration being the sum of the resultant provincial net in-migration.

Generally these adjustments were determined by subtracting the projected numbers in fiveyear age groups before adjustment from the census count in these age groups.  ${}_{5}M_{x-5}$  was set to  $({}_{5}P^{c}{}_{x-5}P_{x})/10$ ,  ${}_{5}M_{0}$  to  $({}_{5}P^{c}{}_{5-5}P_{5})/5$  and  $M_{85+}$  to  ${}_{5}M_{80}$ , where  ${}_{5}P_{x}$  represents the number of people in the population aged between x and x+5, the superscript c represents the census count and  ${}_{5}M_{x}$  represents the additional number of migrants aged between x and x+5 required for the adjustment. The age range requiring adjustment for each census was limited to that needed to correct for major deviations in one census from what would be expected given the other two, on the assumption that the estimates of migration reported by census questions are likely to be less accurate than the census counts.

The numbers at each age for 2011 to 2015 were set equal to those for 2010. Beyond 2015, the numbers at each age are assumed to trend to zero over the next 30 years, in line with the approach used in ASSA2008.

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.

# 7. Statistical analysis

The model is calibrated to historic HIV prevalence data and mortality data, using a Bayesian approach. The sections that follow describe the different steps in more detail.

## 7.1 Prior distributions

The parameters that are allowed to vary in the calibration, and the corresponding prior distributions chosen to represent the uncertainty around these parameters, are summarized in Table 7.1. Most of these prior distributions have been referred to 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 [321], it is unlikely that HIV prevalence in women aged 15-49 in 1985 would have been more than 0.04% ( $0.0076 \times 1.8^{-5}$ ), since antenatal HIV prevalence tends to exceed prevalence in the general female population [322]. Since we assume that 25% of women are 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 [323].

	Prior	Prior mean,	Ref.
	distribution	std deviation	
Average survival in absence of ART (years)	Gamma (144, 12)	12, 1	3.1
RR of HIV disease progression in women	Gamma (369, 384)	0.96, 0.05	3.1
Increase in HIV disease progression per	Gamma (9, 50)	0.18, 0.06	3.1
10-year increase in age			
RR of HIV disease progression per calendar year	Gamma (23669, 23669)	1, 0.0065	3.1
IeDEA-SA bias <6 months after ART start	Gamma (13.69, 7.40)	1.85, 0.50	3.4
Ratio of IeDEA-SA bias >42 months after ART	Gamma (64.0, 80.0)	0.80, 0.10	3.4
start to bias <6 months after ART start			
Reduction in mortality* per unit increase in rate of	Gamma (4.59, 0.612)	7.5, 3.5	3.4
ART initiation (at CD4<200) over last 3 years			
Female-to-male transmission probability in short-term/	Beta (7.05, 874)	0.008, 0.003	4.1
non-spousal partnerships			
Male-to-female transmission probability in short-term/	Beta (5.68, 468)	0.012, 0.005	4.1
non-spousal partnerships			
Ratio of increase in infectivity* to increase in	Gamma (1.56, 1.56)	1.0, 0.8	4.5
disease progression,* per unit change in SPVL			
Initial HIV prevalence in high risk women, ages 15-49	Uniform (0, 0.002)	0.001, 0.00058	7.1
RR of HIV disease progression in women Increase in HIV disease progression per 10-year increase in age RR of HIV disease progression per calendar year IeDEA-SA bias <6 months after ART start Ratio of IeDEA-SA bias >42 months after ART start to bias <6 months after ART start Reduction in mortality* per unit increase in rate of ART initiation (at CD4<200) over last 3 years Female-to-male transmission probability in short-term/ non-spousal partnerships Male-to-female transmission probability in short-term/ non-spousal partnerships Ratio of increase in infectivity* to increase in disease progression,* per unit change in SPVL Initial HIV prevalence in high risk women, ages 15-49	Gamma (369, 384) Gamma (9, 50) Gamma (23669, 23669) Gamma (13.69, 7.40) Gamma (64.0, 80.0) Gamma (64.0, 80.0) Gamma (4.59, 0.612) Beta (7.05, 874) Beta (5.68, 468) Gamma (1.56, 1.56) Uniform (0, 0.002)	0.96, 0.05 0.18, 0.06 1, 0.0065 1.85, 0.50 0.80, 0.10 7.5, 3.5 0.008, 0.003 0.012, 0.005 1.0, 0.8 0.001, 0.00058	$3.1 \\ 3.1 \\ 3.1 \\ 3.4 \\ 3.4 \\ 3.4 \\ 4.1 \\ 4.1 \\ 4.5 \\ 7.1 \\ $

Table 7.1: Prior distributions

\* On a natural log scale.

#### 7.2 Likelihood definition

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

#### 7.2.1 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 2014 (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  $H_{x,t}(\mathbf{\varphi})$  is the model estimate of HIV prevalence in pregnant women aged x to x + 4, in year t, where the vector  $\mathbf{\varphi}$  represents the values of the model input parameters. This is calculated from equation (6.3) as

$$H_{x,t}(\mathbf{\phi}) = 1 - \frac{\sum_{j=x}^{x+4} F(j,t) N_{0,0,0}^{1}(j,t)}{\sum_{j=x}^{x+4} \overline{F}(j,t) \sum_{i,a,s,d} N_{a,s,d}^{i}(j,t)}.$$
(7.1)

The corresponding prevalence of HIV actually measured in the antenatal survey is represented by  $y_{x,t}$ . It is assumed that if  $\varphi$  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

$$\log\left(\frac{y_{x,t}}{1-y_{x,t}}\right) = \log\left(\frac{H_{x,t}(\mathbf{\varphi})}{1-H_{x,t}(\mathbf{\varphi})}\right) + b + m_{x,t} + \varepsilon_{x,t}, \qquad (7.2)$$

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

$$\hat{b} = \frac{1}{90} \sum_{x} \sum_{t=1997}^{2014} \left( \log \left( \frac{y_{x,t}}{1 - y_{x,t}} \right) - \log \left( \frac{H_{x,t}(\boldsymbol{\varphi})}{1 - H_{x,t}(\boldsymbol{\varphi})} \right) \right).$$
(7.3)

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  $\sigma_m^2$  parameter is estimated using the formula

$$\hat{\sigma}_{m}^{2} = \frac{1}{90} \sum_{x} \sum_{t} \left( \log \left( \frac{y_{x,t}}{1 - y_{x,t}} \right) - \log \left( \frac{H_{x,t}(\mathbf{\varphi})}{1 - H_{x,t}(\mathbf{\varphi})} \right) - \hat{b} \right)^{2} - \sigma_{x,t}^{2}.$$
(7.4)

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

$$L(\mathbf{y} \mid \boldsymbol{\varphi}) = \prod_{x} \prod_{t} \left( 2\pi (\hat{\sigma}_{m}^{2} + \sigma_{x,t}^{2}) \right)^{-0.5} \exp \left[ -\frac{\left( \text{logit}(y_{x,t}) - \text{logit}(H_{x,t}(\boldsymbol{\varphi})) - \hat{b} \right)^{2}}{2 (\hat{\sigma}_{m}^{2} + \sigma_{x,t}^{2})} \right], \quad (7.5)$$

where **y** represents the matrix of  $y_{x,t}$  values, across age bands 15-19 to 35-39, and across calendar years 1997 to 2014.

#### 7.2.2 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 [16], 2008 [17] and 2012 [117]. 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 [324, 325], 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 antenatal survey estimates, and the model error would therefore be small relative to the survey error.

#### 7.2.3 Likelihood definition for recorded death data

To calculate the likelihood in respect of the reported death data, we restrict this analysis to deaths occurring over the period from the start of 1997 to the end of 2014 [326]. Because cause of death information is seldom captured accurately, and reported AIDS deaths are

likely to be only a fraction of the actual HIV-related deaths [327], we compare model estimates of all-cause mortality with reported levels of all-cause mortality. This comparison is only likely to be meaningful in those age groups in which a substantial proportion of deaths are HIV-related, and this analysis is therefore restricted to deaths occurring from ages 20 to 59. Mortality data are grouped in 5-year age bands for calibration purposes, and estimates are considered separately for males and females.

Suppose that  $\Theta_{g,x,t}(\varphi)$  represents the model estimate of the number of deaths in individuals of sex g, between ages x and x + 4, in year t, where the vector  $\varphi$  represents the values of the model input parameters. Further suppose that  $R_{g,x,t}$  represents the reported number of deaths in individuals of sex g, between ages x and x + 4, in year t. In order to specify a likelihood function for the reported death data, it must be assumed that a certain proportion of adult deaths,  $\gamma_{g,x,t}$ , is reported. It is assumed that if  $\varphi$  is the true set of parameter values, then the difference between the log-transformed model estimate of the number of reported deaths ( $\Theta_{g,x,t}(\varphi)\gamma_{g,x,t}$ ) and the log-transformed actual number of reported deaths is normally distributed with zero mean. More formally, the likelihood is calculated on the assumption that

$$\log(R_{g,x,t}) = \log(\Theta_{g,x,t}(\varphi)\gamma_{g,x,t}) + \varepsilon_{g,x,t}, \qquad (7.6)$$

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

The  $\gamma_{g,x,t}$  parameters have been estimated from a variety of sources. Over the period from October 1996 to October 2001, Dorrington et al [328] estimate that the fraction of adult deaths recorded was 84%, based on death distribution methods (i.e. based on comparing the recorded numbers of adult deaths to the changes in the population sizes in each age cohort over the inter-census period). The authors also estimate that the annual increase in the proportion of deaths recorded, over this 5-year period, was 1.7% in men and 2.1% in women, based on an assumption of stable mortality rates at ages 65 and older (where AIDS would be expected to have relatively little impact on mortality). In the period after 2001, estimates of the completeness of adult death recording have been around 93%, based on similar methods [329-331]. Based on these estimates, we set initial completeness assumptions – independent of age and sex – that increase linearly from 80.2% in 1997 to 87.8% in 2001 (an increase of 1.9% per annum, with 84% completeness in 1999) and 93% in 2004, after which completeness is assumed to remain constant (Table 7.2). The assumption of constant completeness after 2004 is supported by an analysis of factors affecting the recording of deaths in ART patients, which showed no significant change in the completeness of vital registration over the 2004-2014 period [332].

In the final set of completeness assumptions, we use the completeness estimates by age and sex, as estimated in the analysis of factors affecting the recording of deaths in ART patients over the 2004-2014 period [332], and scale these down by the ratio of initial completeness assumptions to 0.93 in the period prior to 2004. The completeness assumptions are shown in Table 7.2.

Year	1997	1998	1999	2000	2001	2002	2003	2004+
Initial completeness assumptions								
	0.802	0.821	0.84	0.859	0.878	0.897	0.914	0.930
Final completeness assumptions								
Women aged								
20-24	0.798	0.817	0.836	0.855	0.874	0.892	0.909	0.925
25-29	0.809	0.828	0.847	0.866	0.886	0.905	0.922	0.938
30-34	0.817	0.836	0.855	0.875	0.894	0.913	0.931	0.947
35-39	0.823	0.842	0.862	0.881	0.901	0.920	0.937	0.954
40-44	0.827	0.847	0.866	0.886	0.905	0.925	0.943	0.959
45-49	0.831	0.850	0.870	0.890	0.909	0.929	0.947	0.963
50-54	0.834	0.853	0.873	0.893	0.913	0.932	0.950	0.967
55-59	0.836	0.856	0.876	0.895	0.915	0.935	0.953	0.969
Men aged								
20-24	0.756	0.774	0.792	0.810	0.828	0.846	0.862	0.877
25-29	0.772	0.791	0.809	0.827	0.845	0.864	0.880	0.896
30-34	0.789	0.807	0.826	0.845	0.863	0.882	0.899	0.914
35-39	0.802	0.821	0.840	0.859	0.878	0.897	0.914	0.930
40-44	0.813	0.832	0.852	0.871	0.890	0.909	0.927	0.943
45-49	0.821	0.841	0.860	0.880	0.899	0.918	0.936	0.952
50-54	0.827	0.847	0.866	0.886	0.906	0.925	0.943	0.959
55-59	0.832	0.851	0.871	0.891	0.910	0.930	0.948	0.964

Table 7.2: Completeness assumptions (fraction of deaths that are recorded)

The maximum likelihood estimate of the parameter  $\sigma_d^2$  is calculated as

$$\hat{\sigma}_{d}^{2} = \frac{1}{288} \sum_{g} \sum_{x} \sum_{t=1997}^{2014} \left[ \log(R_{g,x,t}) - \log(\Theta_{g,x,t}(\phi)\gamma_{g,x,t}) \right]^{2}.$$
(7.7)

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

$$L(\mathbf{R} \mid \mathbf{\phi}) = \prod_{g} \prod_{x} \prod_{t=1997}^{2014} \left( 2\pi \hat{\sigma}_{d}^{2} \right)^{-0.5} \exp\left( -\frac{\left( \log(R_{g,x,t}) - \log(\Theta_{g,x,t}(\mathbf{\phi})\gamma_{g,x,t}) \right)^{2}}{2\hat{\sigma}_{d}^{2}} \right), \quad (7.8)$$

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

#### 7.3 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 7.1 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.

# 8. Results of model calibration

## 8.1 Comparison of prior and posterior distributions

Table 8.1 compares the prior and posterior means for the 11 parameters that are allowed to vary when fitting the model to the adult HIV prevalence data and mortality data. For most of these parameters, the prior and posterior distributions overlap substantially, though the posterior 95% confidence intervals are substantially narrower, reflecting the increased precision due to the HIV prevalence data and mortality data. There is significant evidence to suggest that HIV virulence has declined over time, with the posterior distribution for the relative rate of disease progression per calendar year being significantly different from the corresponding prior distribution.

• • • •	Prior distribution	Posterior distribution
	(mean, 95% CI)	(mean, 95% CI)
Average survival in absence of ART (years)	12.00 (10.12-14.04)	11.51 (11.23-11.82)
RR of HIV disease progression in women	0.960 (0.864-1.060)	0.929 (0.901-0.959)
Increase in HIV disease progression per	0.180 (0.082-0.315)	0.241 (0.215-0.265)
10-year increase in age		
RR of HIV disease progression per calendar year	1.000 (0.987-1.013)	0.977 (0.971-0.982)
IeDEA-SA bias <6 months after ART start	1.850 (1.004-2.951)	1.270 (1.018-1.512)
Ratio of IeDEA-SA bias >42 months after ART	0.800 (0.616-1.008)	0.702 (0.597-0.836)
start to bias <6 months after ART start		
Reduction in mortality* per unit increase in rate of	7.50 (2.29-15.76)	4.59 (3.71-5.64)
ART initiation (at CD4<200) over last 3 years		
Female-to-male transmission probability in short-term/	0.0080 (0.0032-0.0149)	0.0071 (0.0067-0.0074)
non-spousal partnerships		
Male-to-female transmission probability in short-term/	0.0120 (0.0043-0.0236)	0.0206 (0.0197-0.0217)
non-spousal partnerships		
Ratio of increase in infectivity* to increase in	1.000 (0.078-3.066)	0.091 (0.072-0.112)
disease progression,* per unit change in SPVL		
Initial HIV prevalence in high risk women, ages 15-49	0.100% (0.005-0.195%)	0.187% (0.17-0.194%)

## 8.2 Calibration to adult HIV prevalence data

Figure 8.1 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 8.2).



Figure 8.1: HIV prevalence levels in pregnant women attending public antenatal clinics Dots represent HIV prevalence levels reported in surveys conducted from 1990-2014 (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. Survey data in the pre-1997 period are included in the graphs even though they were not used in defining the likelihood function.



Figure 8.2: 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.

The model does not provide a good fit to the HIV prevalence data from sex workers (Figure 8.3(a)), with the early surveys [14, 43, 164, 334, 335] tending to measure a higher prevalence than estimated by the model, and the more recent surveys estimating a lower prevalence than the model [38, 46, 49, 336, 337]. However, none of the sex worker surveys is nationally representative, and some degree of divergence is therefore to be expected. Survey estimates of HIV prevalence in MSM are highly variable, reflecting variation in geographic locations and sampled populations [5-7, 9, 338], although the model estimates of HIV prevalence in MSM are roughly consistent with the average of the survey estimates (Figure 8.3(b)).



Figure 8.3: HIV prevalence in key populations 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.

#### 8.3 Calibration to adult mortality data

Figure 8.4 compares the model estimates of deaths over the 20-59 age range with the corresponding recorded numbers of deaths (after adjusting the latter for incomplete vital registration). Model estimates are in good agreement with the data in most years, although the model slightly over-estimates the numbers of recorded deaths in men in the most recent year for which data are available (2014), as well as the numbers of recorded deaths in women in 2005 and 2006. Similar patterns are observed when age-specific comparisons are performed (Figure 8.5). The model does not fit the recorded numbers of male deaths in the 50-59 age group well, which could be an indication of problems with the non-HIV mortality assumptions.



Figure 8.4: Numbers of deaths in adults aged 20-59

Dots represent recorded numbers of deaths, after adjusting for incomplete registration. Solid lines represent the posterior mean model estimates.



Figure 8.5: Numbers of deaths in adults, by five-year age group Dots represent recorded numbers of deaths, after adjusting for incomplete registration. Solid lines represent the posterior mean model estimates.

# 8.4 Calibration to paediatric HIV prevalence and mother-to-child transmission data

Figure 8.6 compares the model estimates of HIV prevalence in children with the results from the three HSRC surveys conducted in 2005, 2008 and 2012. Although the model estimate of HIV prevalence in 2005 is significantly lower than the survey estimate in that year, model estimates in subsequent year appear more consistent with the surveys.



Figure 8.6: HIV prevalence in children aged 2-14 Dots represent survey prevalence estimates. Solid lines represent the posterior mean model estimates of HIV prevalence.

Figure 8.7 compares the model estimates of mother-to-child transmission rates from recent surveys with corresponding model estimates. Model estimates of perinatal mother-to-child transmission rates are reasonably close to routine data sources (Figure 8.6(a)), which include the District Health Information System (DHIS) [339] and the National Health Laboratory Service (NHLS) [302]. However, these estimates of perinatal transmission are underestimates of the total perinatal transmission because they do not reflect transmission from mothers who are undiagnosed. There is a lack of data on postnatal transmission rates, although the SAPMTCTE study, which followed mothers who were diagnosed either antenatally or at their 6-week immunization visit, found that cumulative transmission (perinatal and postnatal) up to 18 months was 4.3% (95% CI: 3.8-5.0%) [340]. Our model estimates are consistent with this survey (Figure 8.6(b)), although the definition of postnatal transmission considered here is an under-estimate of all postnatal transmission, since some transmission occurs after 18 months, and substantial transmission occurs from mothers who are undiagnosed.



Figure 8.7: Mother-to-child transmission rates

Dots represent survey prevalence estimates. Solid lines represent the posterior mean model estimates of HIV prevalence. In panel (a), the denominator is all HIV-positive women who were diagnosed antenatally (excluding mothers who were not diagnosed), and in panel (b) the denominator is the number of HIV-positive mothers who were diagnosed either antenatally or at their 6-week immunization visit (again excluding mothers who were not diagnosed). Panel (a) represents only perinatal transmission, while panel (b) represents combined perinatal and postnatal transmission.

#### 8.5 Calibration to ART data

Figure 8.8 compares the model estimates of numbers of ART patients (after adjusting to exclude the independently-estimated numbers receiving ART in the private sector) with the reported numbers of patients receiving ART in the public sector. In the period up to 2009, when public sector statistics reflected mostly cumulative enrolment, model estimates of cumulative enrolment appear consistent with the reported data. However, from 2012 onward, model estimates of current enrolment are more consistent with the data than the model estimates of cumulative enrolment, reflecting the gradual transition to reporting of current enrolment that started in late 2009.



Figure 8.8: ART enrolment in the South African public sector

Dots represent reported numbers receiving ART in the public sector. Solid and dashed lines represent the posterior mean model estimates of numbers currently and cumulatively enrolled on the ART programme, respectively.

Figure 8.9 shows that the modelled age distribution of adults starting ART matches that in South African patients starting ART between 2002 and 2009, in a number of cohorts participating in the IeDEA-SA collaboration [341].



Figure 8.9: Fraction of adult age patients starting ART in different age groups

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 [155] (Figure 8.10). Although these data have not been used in defining the likelihood function, the model is remarkably consistent with the observed age distribution.


Figure 8.10: Fractions of children starting ART in different age groups Solid lines represent posterior means. Dots represent data from the national ART monitoring system [155].

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# Appendix A: Mathematical approach to modelling sexual behaviour

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

#### A.1 Non-spousal heterosexual relationships

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

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

where  $c_{g,i,l}(x)$  is the annual rate of non-marital partnership formation in individuals aged x, of sex g and marital status l, who are in risk group i (1 for high risk, 2 for low risk). For low-risk women the number of new partnerships is just

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

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

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

where  $f_{g,l}(y | x)$  is the probability that for an individual of sex g and age x, in a relationship of type l, the partner's age is y (as defined in section 2.6). The rate at which unmarried men in the high risk group form new heterosexual partnerships in year t is then calculated by observing that

$$\Phi_{1,1}(y,t) + \Phi_{1,2}(y,t) = (N_{1,1,0}(y,t) + N_{1,1,3}(y,t)(1 - \Omega(y)))c_{1,1,0}(y,t) + + (N_{1,2,0}(y,t) + N_{1,2,3}(y,t)(1 - \Omega(y)))c_{1,1,0}(y,t)L_1 + (N_{1,1,1}(y,t) + N_{1,1,2}(y,t))c_{1,1,0}(y,t)R_1$$

where  $L_1$  and  $R_1$  are the relative rates of non-spousal partnership formation in unmarried low-risk men and married high-risk men respectively (expressed as multiples of the rate in unmarried high-risk men) and  $\Omega(y)$  is the fraction of partners who are men, among MSM aged y. From this we calculate

$$c_{1,1,0}(y,t) = \frac{\Phi_{1,1}(y,t) + \Phi_{1,2}(y,t)}{N_{1,1,0}(y,t) + N_{1,2,0}(y,t)L_1 + (N_{1,1,3}(y,t) + N_{1,2,3}(y,t)L)(1 - \Omega(y))} + (N_{1,1,1,1}(y,t) + N_{1,1,2}(y,t))R_1$$

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

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

$$f_{1,0}(x \mid y,t) = \frac{\left(\Phi_{2,1}(x,t) + \Phi_{2,2}(x,t)\right)f_{2,0}(y \mid x)}{\Phi_{1,1}(y,t) + \Phi_{1,2}(y,t)}$$

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

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

$$\Phi_{1,1}(.,t) = \sum_{y=10}^{90} \left\{ N_{1,1,0}(y,t) + N_{1,1,3}(y,t) (1 - \Omega(y)) + \left( N_{1,1,1,1}(y,t) + N_{1,1,1,2}(y,t) \right) R_1 \right\} c_{1,1,0}(y,t)$$

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

$$\Phi_{1,2}(.,t) = \sum_{y=10}^{90} \left( N_{1,2,0}(y,t) + N_{1,2,3}(y,t) (1 - \Omega(y)) \right) c_{1,1,0}(y,t) L_1.$$

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

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

where  $\varepsilon$  is the assortativeness parameter described in section 2.5, and I(i = j) is an indicator function (taking on value 1 when i = j and value 0 when  $i \neq j$ ). For men who are in risk group j in year t, the probability that their female non-spousal partner is in risk group i is calculated as

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

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

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

$$f_{1,1}(x \mid y,t) = \frac{\left(N_{2,1,1,1}(x,t) + N_{2,1,1,2}(x,t) + N_{2,2,1,1}(x,t) + N_{2,2,1,2}(x,t)\right)f_{2,1}(y \mid x)}{\sum_{\nu=15}^{90} \left(N_{2,1,1,1}(\nu,t) + N_{2,1,1,2}(\nu,t) + N_{2,2,1,1}(\nu,t) + N_{2,2,1,2}(\nu,t)\right)f_{2,1}(y \mid \nu)}.$$

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

The number of men in risk group *i* who enter spousal relationships in year *t* is calculated as

$$D_{1,i}(t) = \sum_{y=15}^{90} \left( N_{g,i,0}(y,t) + N_{g,i,3}(y,t) \right) m_{g,i}(y,t),$$

where  $m_{g,i}(y,t)$  is the annual probability of forming a new spousal relationship at age y. A similar formula is used to calculate the number of women who enter spousal relationships, except that the MSM term  $(N_{g,i,3}(y,t))$  is omitted. For women who are in risk group *i*, entering into a spousal relationship in year *t*, the probability that their new partner is in risk group *j* is

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

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

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

100

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

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

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

where  $w_l(x)$  is the rate at which HIV-negative men visit sex workers (as defined in section 2.4), Y(a, s, d) is the adjustment made to the coital frequencies of HIV-positive individuals (as defined in section 4.6), and C is the assumed average annual number of clients per sex worker. MSM are assumed to have no contact with female sex workers. As explained in section 2.4, there is assumed to be a constant sex worker age distribution, with  $\phi(x)$  representing the fraction of sex workers who are aged x years. The required number of sex workers aged x at time t is therefore  $E(t)\phi(x)$ .

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

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

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

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

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

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

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

The variables  $\tau(a, s, d)$  and W(a, s, d), discussed in section 2.4, are a function only of current CD4 count in untreated individuals (*s*), but for treated individuals the variable *s* represents the baseline CD4 category. In treated individuals the  $\tau(a, s, d)$  and W(a, s, d) variables are therefore calculated based on the expected distribution of current CD4 counts in individuals who started ART in CD4 category *s*, *d* years previously. This expected CD4 distribution is defined in Table 4.3.

#### A.5 Divorce and widowhood

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

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

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

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

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

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

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

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

A.6 Partner age preferences in MSM

Few studies report on age mixing patterns in MSM relationships in the South African setting. Arnold *et al* [31] found that in 758 male-male sexual relationships in Soweto, the average partner age difference was small (0.25 years) but there was high variation in partner age differences (standard deviation of 5.8 years). Based on what is known about the age distribution of sexually active MSM in South Africa, it is possible to use this information to determine how patterns of age mixing vary in relation to age. If N(x) is the age distribution of sexually active MSM and  $f_{1,3}(y | x)$  represents the proportion of male partners aged y for an MSM aged x, then for a random sample of MSM, the expected proportion of their partners who are aged y is

$$\int N(x)f_{1,3}(y \mid x)dx.$$

If the sample of sexually active MSM is truly representative, then we would expect that this proportion should be the same as N(y). We would also expect that

$$\int N(x) \int f_{1,3}(y \mid x) (x - y)^2 \, dy \, dx = 5.8^2 \,,$$

if the estimated standard deviation of 5.8 years [31] is correct. These constraints allow us to determine the likely patterns of sexual mixing. It is assumed that N(x) is a gamma distribution, with a mean of 25 years and a standard deviation of 7 years [31, 338], with an age offset of 10 years to prevent implausible levels of sexual activity in very young boys. The  $f_{1,3}(y | x)$  distribution is also assumed to be of gamma form, with mean of  $\mu(x) = \max(x-10, x + A(25-x))$  and variance of  $B^2$  (again, with an offset of 10 years to prevent sexual activity at young ages). The two free parameters, A and B, have been set to 0.45 and 5.0 years respectively, to yield a variance of partner age differences equal to  $5.8^2$ , as well as a distribution of  $\int N(x) f_{1,3}(y | x) dx$  values roughly consistent with the distribution of N(y) values (Figure A1).



Figure A1: Age distribution of sexual activity in South African MSM