Thembisa version 4.2:
A model for evaluating the impact of HIV/AIDS in South Africa

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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 are published separately [1]. Readers who are interested in the outputs of the model are referred to the Thembisa website (www.thembisa.org), which includes various model output files.

This document describes version 4.2 of the Thembisa model, and is similar in structure and content to the previous report that described version 4.1 of the model [2]. Briefly, the main changes to the previous version of the model are as follows:

- The paediatric HIV model has been revised, based on calibration to recorded numbers of deaths in children. This has led to substantially different estimates of untreated HIV mortality (higher in the first year of life but lower than assumed previously in older children).
- The model of male circumcision has been revised, assuming that the demand for traditional and medical male circumcision are mutually exclusive, i.e. that the men who choose to get medically circumcised would not otherwise have been circumcised.
- The model of HIV testing has been revised to allow for age differences in HIV testing in children, as well as changes over time in the relative rate of testing in previously-tested individuals.
- The model has been updated using more recent programmatic data (numbers of individuals tested for HIV, numbers of patients receiving antiretroviral treatment (ART), numbers of medical male circumcision (MMC) operations).
- The model of viral suppression after ART initiation has been updated to include more recent viral suppression data and to allow for non-linear trends in viral suppression. The revised model also allows for different rates of viral suppression in adults and children.
- The model now assumes shorter average PrEP durations, based on the low rates of retention observed in South African PrEP programmes.
- Several new data sources have been incorporated in the model calibration process, including the 2015-2016 recorded death statistics, the 2016 Demographic and Health Survey HIV prevalence data, and the 2017 HSRC household survey estimates of the fractions of adults ever tested for HIV.

The model is deterministic and compartmental. Being compartmental means that the population is divided into various cohorts and sub-cohorts; these are summarized in Table 1.1. The indexing variables for each compartment, which are used throughout this report, are also shown in Table 1.1.

Table 1.1: Index variables and compartments in Thembisa

Symbol	Description	Value	Definition
a	ART status	0	ART-naïve
		1	On ART or previously treated
d	Time since	0	ART-naïve
	ART	1	1st 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**	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 ≥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)
y	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.

The large number of parameters in the Thembisa model makes the calibration of the model challenging. There are many data sources that the model needs to be calibrated to, and there are also many parameters that can be varied in the calibration process. Rather than simultaneously vary all of the parameters to fit the model to all the available data (which would be computationally impractical), we break the calibration down into a number of steps. Each step involves varying a subset of the model parameters to match the model to a subset of the calibration data, the parameter subsets being chosen based on their relative importance in determining the model fit to the relevant data source. The steps in the calibration process are summarized in Table 1.2. Some of the model parameters can only be determined at a national level, as province-specific data are lacking, while in other cases (for example, annual numbers of patients starting ART), the parameters are estimated at a provincial level and are then aggregated to obtain the national model parameters. In a few cases (for example, the

initial HIV prevalence), the model parameter is estimated independently for the national and provincial models. Although the main focus of this report is on the calibration of the model to the adult HIV prevalence and mortality data at a national level (described in more detail in section 7 of the report), the appendices and the provincial modelling report describe the other steps in the calibration in more detail (as shown in the last column of Table 1.2).

Table 1.2: Steps in the Thembisa calibration process

Step	Data sources in calibration	Parameters varied	Description
1. Calibrate to provincial ART totals	Reported total numbers of patients on ART, by province	Annual numbers starting ART Changes in ART reporting	Provincial modelling report
2. Calibrate to provincial ART totals (paediatric)	Reported total numbers of children on ART, by province	Annual numbers of children starting ART	Provincial modelling report
3. Calibrate to HIV testing data	% of adults ever tested HIV prevalence in adults tested HIV prevalence in children tested Number of HIV tests in children Reported total numbers of children on ART	Rates of HIV testing in adults Rates of HIV testing in children	Appendix B
4. Calibrate to key population prevalence data	HIV prevalence data in FSWs HIV prevalence data in MSM	Client-to-FSW and male-to-male transmission probabilities Effect of HIV diagnosis on entry into commercial sex	Appendix C
5. Calibrate to paediatric HIV data	Paediatric HIV prevalence in household surveys Reported total numbers of children on ART Age distribution of children starting ART Recorded numbers of deaths in children	Rates of mother-to-child transmission of HIV Paediatric disease progression Paediatric linkage to ART after diagnosis Mortality after ART initiation in children	Appendix E
6. Calibrate to adult mortality & HIV prevalence data	HIV prevalence in antenatal and household surveys Recorded numbers of adult deaths	Heterosexual transmission probabilities per sex act Initial HIV prevalence (1985) Adult HIV disease progression ART impact on mortality	Section 7
7. Calibrate to provincial HIV prevalence data	HIV prevalence in antenatal and household surveys	Sexual behaviour Antenatal bias Initial HIV prevalence (1985)	Provincial modelling report

ART = antiretroviral treatment. FSW = female sex worker. MSM = men who have sex with men.

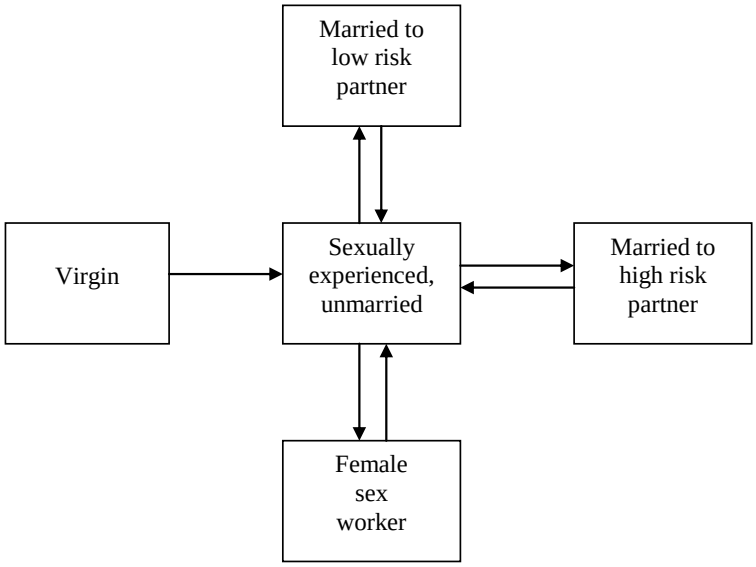
Two versions of the Thembisa model have been developed: one programmed in C++ and one programmed in Excel and Visual Basic. This report describes the C++ version of the model. Although the Excel model is almost identical, there are a few minor technical differences, and the outputs of the Excel model are therefore not exactly the same as those of the C++ model. The Excel version of the model is freely available from the Thembisa website (www.thembisa.org), together with a user guide. The C++ model, although not programmed in a user-friendly format, is available on request.

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 same-sex activity. There are thus three types of relationship considered in the model: long-term relationships (marital/cohabiting), short-term relationships (non-marital and non-cohabiting) and 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 same-sex 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 [3-6]. 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 [4, 7]. 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 ensures some degree of consistency with the low rates of marriage noted previously.

(a) High risk females



(b) High risk males

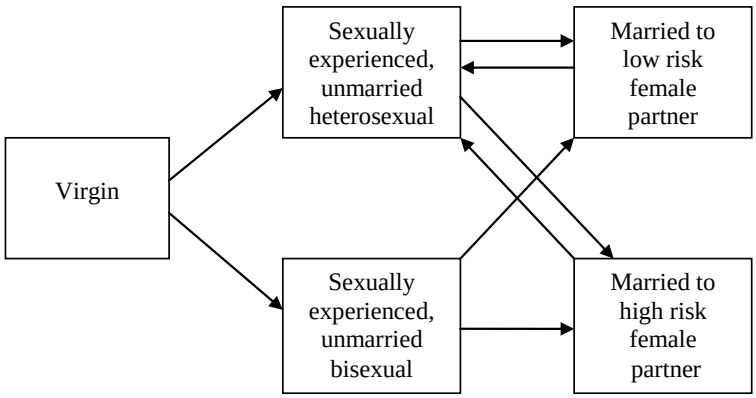


Figure 2.1: Transitions between relationship states

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 [8-10].

Table 2.1: Sexual behaviour assumptions

Parameter	Men*	Women	Reference
Initial % of population in high-risk group	35%	25%	[8-10]
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	
Relative rate of short-term partnership formation in married high risk adults (compared to unmarried high risk)	0.33	0.14	Calibrated (see [11])
Relative rate of short-term partnership formation in unmarried low risk adults (compared to unmarried high risk)	0.37	0.16	Calibrated (Thembisa v2.5)
Mean age difference between partners in short-term relationships	-	3	[12-16]
Standard deviation of age difference in short-term relationships	-	3	
Mean age difference between partners in long-term relationships	-	6	[17]
Standard deviation of age difference in long-term relationships	-	5	

* 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 [18-23]. 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 [14, 24, 25], as demonstrated in Figure 2.2. Rates of sexual debut are assumed to be the same for heterosexual and bisexual men [26, 27].

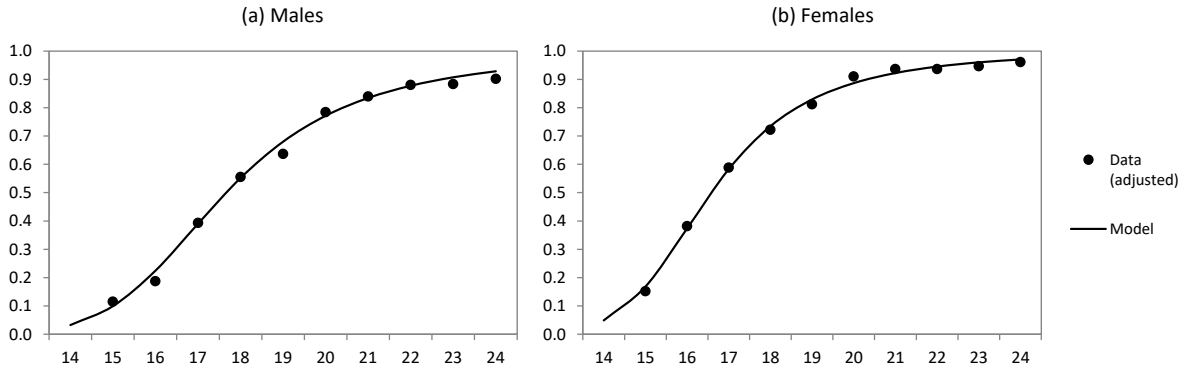


Figure 2.2: Proportion of youth who are sexually experienced, by age and sex
Data in panel (b) have been adjusted to reflect probable under-reporting of sexual experience by young women (assuming that the odds ratio relating true sexual experience to reported average sexual experience is 2 [28]).

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

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

where the λ and α parameters determine the mean and variance of the gamma distribution, and the offset of 10 years is included to prevent sexual activity below age 10. 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 [29]. The mean and standard deviation of the gamma density have been set to 38.71 and 19.38 respectively, and λ and α 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

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

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

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

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 [11]. 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 [30] 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 [29], 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 [31], applying a multiple of 2 to the crude rates to reflect known biases in divorce statistics [32]. Age-specific rates of marriage and divorce are shown in Table 2.3.

Table 2.3: Age-specific behavioural parameters

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

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

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) [33] and that the effect of age is determined by a gamma scaling function with parameters λ_1 and α_1.The formula used to determine the rate of male contact with sex workers is thus

$$w_l(x) = K \frac{\lambda_1^{\alpha_1}(x-10)^{\alpha_1-1}\exp(-\lambda_1(x-10))}{\lambda_1^{\alpha_1}(21.5-10)^{\alpha_1-1}\exp(-\lambda_1(21.5-10))}0.25^l$$
$$= K \times \left(\frac{x-10}{11.5}\right)^{\alpha_1-1} \exp(-\lambda_1(x-21.5)) \times 0.25^l, \quad (2.4)$$

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 [34].) The parameters λ_1 and α_1 are set at 0.37 and 11.1 respectively. With these parameters, the model simulates a client age distribution in 1995 that has a mean of 35.0 years and a standard deviation of 7.9 years, roughly consistent with observed client age distributions in the early stages of South Africa's HIV epidemic [35, 36] as well as a more recent survey (Tim Lane, personal communication [37]). 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 [38], assuming that the average sex worker has 750 client contacts per annum [39-46]. (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 [12, 41, 43-50]. Women are assumed to retire from commercial sex at a rate of 0.33 per annum [41, 42, 44].

2.5 Preferences regarding partner risk group

Mixing between the high- and low-risk groups is determined by a sexual mixing parameter, ε. This parameter takes on values between 0 and 1, 0 implying completely assortative sexual mixing (i.e. individuals only choose sexual partners from their own risk group), and 1 implying random sexual mixing (i.e. individuals have no preferences regarding the risk group of their partners and choose partners in proportion to their availability) [51]. The ε parameter is difficult to determine from empirical data, and we have therefore assigned a beta prior distribution to represent the uncertainty around this parameter. The mean and standard

deviation of this prior distribution are 0.48 and 0.10 respectively, based on the distribution of values estimated when the model was previously fitted for each of the 9 provinces [52]. 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 $f_{g,l}(y \mid x)$ represents the probability that, for an individual of sex *g* and age *x*, in a relationship of type *l*, the partner's age is *y*. We model female age preferences regarding married partner ages using gamma distributions. For married women aged *x*, the *preferred* age distribution of the marital partners is assumed to have a mean of (*x* + 6), and a standard deviation of 5 years. This gamma distribution is adjusted to take into account relative numbers of available men at different ages. These assumptions yield marital partner age distributions consistent with those observed in the 1998 Demographic and Health Survey (DHS). Mathematically, the probability that a married woman aged *x* has a husband between the ages of *y* and *y* + 1 is

$$f_{2,1}(y \mid x) \equiv \int_{y}^{y+1} \frac{\left(\lambda_2(x)+\xi(x)\right)^{\alpha_2(x)}\left(t-\min(x)\right)^{\alpha_2(x)-1}}{\Gamma\left(\alpha_2(x)\right)\exp\left(\left(\lambda_2(x)+\xi(x)\right)\left(t-\min(x)\right)\right)}dt\,, \qquad (2.5)$$

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 $x \geq 17$ (so that the origin of the gamma distribution is at this minimum age and not at zero, in order to prevent unrealistically low married male ages). The $\xi(x)$ parameters are updated dynamically each year as the population pyramid changes.

For women who are aged *x* and in non-marital relationships, the age distribution of non-marital partners is assumed to have a mean of (*x* + 3), and a standard deviation of 3 years, consistent with partner age distributions reported by young women in various South African studies [12-16]. 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 ($f_{1,l}(y \mid x)$) are calculated to be consistent with the distributions specified for women, taking into account the relative rates of partnership formation at different ages, and relative numbers of men and women at different ages. Further mathematical detail is provided in Appendix A. Appendix A also describes the approach to modelling age mixing patterns in MSM ($f_{1,4}(y \mid x)$).

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

[14, 16, 53, 54] and an average non-marital relationship duration of 6 months [29]. 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 [29].

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, γ^*, which is the probability of condom use for a woman aged 20 in a short-term relationship in 1998. The following formula is used to calculate $\gamma_{2,l}(x,t)$:

$$\ln\left(\frac{\gamma_{2,l}(x,t)}{1-\gamma_{2,l}(x,t)}\right)=\ln\left(\frac{\gamma^*}{1-\gamma^*}\right)+\chi_l+\nu_l(x-20)+\varsigma_l(t) \qquad (2.6)$$

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;
$\exp(\nu_l)$ = the factor by which the odds of condom use reduces, per year of age;
$\exp(\varsigma_l(t))$ = the odds of using a condom in year *t*, relative to that in 1998, for relationship type *l*.

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,

$$\varsigma_l(t)=\kappa_l^1+\left(\kappa_l^2-\kappa_l^1\right)\left(1-0.5^{(t/M_l^1)^{Q_l}}\right)-\left(\kappa_l^2-\kappa_l^3\right)\left(1-0.5^{(t/M_l^2)^{2Q_l}}\right) \qquad (2.7)$$

where *t* is time in years since 1985, and the other variables are defined as follows:
κ_l^1 represents the initial rate of condom use in relationship type *l*, in 1985 (relative to the baseline in 1998);
$\kappa_l^2-\kappa_l^1$ represents the increase in condom use in relationship type *l*, following initial HIV communication programmes;

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

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

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

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

The values assumed for these parameters, and the data sources on which they are based, are summarized in Table 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 [11], and the calibrated parameters were therefore adjusted downward so that the modelled proportions of women using condoms were closer to the proportion of women who reported using condoms for contraceptive purposes.

Table 2.4: Condom usage assumptions

Parameter	Symbol	Value	Source
'Baseline' condom usage	γ^*	0.104	[17], calibrated
OR for condom use in marital relationships (1998)	$\exp(\chi_1)$	0.46	[17]
OR for condom use in commercial sex (1998)	$\exp(\chi_2)$	6.0	[12, 47]
OR for condom use per year increase in age	$\exp(\nu_l)$	0.975†	[17, 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	[36]
Maximum OR for condom use (relative to 1998)			
Non-marital relationships	$\exp(\kappa_0^2)$	4.6	[14, 15, 25], calibrated
Marital relationships	$\exp(\kappa_1^2)$	2.16	
Commercial sex	$\exp(\kappa_2^2)$	3.8	[50, 58], calibrated
Shape parameter: speed of behaviour change			
Non-marital relationships	Q_0	3.6	Calibrated
Marital relationships	Q_1	3.24	Calibrated
Commercial sex	Q_2	3.8	Calibrated
Median time to reversal of behaviour change (in years since 1985)	M_l^2	26	Calibrated

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

We define $R = \left(\kappa_l^2 - \kappa_l^3\right)/\kappa_l^2$ to be the extent of the reversal in condom use (due to risk compensation and/or reductions in condom promotion). When $R = 0$, there is no reversal of the behaviour change that occurred early in the HIV epidemic, and when $R = 1$, $\varsigma_l(t)$ tends to zero as *t* tends to infinity, i.e. condom use returns to the 'base' levels assumed in 1998. As the parameter *R* is difficult to quantify precisely, we assign a uniform (0, 1) prior distribution to represent the uncertainty regarding the *R* parameter. The model allows for reversals of condom use only in the context of short-term and long-term relationships, and not in the

context of sex worker-client interactions (as condom use amongst sex workers has been high in recent surveys [50, 58]).

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

$$M_l^1 = 13\left\{\left(\ln\left[\kappa_l^3 + \left(\kappa_l^2 - \kappa_l^3\right)0.5^{(13/M_l^2)^{2Q_l}}\right] - \ln\left(\kappa_l^2 - \kappa_l^1\right)\right) \Big/ \ln(0.5)\right\}^{-1/Q_l} \qquad (2.8)$$

The resulting trends in women's condom use, by relationship type, are shown in Figure 2.3 (for the purpose of this illustration, we have set R = 0.5). 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 $f_{1,l}(y \mid x)$ is the probability that a female partner is aged y, if the male partner is aged x. The rate of condom use among clients of sex workers is the same as that estimated for sex workers, with no age dependency. It is also assumed that the rate of condom use in same-sex relationships is the same as that in heterosexual relationships [26, 27, 59].

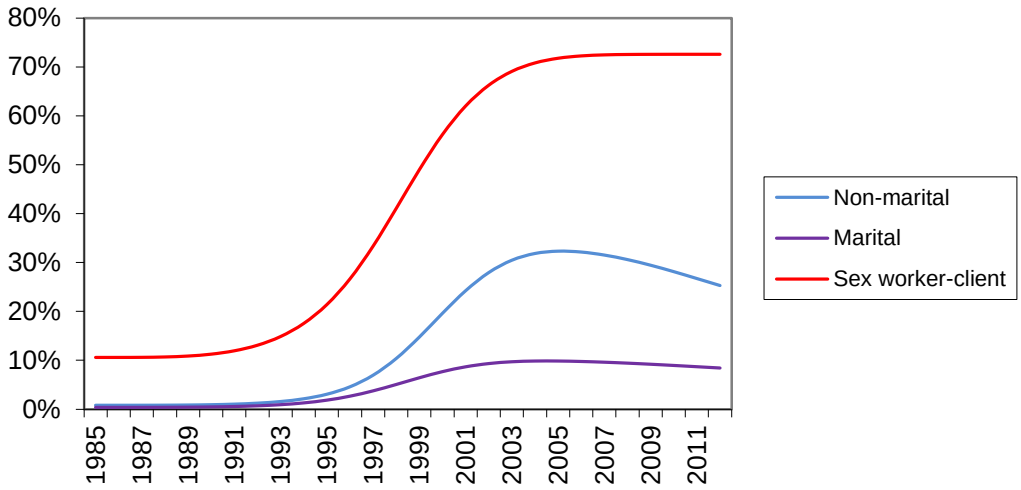


Figure 2.3: Trends in proportion of sex acts that are protected among 20-year old HIV-negative women having sex with HIV-negative or undiagnosed positive partners
Rates are adjusted to take into account knowledge of HIV status and ART (see sections 2.10 and 2.11).

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 ≥500/μl is the same as would be expected in HIV-negative adults with the same characteristics. The frequency of sex is assumed to be reduced by 8% in

individuals with CD4 counts of 350-499/μl, by 24% in individuals with CD4 counts of 200-349/μl, and by 45% in individuals with CD4 counts of <200/μl (relative to individuals with CD4 counts of ≥500/μl in all cases). These assumptions are based on meta-analyses of various studies that have assessed either differences in sexual behaviour or differences in the incidence of pregnancy between CD4 stages [60-66]; results of the individual studies are shown in Figure 2.4.

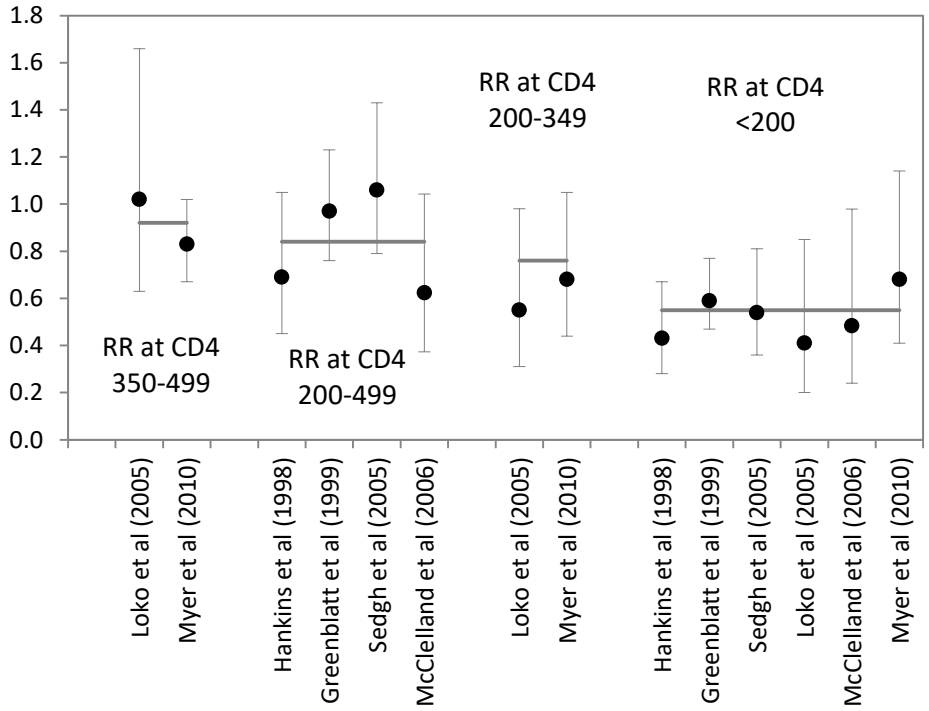


Figure 2.4: Comparison of model assumptions about relative frequency of sex at different CD4 levels and empirical estimates

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/μl category is taken as the average of that in the 350-499/μl and 200-349/μl categories. For convenience, we have treated the Sedgh *et al* (2005) estimates as if they are based on CD4 cut-offs of 200 and 500 (not 250 and 500).

It is assumed that the frequency of sex is the only sexual behaviour parameter that changes in relation to the CD4 count in HIV-infected adults. In the interests of simplicity, we do not model the possible effect of the CD4 count on rates at which new partnerships are formed, rates of partnership dissolution or rates of condom usage. However, in high risk women, it is assumed that rates of entry into commercial sex are reduced by 12% at CD4 counts of 350-499, by 35% at CD4 counts of 200-349 and by 60% at CD4 counts of <200 cells/μl. Rates of exit from commercial sex are increased by factors that are inversely related to these reduction factors (for example, a sex worker with a CD4 count <200/μl is assumed to cease commercial sex at a rate that is 1/(1 – 0.6) = 2.5 times that in HIV-negative sex workers). These assumptions are consistent with data from sex workers in Kenya [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). To represent the uncertainty around the reduction in unprotected sex after diagnosis, we assign a beta prior with a mean of 0.60 and a standard deviation of 0.08. This is equivalent to assuming an average relative rate of unprotected sex after HIV diagnosis of 0.40, with 95% confidence interval from 0.25-0.56, i.e. roughly consistent with the results of our meta-analysis.

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

Study	Location	Definition of risk behaviour	Controls	Effect on risk behaviour in HIV-diagnosed (OR, 95% CI)
Marlow *et al* [72]	South Africa	No condom use at 14 weeks postpartum	HIV-negative women	0.59 (0.48-0.72)
Ngubane *et al* [73]	South Africa	No condom use 0-12 mo postpartum 13-24 mo postpartum	HIV-negative women	 0.58 (0.47-0.72) 0.62 (0.44-0.87)
Morroni *et al* [74]	South Africa	No condom use at last sex	Women at FP/ STI clinics	0.28 (0.16-0.51)
Mwangi *et al* [75]	Kenya	Any unprotected sex with a partner who was HIV-negative or of unknown HIV status	Individuals who were HIV-positive but undiagnosed	0.05 (0.02-0.12)
Voluntary HIV-1 Counselling and Testing Efficacy Study Group [76]	Kenya, Tanzania, Trinidad	Any unprotected sex with primary partner Any unprotected sex with non-primary partner: Women Men	Individuals who tested HIV-negative	0.60 (0.40-0.89) 0.90 (0.49-1.66) 0.19 (0.05-0.81)
Müller *et al* [77]	Thailand	<100% condom use in last 3 sex acts	Individuals who were HIV-positive but undiagnosed	0.15 (0.09-0.24)
Cremin *et al* [70]	Zimbabwe	Inconsistent condom use with regular partners: Women Men	Individuals who were HIV-positive but undiagnosed	 0.53 (0.24-1.16) 0.61 (0.25-1.47)
Pooled OR				0.39 (0.28-0.56)

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.)

The model also allows for an effect of women's knowledge of their HIV status on entry into commercial sex work. It is assumed that women who have been diagnosed HIV-positive are less likely to start commercial sex than women who are HIV-positive but undiagnosed. However, as there have been no published studies quantifying the likely magnitude of this reduction, we assign a vague prior (uniform on the interval [0, 1]) to represent the proportionate reduction in the probability of entering sex work for women who have been HIV-diagnosed. Further explanation is provided in Appendix C.

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 meta-analysis [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 [3]. 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 [4-6]. Although this may be an under-estimate 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 ≥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.

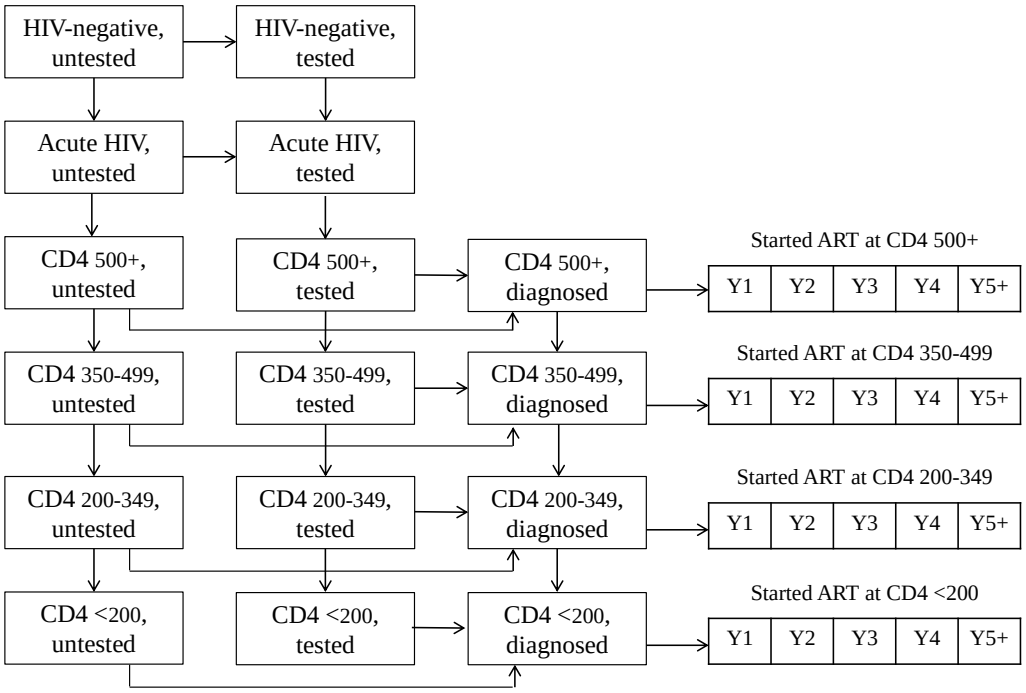


Figure 3.1: Multi-state model of survival in HIV-positive adults

It is worth noting that the model does not define a separate state to represent individuals who have interrupted ART. However, the model does calculate, for each of the times since ART initiation, the probability that the individual is on ART versus interrupting ART, and these duration-specific probabilities are used in calculating the number of adults currently on ART at any point in time. A more detailed explanation of the assumptions about rates of ART interruption is provided in Appendix G.

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

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

where λ_s is the rate that applies in men aged 30 in 1999, ϖ 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

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

where μ_s is the HIV mortality rate that applies in men aged 30. The adjustment factors for the effects of age and sex on HIV disease progression are thus the same as the adjustment factors for the corresponding effects on HIV-related mortality (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 ϖ 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 λ_s and μ_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 [105].

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 [106, 107]. 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 [108]). However, evidence from high-income countries generally suggests a shift towards *increased* HIV virulence over time [109, 110]. Given the inconsistent estimates from the literature, a gamma prior was previously assigned to represent the uncertainty in the *E*

parameter, with a mean of 1 and a standard deviation of 0.0065 [91]. Although our original analysis estimated the value of E to be significantly less than one [91], a subsequent analysis found that after allowing more realistically for the effect of ART interruptions in the model, the E estimate was not significantly different from one [91]. We have therefore fixed $E = 1$ for the purpose of this analysis.

Table 3.1: Parameters by HIV disease stage

Parameter	Acute HIV	CD4 range 500+	350-499	200-349	<200	Source
Average time (in years) to next stage, in absence of ART* ($1/\lambda_s$)	0.25	3.16†	2.13†	3.20†	-	Calibrated
Annual HIV mortality rate, in absence of ART* (μ_s)	0.00	0.00	0.00	0.033†	0.254†	Calibrated
Annual incidence of OIs, in absence of ART						[111, 112]
All WHO stage III and IV OIs	0.05	0.05	0.12	0.27	0.90	
WHO stage IV	0.01	0.01	0.02	0.06	0.28	
Pulmonary TB	0.01	0.01	0.015	0.04	0.07	
Relative infectiousness if untreated (I_s)	10	1	1	2	7	[113-115]
Annual male HIV mortality after ART initiation, by baseline CD4‡						
1st 6 months of ART	-	0.0002	0.0016	0.0146	0.2554	[116]
Months 7-18	-	0.0009	0.0050	0.0132	0.0613	
Months 19-30	-	0.0027	0.0085	0.0116	0.0306	
Months 31-42	-	0.0042	0.0076	0.0076	0.0202	
Months 43+	-	0.0049	0.0063	0.0063	0.0166	
Annual female HIV mortality after ART initiation, by baseline CD4‡						
1st 6 months of ART	-	0.0001	0.0016	0.0159	0.2072	[116]
Months 7-18	-	0.0008	0.0045	0.0101	0.0490	
Months 19-30	-	0.0020	0.0057	0.0057	0.0235	
Months 31-42	-	0.0027	0.0034	0.0034	0.0141	
Months 43+	-	0.0025	0.0025	0.0025	0.0103	

* Parameters are specified for 30-year old males, and adjustments for age and sex 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, and effects of increasing baseline CD4 counts over time. 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):

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

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; $r_i(t)$ is an adjustment factor to represent the effect of testing history; Ω_s is the annual incidence of OIs in CD4 stage s; $d_i(t)$ is the fraction of OI

patients who are tested for HIV in year t; $F_{g,s}(x,t)$ is the fertility rate in sexually experienced women aged x, in HIV stage s, during year t (set to zero for men); and $v_i(t)$ 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

$$A_g(x,t) = B_g(t)\left(\frac{x}{25}\right)^{\alpha_g - 1} \exp\left(-\sigma_g\left(x-25\right)\right), \quad (3.4)$$

where $B_g(t)$ is a time-dependent sex adjustment factor, and α_g and σ_g are coefficients for the effect of age on the rate of HIV test uptake. The testing history (i) is classified as never tested (0), last tested negative (1), tested positive but never started ART (2), or initiated ART (3). It was previously assumed that the effect of HIV testing history remained constant over time, but the new model allows for the effect of testing history to change over time, anticipating that the relative rate of testing in previously-tested individuals will tend to increase as the frequency of testing increases. For previously-tested individuals who last tested negative, the relative rate of testing in year t is calculated as

$$r_1(t) = r_1(0) + (r_1(\max) - r_1(0)) \times b(t-1) / 0.5, \quad (3.5)$$

where $r_1(0)$ and $r_1(\max)$ are the baseline and 'maximum' relative rates of retesting (compared to individuals who have never tested). The factor of 0.5 is somewhat arbitrary, but is based on previous fits of the model to provincial HCT statistics [52]; fitted values of $b(t)$ were seldom found to increase above 0.5. For previously diagnosed individuals who are either ART-naïve (i = 2) or on ART (i = 3), the relative rate of testing in year t is calculated as

$$r_i(t) = r_i \times r_1(t) / r_1(0), \quad (3.6)$$

where r_i is the relative rate that would be expected at low rates of HIV screening, when access to HIV testing is very limited.

The parameterization of the model was originally based on data collected up to 2012 [117], but has been updated to take into account more recent HIV testing data (as described in Appendix B). 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 (2002-2017), proportions of individuals testing for HIV who test positive, and proportions of adults who report previous HIV testing in four national surveys [14, 15, 118, 119], 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 [120, 121] and observed increases in rates of testing in previously-tested individuals [48, 122, 123]. The assumed incidence of OIs by HIV stage (Ω_s) is shown in Table 3.1, and the assumed proportions of Ois tested for HIV are shown in Table 3.2. The assumed fractions of pregnant women tested for HIV are also shown in Table 3.2, and assumptions regarding fertility rates and the effect of HIV on fertility are described in section 6.2.

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

Year	Antenatal testing ($v_i(t)$)		Testing of OI patients ($d_i(t)$)*		Linkage to ART in pregnancy ($l_2(5,t)$)	
	Rate	Sources	Rate	Sources	Rate	Sources
Pre-1999	0.0%		12%		0.0%	
1999-00	0.9%		12%		0.0%	
2000-01	2.9%		12%		1.9%	
2001-02	7.5%	[124]	12%		2.5%	
2002-03	15.6%	[125, 126]	12%		2.5%	
2003-04	31.3%		12%		3.6%	
2004-05	42.0%	[127]	18%	[128]	12.6%	
2005-06	54.5%	[129]	39%	[130]	22.6%	[131]‡
2006-07	72.2%	[132]	53%	[130]	29.1%	
2007-08	84.0%	[133]	61%	[130, 134]	35.5%	[135]‡
2008-09	89.0%	[136]	62%	[130, 134]	44.5%	[137]‡
2009-10	93.0%		39%	[130]	55.0%	
2010-11	97.0%	[138]	61%	[139] [140]	64.1%	[141]
2011-12	98.0%	[142]	85%	[140]	75.4%	[141]
2012-13	98.0%		88%	[140]	75.9%	
2013-14	98.0%		91%	[140]	76.3%	[140]
2014-15	98.0%		95%	[140]	91.2%	[140]
2015-16	98.0%		95%	[140]	93.0%	[140]
2016-17	98.0%**		95%†		95.0%†	[143]

* Rates are generally higher than those in the sources cited because it is assumed that some OI patients would be referred for HIV testing at other health services or would independently seek HIV testing even if not referred (for more detail, see Appendix B). ** Rates are assumed to remain constant at 98% after 2016. † Rates are assumed to remain constant at 95% after 2016. ‡ 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 five-year period from mid-2013 to mid-2018, is 0.20. 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-2018 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 [144-148] – 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 [149-151], and these adjustments are necessary to bring the model estimates in line with reported fractions of ART initiators in the CD4 200-349 category [152, 153].

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

	2000-2003*	2003-2009	2009-2010	2010-2011	2011-2012	2012-2014	2014-2015	2015-2016	Post-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

$$S_g^0(t) = \sum_{i=0}^{1}\sum_{s=2}^{5}\sum_{x=15}^{90} N_{g,i,s}(x,t)\left\{b(t)A_g(x,t)r_i(t)l_0(s,t) + \Omega_s d_i(t)l_1(s,t)\right\} + \sum_{i=0}^{2}\sum_{s=2}^{5}\sum_{x=15}^{49} N_{g,i,s}(x,t)F_{g,s}(x,t)v_i(t)l_2(s,t) \quad , \qquad (3.7)$$

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 [131, 135, 137], 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 [141]. 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 [143], it is assumed that coverage increased to 95% in 2016/17 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 sicker and thus likely to be fast-tracked through the patient preparation process, and (b) symptomatic patients are likely to be more motivated to start ART [154-156]. Data from the 2015-16 District Health Barometer indicate that 85% of TB patients with HIV were on ART [140], though this is likely to be an over-estimate of the rate of linkage to ART after TB diagnosis, given that the indicator includes patients who were already on ART prior to developing TB (Katherine Hildebrand, personal communication). In a Cape Town study, the fraction of TB patients diagnosed with HIV who received a CD4 count within 6 months after diagnosis was 16.5% lower than among pregnant women diagnosed with HIV [137]. We have therefore set the assumed value of $l_1(s,t)$ in 2015/16 to 78% (lower than the 93% assumed for pregnant women), and in all other years the value of $l_1(s,t)$ is set to $l_2(s,t) \times 0.78/0.93$, i.e. scaling down the values assumed for pregnant women (Table 3.2).

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

In a 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 [157]. Restricting attention to those studies conducted in South Africa, the median proportion of patients who received CD4 testing following HIV diagnosis was around 75% and the median proportion of those receiving CD4 testing who collected their test results was around 80%. Of those who were determined to be ART-eligible, the average proportion who started ART was around 67%. This suggests that of all individuals who are newly diagnosed and ART-eligible, the proportion who actually start ART within a few months of diagnosis is only about 40% (0.75 × 0.80 × 0.67). We have therefore set the rate of linkage to care in 2012/13 ($l_0(s,2012)$) to 0.4, for all individuals who are ART-eligible. This is roughly half of the rate assumed for pregnant women. We have therefore set the $l_0(s,t)$ parameters for all years prior to 2012 to be half of the corresponding rates assumed for pregnant women (Table 3.2). The rate of linkage of 0.4 estimated in 2012/13 is assumed to also apply in subsequent years. Although it might be expected that a higher rate of linkage would apply after the move to universal ART eligibility in 2016 (since CD4 testing is no longer a requirement prior to ART initiation), the South African experience has suggested that removing the delay due to CD4 testing makes little difference to the proportion of patients who initiate ART soon after diagnosis [158].

3.3.4 ART initiation in previously-diagnosed adults who did not link to ART soon after diagnosis, up to mid-2018

In the period up to mid-2018, 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-2018, $S_g(t)$ 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 (3.7) but converting the annual total into a monthly number. Let $N_{g,s}(x,t)$ be the number of HIV-diagnosed individuals in CD4 category s, who are ART-naive at time t, of age x and sex g. Let $\mu_{g,s}(x,t)$ be the monthly HIV mortality rate that applies in these individuals, and let $J_s(t)$ be the relative rate of ART initiation in stage s relative to that in the CD4 <200/μl category (s = 5). In most periods $J_s(t)$ will be zero for s < 5, since South African ART guidelines have only recently changed to allow for ART initiation at higher CD4 counts. 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 [159], and are consistent with the relative rates at which individuals enrolled in pre-ART care return for regular CD4 testing [87, 149].) We wish to estimate the monthly rate at which previously-diagnosed individuals in the CD4 <200/μl category initiate ART, $\rho_g(t)$. We estimate this by noting that

$$\begin{aligned} S_g(t) - S_g^0(t) &= \sum_{x=15}^{90}\sum_{s=1}^{5} N_{g,s}(x,t)\int_0^1 \rho_g(t)J_s(t)\exp\left(-\left(\mu_{g,s}(x,t)+\rho_g(t)J_s(t)\right)u\right)du \\ &\approx \sum_{x=15}^{90}\sum_{s=1}^{5} N_{g,s}(x,t)\rho_g(t)J_s(t)\left(1-0.5\left(\mu_{g,s}(x,t)+\rho_g(t)J_s(t)\right)\right) \end{aligned} \qquad (3.8)$$

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 were conducted every two years up to 2014, to determine total numbers of patients currently receiving ART [160]. In more recent years private sector data have been collected by the South African National AIDS Council (Billia Luwaca, personal communication), and these data have been validated using private sector drug sales [161]. 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 [141, 162]. 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 [83]. 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.

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 cells/μl

	Men (15+)	Women (15+)	Children (<15)	Implied ART delay ($1/\rho(t)$) Men	Women	Children
Pre-2000	0	0	0	-	-	-
2000-01	3520	4454	589	211.8	241.0	1081.9
2001-02	4123	5218	715	246.4	293.9	1237.8
2002-03	4833	6116	869	271.9	339.9	1169.3
2003-04	10916	15058	2196	142.6	170.0	454.5
2004-05	22137	42794	7035	97.1	79.8	159.1
2005-06	36605	71184	10717	102.9	74.5	119.9
2006-07	62727	120445	17456	68.0	50.6	69.7
2007-08	82840	160897	22352	56.8	41.1	53.4
2008-09	113598	213143	29495	40.4	30.3	39.4
2009-10	158525	283649	40961	21.9	18.9	27.5
2010-11	205354	393639	49582	16.7	12.4	13.4
2011-12	211906	413705	33399	21.9	14.6	11.7
2012-13	226842	416254	30169	22.7	13.3	7.5
2013-14	193330	356544	19167	23.0	10.7	7.3
2014-15	163996	304239	20131	34.4	21.3	4.7
2015-16	176710	327839	18171	32.0	27.2	2.3
2016-17	192525	357345	16849	32.6	28.2	11.5
2017-18	190407	346979	14062	28.3	22.4	15.6

3.3.5 ART initiation in previously-diagnosed adults who did not link to ART soon after diagnosis, after mid-2018

Because we do not yet have data on the absolute numbers starting ART after mid-2018, we specify the $\rho_g(t)$ parameters directly for this period. These parameters can also be expressed in terms of average delays (in months) between diagnosis and ART initiation, if the individual does not link to ART soon after ART initiation ($1/\rho_g(t)$). The average delays implied by our assumed absolute numbers are shown in the last two columns of Table 3.4. Our simulations suggest that in both men and women with CD4 counts of <200 cells/μl, this average delay has increased substantially since 2010/11, 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. For the period after 2022, we assume an average treatment delay of 30 months and 22 months in men and women respectively who have CD4 counts <200 cells/μl, roughly consistent with the average delay over the period from mid-2013 to mid-2018. In the period up to 2022, 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 [116]. However, the IeDEA-SA data relate mainly to individuals who start ART with CD4 counts below 350 cells/μl, and the few patients starting ART at higher CD4 counts are mostly patients who started ART because they qualified on the basis of HIV-related symptoms. Although we lack South African data on mortality in asymptomatic patients starting ART at higher CD4 counts, observational data from high income countries suggest that untreated patients with CD4 counts above 250 cells/μl have similar long-term mortality rates, as long as they start ART before their CD4 count declines below 250 cells/μl [163]. 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 $\exp\left(-m\rho_g(t^-)\right)$ in year *t*, where $\rho_g(t^-)$ is the average rate of ART initiation in the 3 years prior to year *t*, in adults of sex *g* with CD4 <200 cells/μl, and *m* is a scaling factor. This scaled difference is added to the minimum mortality rate to determine the modelled mortality rate in year *t*. 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 have previously been adjusted to take into account potential 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 may 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. Prior distributions were previously assigned to represent the uncertainty around I_0 and the ratio I_4/I_0. The I_d values at other durations are calculated by interpolating between the I_0 and I_4 values. Although our original analysis suggested that the I_0 parameter was significantly greater than one [91], a more recent analysis found that after modelling ART interruptions more realistically, the I_0 parameter was not significantly different from one [2]. We have therefore fixed $I_0 = 1$, and have fixed $I_4/I_0 = 0.741$, the same value as estimated in this more recent analysis.

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 $\beta_{g,l}$ represents the average HIV transmission probability, in a single act of unprotected sex, from an untreated HIV-positive individual of sex *g*, to an HIV-negative partner in relationship type *l*. Table 4.1 summarizes the assumed prior distributions for these parameter values. Although empirical estimates suggest high female-to-male transmission probabilities per act of unprotected sex in unmarried men [164, 165], these are likely to be over-estimates, as they may be inflated by male acquisition of HIV infection through sex worker contact, which is often substantially under-reported [166]. 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. A justification for the prior distributions on the male-to-male and client-to-sex worker transmission probabilities is provided in Appendix C.

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

Relationship type	Symbol	Susceptible female			Susceptible male[c]		
		Mean	Std dev.	Ref.	Mean	Std dev.	Ref.
CSW-client relationships	$\beta_{g,2}$	0.001[a]	0.0005	[167, 168]	0.008[b]	-	-
Short-term relationships	$\beta_{g,0}$	0.012	0.005	[169, 170]	0.008	0.003	[164, 165]
Long-term relationships	$\beta_{g,1}$	0.0043[a]	-	[85, 171, 172]	0.0010[a]	-	[85, 171, 172]
MSM relationships	$\beta_{1,4}$	-	-		0.020[a]	0.005	[173-175]

CSW = commercial sex worker.
[a] Fixed parameter, not included in Bayesian analysis, based on previous model calibrations. [b] Parameter value is assumed to be the same as in short-term relationships. [c] For a male partner who is uncircumcised.

4.2 The effect of risk group

Sexually transmitted infections (STIs) have been shown to have a significant effect on HIV transmission probabilities, both when present in the HIV-susceptible partner [176, 177] and when present in the HIV-infected partner [178]. 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 [179], 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-term contacts		Marital contacts	
	HIV+ male partner	HIV+ female partner	HIV+ male partner	HIV+ female partner
High risk male, high risk female	1.23	1.20	1.62	1.38
High risk male, low risk female	1.25	1.14	1.57	1.35
Low risk male, high risk female	1.08	1.09	1.33	1.24
Low risk male, low risk female	1.00	1.00	1.00	1.00

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 $\log_{10}$ scale (although higher values are possible, these have little effect on the HIV transmission dynamics in which we are interested). Variable $X_{a,s}$ is assumed to be Weibull-distributed, with parameters $\omega_{a,s}$ and ϕ. The probability of viral suppression (a viral load of less than 400 copies/ml) in treated individuals is thus

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

from which it follows that if $V_s(t)$ is the probability of viral suppression in year *t*, at a threshold of <400 copies/ml, then

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

In fitting Weibull distributions to viral load data from both treated [101, 104] and ART-naïve South Africans [180], we have found that a ϕ parameter of 1.5 produces reasonable fits. For a given level of viral suppression, $V_5(t)$, it is then possible to calculate $\omega_{1,5}$. For example, if the rate of viral suppression in patients starting ART with CD4 <200 cells/μl is set to 0.77, based

on data from South Africa's public sector ART programme [162, 181], substituting $V_5(t)$ = 0.77 into equation (4.2) yields a $\omega_{1,5}$ estimate of 0.042. For ART-naïve patients, a different approach is adopted in estimating $\omega_{a,s}$. 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 [180], we estimate the $\omega_{0,5}$ parameter to be 0.635.

The $V_5(t)$ parameters have been estimated from reported levels of viral suppression. The model allows for a change in the rate of viral suppression over time; a more detailed explanation of the data sources and assumptions is provided in Appendix F. It is expected that in 2019 dolutegravir will replace efavirenz as the standard first line drug, and most new patients (as well as most patients who are virally suppressed) will be switched to dolutegravir. Dolutegravir is associated with significantly greater viral suppression than efavirenz; in a recent network meta-analysis, the odds of viral suppression on dolutegravir was estimated to be 1.87 times that on efavirenz [182]. Based on this, the odds of viral suppression $V_5(t)$ in 2019 is assumed to be 1.87 times that in 2018, and the odds of viral suppression is assumed to remain constant at this level in future years.

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

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

where c is the maximum HIV transmission risk (when $x = 0$) and parameter θ determines the extent of the association between viral load and HIV transmission risk. Including $\phi > 1$ in the above equation ensures that the effect of viral load is less substantial at higher viral load levels than at lower viral load levels [183]. For reasons of mathematical convenience, explained below, we use the same value of $\phi = 1.5$ as estimated in the model of viral load distributions. The θ parameter is estimated by noting that if the factor by which infectiousness increases, per unit increase in viral load, is of the order of 2.5 [85, 184, 185], this implies that

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

From this it follows that $\theta\phi x^{\phi-1} = \ln(2.5)$. Substituting $\phi = 1.5$ and $x = 2$ [85, 184] yields θ = 0.432. The average HIV transmission probability, for patients with ART status a and CD4 stage s, is then

$$\begin{aligned}\int_0^{\infty} \omega_{a,s}\phi x^{\phi-1}\exp\left(-\omega_{a,s}x^{\phi}\right)c\exp\left(-\theta x^{\phi}\right)dx &= c\int_0^{\infty}\omega_{a,s}\phi x^{\phi-1}\exp\left(-\left(\theta+\omega_{a,s}\right)x^{\phi}\right)dx \\ &= \frac{c\omega_{a,s}}{\omega_{a,s}+\theta}.\end{aligned} \tag{4.5}$$

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

$$R_s = \frac{\omega_{1,s}}{\omega_{1,s} + \theta} \Big/ \frac{\omega_{0,s}}{\omega_{0,s} + \theta}. \qquad (4.6)$$

Substituting the values of $\omega_{1,5} = 0.042$ and $\omega_{0,5} = 0.635$ into this equation, for example, yields an R_5 estimate of 0.149. This is somewhat higher than the relative risk estimates of 0.04-0.08 estimated from randomized controlled trials [114, 186], but lower than the relative risk of 0.36 estimated in a meta-analysis of observational studies [187]. It is important to note, however, that the value of R_s changes over time, as the $\omega_{1,s}$ parameter in the numerator changes as the rate of viral suppression changes.

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 [188], 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).

Although most South African data sources report viral suppression at a threshold of <400 copies/ml, global reporting standards recommend a threshold of <1000 copies/ml [189, 190]. For the sake of consistency with these global reporting standards, equation (4.1) is used to estimate viral suppression at this threshold (replacing 400 with 1000), although we have few direct South Africa data to inform the levels of viral suppression at this threshold.

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, 191], it is likely that empirical estimates are biased downward due to over-reporting of condom usage [192, 193]. Levels of condom efficacy close to 90% have also been estimated in MSM [174].

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 [194-196], and their relatively low levels of protective lactobacilli [197]. The model makes allowance for this heightened susceptibility by assuming that the HIV transmission risk per act of sex is increased by a factor of $Z_g(x)$, relative to adults aged 25 and older, in individuals of sex g and age x. The function $Z_g(x)$ is defined as

$$Z_g(x) = \begin{cases} (1+Z_g)^{25-x} & \text{for } x < 25 \\ 1 & \text{for } x \geq 25 \end{cases}. \quad (4.7)$$

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 [198-200]. For males, there does not appear to be strong evidence of age variation in the risk of HIV acquisition per sex act [85, 199], and the Z_1 parameter has therefore been set to zero.

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

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

where 2.5α is the scaling factor for the relationship between HIV virulence and HIV transmissibility. As explained in more detail elsewhere [91], the α 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. However, as noted in section 3.1, the *E* parameter is currently fixed at 1, and the model therefore assumes HIV transmission probabilities in untreated individuals are constant over time.

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 ≥500 cells/μl (*s* = 2), then

$$\beta_{g,l} = \beta^*_{g,l} \frac{\sum_{s=1}^{3} \frac{I_s \Gamma(s)}{\lambda_s} + \frac{I_4 \Gamma(4)}{\lambda_4 + \mu_4} + \frac{\lambda_4}{\lambda_4 + \mu_4} \times \frac{I_5 \Gamma(5)}{\mu_5}}{\sum_{s=1}^{3} \frac{\Gamma(s)}{\lambda_s} + \frac{\Gamma(4)}{\lambda_4 + \mu_4} + \frac{\lambda_4 \Gamma(5)}{(\lambda_4 + \mu_4)\mu_5}}, \quad (4.9)$$

where the I_s factors are the relative levels of infectiousness (Table 3.1), and the CD4 decline parameters (λ_s) and mortality parameters (μ_s) are those specified in section 3.1. We define

I_s^* to be the ratio of infectiousness in stage *s* to average infectiousness, from which it follows that $I_2^* = \beta_{g,l}^* / \beta_{g,l}$, and hence

$$I_2^* = \frac{\sum_{s=1}^{3} \frac{\Gamma(s)}{\lambda_s} + \frac{\Gamma(4)}{\lambda_4 + \mu_4} + \frac{\lambda_4 \Gamma(5)}{(\lambda_4 + \mu_4)\mu_5}}{\sum_{s=1}^{3} \frac{I_s \Gamma(s)}{\lambda_s} + \frac{I_4 \Gamma(4)}{\lambda_4 + \mu_4} + \frac{\lambda_4}{\lambda_4 + \mu_4} \times \frac{I_5 \Gamma(5)}{\mu_5}} . \quad (4.10)$$

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 $I_s^*(1) = I_s^*(\iota_d + (1-\iota_d)R_s)$, where ι_d is the proportion of ART-experienced adults surviving to duration *d* after ART initiation, who are interrupting ART, and R_s is the relative infectivity after ART initiation (as defined in equation (4.6)). The ι_d parameters have been set to 0.053 for the first 6 months after ART initiation, 0.142 for months 7-18, 0.186 for months 19-30, 0.199 for months 31-42 and 0.204 for longer ART durations, based on a model of ART interruptions in South Africa described in Appendix G.

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

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

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 HIV-negative individuals. In the case of ART-naïve individuals (*a* = 0 and *d* = 0), $Y(0,s,0) = \Gamma(s)$. In the case of ART-experienced individuals, we define

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

where $\psi_d(s' \mid s)$ is the proportion of surviving ART patients with current CD4 count in category s' , in the cohort of patients who started ART with a CD4 count of *s* and who are in ART duration category *d*. Individuals who interrupt ART are assumed to experience a return to baseline CD4 levels [84], and the frequency of sex is thus assumed to be a function only of

the *current* CD4 count. The $\psi_d(s' \mid s)$ values are estimated from studies of CD4 distributions after ART initiation [201-203], and the assumed values are shown in Table 4.3.

Table 4.3: Proportions of treated patients in different CD4 categories

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

For the purpose of calculating average transmission probabilities, we define $N^r_{g,i,l,j}(x)$ to be the total number of individuals aged *x* and of sex *g*, who are in risk group *i*, in relationship state *l* (0 for unmarried 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 $X^r_{g,i,l,j}(x,a,s,v,d)$ to be the proportion who are in HIV stage *s*, with ART status *a*, HIV testing history *v* and ART duration *d*. In total there are 35 possible HIV-positive states, summarized in Table 4.4.

Table 4.4: Definitions of HIV-positive states

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

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

As in recent modelling of herpes transmission [204], the model is parameterized in terms of a force (or 'hazard') of transmission per sex act, which is then converted into a cumulative hazard, given the expected number of sex acts in the relationship. For an HIV-positive individual with state covariates (*a*, *s*, *v*, *d*), the cumulative hazard for HIV transmission, per short-term partnership with a partner in risk group *j*, is

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

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

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

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 $T_{g,i,l,k}^{2,r}(j,x)$ 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 (*l*) in the subscript, as some married individuals may engage in extramarital or commercial sex activity. Similarly, the risk group of the long-term partner (*k*) is not necessarily the same as the risk group of the partner under consideration (*j*).

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

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

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

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

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

$$U^1_{g,i}(j,x) = 1 - \frac{\sum_r N^r_{g,i,1,j}(x)\exp\left(-T^{1,r}_{g,i,1,j}(j,x)\right)}{\sum_r N^r_{g,i,1,j}(x)}, \tag{4.18}$$

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

$$U^2_{1,1} = \frac{\sum_{r,l,k,x} N^r_{1,1,l,k}(x) w_l(x) T^{2,r}_{1,1,l,k}(1)}{\sum_{r,l,k,x} N^r_{1,1,l,k}(x) w_l(x)}, \tag{4.19}$$

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

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

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

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:

$$P^0_{1,i,3}(x) = 1 - \exp\left(-\frac{c_{1,i,3}(x)\Omega(x)}{12} Z_1(x) \sum_{y=10}^{90} f_{1,3}(y \mid x) \times \left[\rho_{1,i,3}(1,t) U^0_{1,1}(i,y) + \rho_{1,i,3}(2,t) U^0_{1,2}(i,y)\right]\right) \tag{4.21}$$

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

$$P^{1}_{g,i,1,j}(x) = 1 - \exp\left(- Z_g(x) \sum_{y=10}^{90} f_{g,1}(y \mid x) U^{1}_{3-g,j}(i,y) \right). \qquad (4.22)$$

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

$$P^{2}_{1,1,l}(x) = 1 - \exp\left(- \frac{w_l(x)}{12} Z_1(x) \sum_{y=10}^{90} N^{0}_{2,1,2}(y) T^{2,0}_{2,1,2}(1,y) \Big/ \sum_{y=10}^{90} N^{0}_{2,1,2}(y) \right), \qquad (4.23)$$

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

$$P^{2}_{2,1,2}(x) = 1 - \exp\left(- \frac{C}{12} Z_2(x) U^{2}_{1,1} \right), \qquad (4.24)$$

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 acquisition than uncircumcised men, per act of sex with an HIV-positive partner (the transmission probabilities in Table 4.1 relate to uncircumcised men) [205-208]. Male circumcision is assumed to have no effect on male-to-female rates of HIV transmission [209] or male-to-male transmission [210, 211].

4.7.1 Male circumcision prior to the promotion of MMC as an HIV prevention strategy

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

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

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 ϕ is the shape parameter that determines the concentration of the distribution of circumcision ages (post-birth) around the

median. Since surveys usually report the median age at circumcision for all men (including those who are circumcised at the time of birth), it is useful to parameterize the model in terms of this overall median circumcision age, m_2, noting that

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

Parameters a and b are set at 0.105 and 0.42 respectively. The shape parameter ϕ is set at 4.5, and the median age at circumcision m_2 is set at 18, the median age at circumcision reported by Africans in the 2002 HSRC survey [212]. 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, 212, 213], after correcting the self-reported data to take into account known biases in the reporting of male circumcision [214-219]. These corrections also take into account that many men who report being circumcised are only partially circumcised (i.e. we treat partially circumcised men as if they are uncircumcised and assume that partial circumcision provides no protection against HIV). 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.

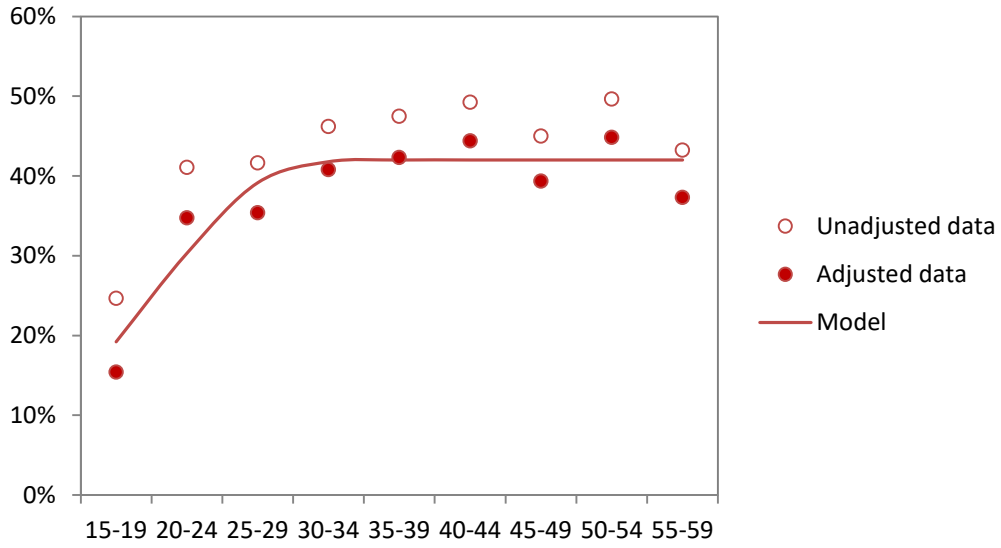


Figure 4.1: Fraction of men who are circumcised, by age, prior to MMC campaigns
Unadjusted data represent the average of the results from national surveys in 2002 and 2003 [56, 212, 213]. Adjusted estimates are calculated on the assumption that the sensitivity and specificity of self-reported male circumcision status (relative to true status) are 96.4% and 88.4% respectively [214-219].

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

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

4.7.2 Male circumcision in the MMC campaign era

Extending the model to include MMC in response to MMC promotion campaigns requires that we define the symbol $p^*(x, t)$ as the proportion of men aged x, at time t, who are circumcised. Of those men who are uncircumcised at age x in year t, the proportion who intend to get traditionally circumcised (i.e. they would want to get circumcised even in the absence of MMC promotion campaigns) is calculated as

$$\frac{b - p(x)}{1 - p^*(x,t)}, \tag{4.28}$$

and the proportion who do not intend to get traditionally circumcised is

$$\frac{1 - p^*(x,t) - \left(b - p(x)\right)}{1 - p^*(x,t)}. \tag{4.29}$$

The implicit assumption is that the men who intend to get traditionally circumcised would not accept MMC, i.e. the demand for traditional MC and the demand for MMC are mutually exclusive. This is different from the assumption made in the previous version of Thembisa (Thembisa 4.1 [2]), in which it was assumed that the demand for MMC was independent of the individual's desire for traditional male circumcision. This change was made because the previous model produced estimates of circumcision coverage that appeared implausibly low relative to the levels reported in recent surveys (even after correcting for misreporting), and because unpublished data from the most recent HSRC household survey suggest there has been no reduction in the prevalence of traditional male circumcision since the start of the MMC rollout (in contrast to what would be expected if some of the men who would previously have been traditionally circumcised instead chose MMC). With the revised assumption, the model yields a slightly higher estimate of male circumcision coverage, more consistent with recent survey data.

Men are assumed to undergo MMC only if they are HIV-negative, as HIV testing is conducted prior to most MMC operations [220, 221], 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 $\eta(x, t)$ is defined as the probability that HIV-negative men who are aged x, uncircumcised at the start of year t, and not intending to get traditionally circumcised, get medically circumcised through MMC campaigns. This is calculated as $\eta(x, t) = \theta(t) \times R(x)$, where $\theta(t)$ is the maximum probability in year t and $R(x)$ is the relative rate of MMC uptake in men aged x, compared to boys aged 10-14. The relative rates of MMC uptake in the 15-19, 20-24, 25-49 and 50+ age groups have been set to 0.59, 0.27, 0.14 and 0.012 respectively; these rates were chosen to ensure the model matched the age profile of MMC operations provided from PEPFAR-supported MMC programmes in South Africa. The $\theta(t)$ values are estimated from the reported number of MMC operations in year t, $\Lambda(t)$, which are shown in Table 4.5. Mathematically,

$$\Lambda(t) = \sum_x N(x,t)\left(1 - \frac{b - p(x)}{1 - p^*(x,t)}\right)\eta(x,t), \tag{4.30}$$

where $N(x, t)$ is the number of uncircumcised, HIV-negative men who are aged x at the start of year t. From the above equation, it follows that

$$\theta(t) = \Lambda(t) \Big/ \sum_x N(x,t)\left(1 - \frac{b - p(x)}{1 - p^*(x,t)}\right) R(x). \qquad (4.31)$$

Combining traditional and medical male circumcision, the net probability of male circumcision in an HIV-negative male aged x at the start of year t is

$$\psi(x,t) = \frac{p(x+1) - p(x) + \left(1 - p^*(x,t) - \left(b - p(x)\right)\right)\theta(t)R(x)}{1 - p^*(x,t)}. \qquad (4.32)$$

For HIV-positive men, the rate of circumcision is calculated using equation (4.27), i.e. assuming that they would only get circumcised traditionally.

Table 4.5: Annual numbers of MMC operations performed through MMC campaigns

Year	Operations	Source
Pre-2008	0	-
2008/09	5190	[222]
2009/10	9168	[222]
2010/11	131117	[222]
2011/12	347973	[223]
2012/13	422262	[223]
2013/14	331668	[224]
2014/15	508404	[225]
2015/16	518130	[226]
2016/17	446678	[227]
2017/18	540327	[228]

Based on equation (4.30), the model estimates the average annual probability of MMC in boys aged 10-14, over the period from mid-2013 to mid-2018, to be 0.21. This value is assumed to continue to apply in all years after 2018.

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, mostly because of differences in PrEP adherence across trials. Although a recent meta-analysis estimated that PrEP reduced heterosexual transmission and transmission between MSM by 46% and 66% respectively [229], these estimates are probably under-estimates, as most of the evidence included in the meta-analysis came from randomized trials that were conducted prior to the effectiveness of PrEP being established. More recent studies, conducted in the context of known PrEP efficacy, have generally found much higher levels of adherence and efficacy [230-232], suggesting that individuals are more

motivated to use PrEP consistently when they know that it works. The assumed efficacy of PrEP is therefore set to 65% in heterosexuals and 85% in MSM. The assumed efficacy of 65% in heterosexuals is based on a meta-analysis that found an average 65% reduction in women's HIV risk in studies in which average PrEP adherence was at least 50% [233], and the assumed effectiveness of 85% in MSM is based on the results of the PROUD and IPERGAY studies, which both found 86% efficacy in MSM [230, 231]. The assumed greater efficacy of PrEP in MSM is supported by in vitro evidence of greater drug concentration in rectal tissue when compared to female genital tract tissue [234].

4.8.2 Risk compensation

Although data from randomized trials generally do not show evidence of risk compensation in PrEP recipients [235-237], 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 an analysis of changes in behaviour after the unblinding of the Partners PrEP trial in heterosexual couples, a statistically significant 10% increase was noted in unprotected extramarital sex, amongst individuals who were receiving open-label PrEP [238]. A recent meta-analysis of PrEP studies conducted in MSM also found that PrEP use was associated with increased STI diagnosis (OR 1.26, 95% CI: 0.99-1.54) and increases in condomless sex [239]. Based on these two studies, 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 [240] 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 [238, 241]. In our model we assume an average PrEP duration of 6 months in women and 1 year in men. This is based on the limited programme data available in South Africa for female sex workers (FSWs) and MSM respectively (Sarah Jenkins, personal communication). We fit simple Weibull models to the data to estimate the time from initiating PrEP to stopping PrEP; in the case of FSWs, a Weibull distribution with a mean of 4.8 months and a shape parameter of 0.45 provides an adequate fit to the data, while in the case of MSM, a Weibull distribution with a mean of 11.1 months and a shape parameter of 0.60 provides an adequate fit to the data (Figure 4.2).

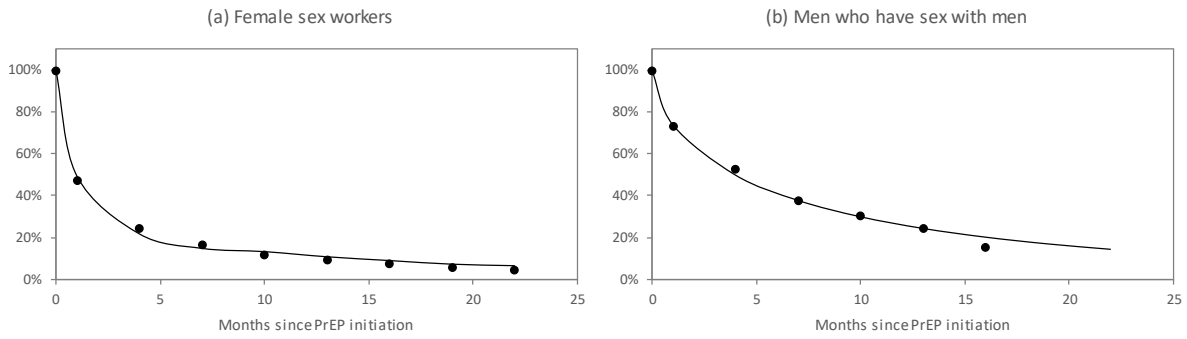


Figure 4.2: Retention in South African PrEP programmes
Data (represented by dots) are from South African PrEP programmes, as at November 2018 (Sarah Jenkins, personal communication). The solid lines represent Weibull fits to the data.

4.8.4 Adoption of PrEP

Model assumptions about rates of PrEP uptake in HIV-negative FSWs and MSM have been set in such a way that the model matches roughly the recorded total numbers of PrEP recipients from routine programme data (Sarah Jenkins, personal communication). These data have been adjusted to exclude individuals who have stopped PrEP (in contrast to most of the cited statistics, which relate to the number of individuals who have *ever* been on PrEP). The annual rate of uptake in FSWs has been set to 0.04 in 2016-17 and 0.05 in 2017-18, while the annual rate of PrEP uptake in MSM has been set to 0.001 in 2016-17 and 0.007 in 2017-18. Figure 4.3 shows that with these assumptions the model produces estimates of numbers of PrEP users roughly consistent with routine data up to the middle of 2018. In the absence of more recent data, the rates of initiation assumed for 2017-18 are assumed to apply in all future years.

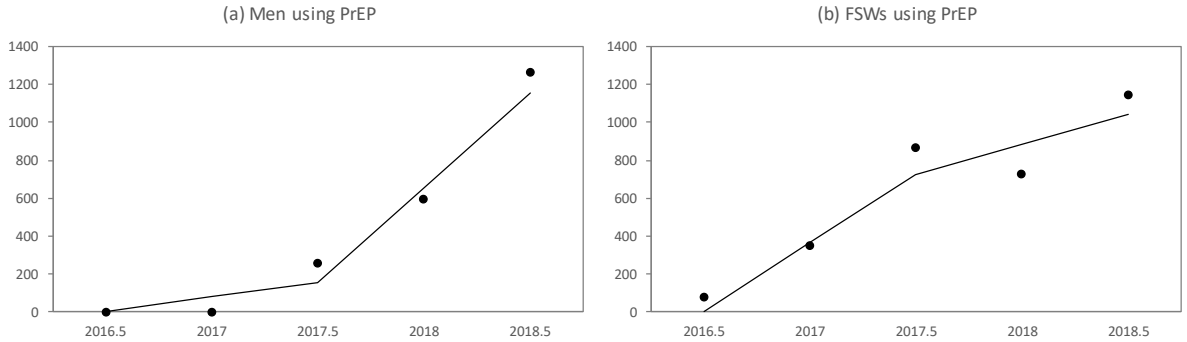


Figure 4.3: Total numbers of individuals receiving PrEP
Data (represented by dots) are from South African PrEP programmes, as at November 2018 (Sarah Jenkins, personal communication). The solid lines represent Thembisa estimates.

A limitation of the data is that the 'risk group' classification is based on the type of facility that provides PrEP rather than the actual profile of PrEP users. For example, some of the individuals classified in the data as receiving PrEP through FSW services might not be FSWs.

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 [242], 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 have received 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 [243]). The $D(t)$ parameters are assumed to increase from zero in 2002/3 up to 90% in the 2010-2012 period [243, 244]. 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	S.D.*	Source
Transmission rate at/before birth, from chronically-infected women with no ARV prophylaxis, with			
CD4 >500	13.4%	-	Meta-analysis of published studies [245]
CD4 350-500	15.2%	-	
CD4 200-349	25.8%	-	
CD4 <200	35.0%	-	
Transmission rate at/before birth, from acutely-infected women with no ARV prophylaxis	25.4%	-	[246-251] and previous calibration [2]
% of HIV-diagnosed women who receive single-dose nevirapine, if not starting ART	71.0%	-	Kate Kerber (pers. comm.), based on national survey data [243]
% reduction in perinatal MTCT if mother receives single-dose nevirapine only	40.0%	-	[252]
% reduction in perinatal MTCT if mother receives short-course zidovudine only	65.0%	-	[253]
% reduction in perinatal MTCT if mother receives single-dose nevirapine + short-course zidovudine	85.8%	-	[254, 255] and previous calibration [2]
Transmission rate at/before birth, from women on long-term ART pre-conception	0.3%	-	[256-261]
Probability of MTCT from chronically-infected mothers, per year of mixed feeding	14.0%	2.5%	Meta-analysis [262], adjusted to reflect effect of excluding EBF
Probability of MTCT from acutely-infected mothers, per month of mixed feeding	16.0%	3.0%	Derived from meta-analysis [242]*
Ratio of postnatal transmission risk per month of EBF to postnatal transmission risk per month of mixed feeding	0.50	0.15	[263, 264]
% reduction in monthly postnatal MTCT risk if child receives extended nevirapine prophylaxis	60.0%	-	[265-267]
% reduction in monthly postnatal MTCT risk if mother receives long-term ART			1 - average MTCT rate per month of BF divided by the rate in women not on ART [262]
ART initiated during pregnancy	78%	-	[268-277]
ART initiated before conception	96%	-	[258, 261, 278]

* Standard deviation (SD) is specified only for those parameters that are considered in the uncertainty analysis; the corresponding values specified in the previous column represent the prior means (see Appendix E for more detail). 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

$$a + b_s R^x, \tag{5.1}$$

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

$$\int_0^\infty g(x)\left(a + b_s R^x\right) dx = a + b_s \int_0^\infty \frac{\lambda(t)^\alpha x^{\alpha-1} \exp\left(-\lambda(t)x\right)}{\Gamma(\alpha)} R^x dx$$
$$= a + b_s \left(\frac{\lambda(t)}{\lambda(t) - \ln(R)} \right)^\alpha . \qquad (5.2)$$

where α and $\lambda(t)$ are the parameters of the gamma distribution. Based on South African data sources [256, 257, 279, 280], the mean and standard deviation of the gamma distribution in the baseline scenario have been set to 10.6 weeks and 8 weeks respectively (α = 1.7556 and $\lambda(t)$ = 0.1656 for t < 2010), and the R parameter has been set to 0.9. Parameter a has been set to 0.003, the average transmission risk from studies that evaluated the perinatal transmission rate from mothers who started ART prior to conception [256-261] (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 [256, 257, 259, 268-270, 272, 273, 276, 277, 279, 281, 282]. 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 [283], which led to more rapid initiation of ART during pregnancy. For example, Van Schalkwyk *et al* [280] 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 [284]. Stinson *et al* [285] 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 [223] 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 [17, 286, 287] and delivery at 39 weeks [287], 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 [288]. 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 25.4% 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 [289, 290], with the most 2016/17 DHIS data suggesting a proportion close to 100%. 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 [17]. All of these women are assumed to practise mixed feeding, as exclusive breastfeeding (EBF) is ually of very short duration in HIV-negative (or undiagnosed positive) mothers [17, 291]. Of women who were diagnosed HIV-positive antenatally in the period up to 2011, it is assumed 56% avoided breastfeeding completely [138], 30% practised EBF and 14% practised mixed feeding [292]. 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 [292-294]. 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 [295], 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 [296].

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 [283], 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. After the introduction of Option B in 2013, it is assumed that this provision of extended nevirapine (throughout the breastfeeding period) was phased out.

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 a 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 [262]. 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. The model is an adaptation of a previous model of paediatric HIV survival [297], which has been extended to include HIV diagnosis after infancy. 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 [298]). 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. Although the model distinguishes perinatally-infected children according to whether or not they were PMTCT-exposed, this is assumed to have no effect on their rate of HIV disease progression in the current analysis.

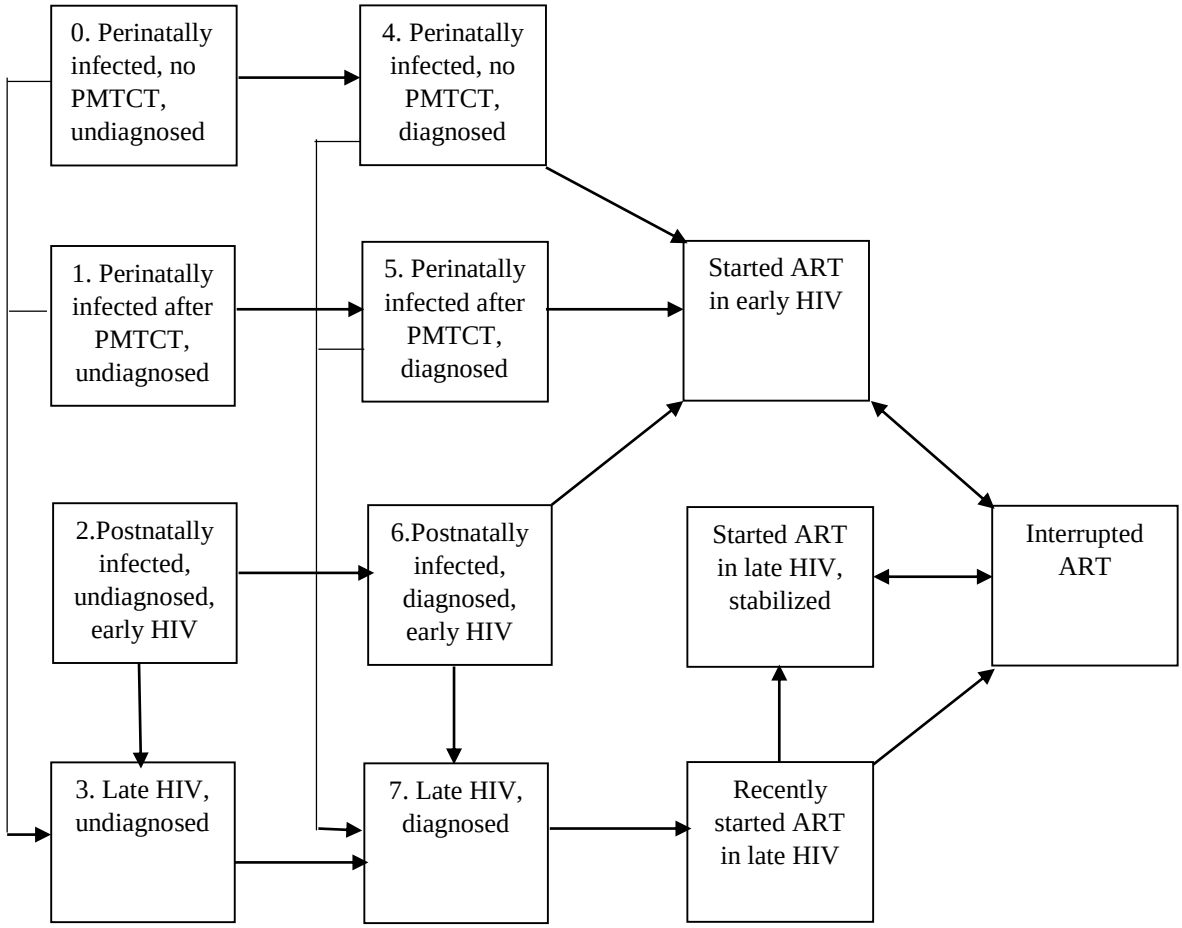


Figure 5.1: Multi-state model of HIV survival in HIV-positive children
All children are assumed to experience non-AIDS mortality rates that vary by age and sex, and all children who are in the late disease stage or are ART-experienced are assumed to be at risk of AIDS mortality (not shown).

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

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

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

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

Parameter	Symbol	Value	S.D.*	Source
Children infected at/before birth				
Annual rate of progression to late disease in older children	G_p	0.40	0.10	θG_p = 0.14 is consistent with rates of progression observed by Charlebois *et al* [299] in children aged ≥1 year
Excess annual rate of progression to late disease in neonates	H_p	2.00	0.50	[300, 301]
Excess progression reduction factor, per year of age	c	0.25	0.10	[300-303]
Relative rate of progression to late disease if infected after birth	θ	0.35	0.15	[304-307]
Children in late disease, untreated				
Annual rate of AIDS mortality in older children	G_m	0.12	0.03	[308, 309]
Excess annual rate of AIDS mortality in neonates	H_m	3.50	0.70	Based on fitting model to mortality data from children diagnosed with HIV-related symptoms at different ages [309]
Excess mortality reduction factor, per year of age	d	0.05	0.10	
Relative rate of AIDS mortality in 'stabilized' children who started ART in late disease	Φ_1	0.10	0.05	Based on fitting model to mortality data from IeDEA Southern Africa Collaboration [310]
Reduction in mortality (on log scale) per unit increase in rate of ART initiation over last 3 years	m	7.5	3.5	See Appendix D
Children who started ART while in early disease				
AIDS mortality at age 0	β	0.06	-	See Appendix D
Relative rate of AIDS mortality per year of age	P	0.20	-	See Appendix D

* Standard deviation (SD) is specified only for those parameters that are considered in the uncertainty analysis; the corresponding values specified in the previous column represent the prior means (see Appendix E for more detail).

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 [308, 309], 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. A prior distribution is assigned to represent the uncertainty around the Φ_1 parameter, and for simplicity we assume that $\Phi_0 = 0.5 \times (1 + \Phi_1)$, i.e. the reduction in mortality in the ‘high risk’ phase is half of that in the stabilized phase. These rates are also adjusted to take into account changes over time in the relative severity of untreated late disease. This is to compensate for the selective nature of ART initiation; in the early stages of the ART rollout, it is the sickest of the children with late disease who start ART, but as ART uptake expands, the average disease severity among children starting ART declines. For example, in the ‘high risk phase’ after starting ART in late disease in year *t*, the mortality rate is calculated as

$$\Phi_0\,\mu(x)\,[0.43 + (1 - 0.43)\exp(-m\,r_{t\text{-}})], \qquad (5.5)$$

where $r_{t\text{-}}$, is the average rate of paediatric ART initiation over the previous three years, m is a scaling parameter, and 0.43 is the assumed ratio of the minimum ART mortality rate (the rate that might be expected if all children started ART in the early phase of late disease) to the mortality rate that applied in the earliest phase of the paediatric ART rollout. This implies that the mortality rate in the ‘high risk’ phase declines exponentially towards a minimum rate as the rate of ART initiation in children increases, with the m parameter determining the pace of this exponential decay. The adjustment is analogous to that described for adults in section 3.4, and is described more fully in Appendix D.

The AIDS mortality rate in children who start ART in early disease, $\psi(x)$ at age x, was previously calculated as an adjustment to the rate assumed in children who started ART in late disease and who were ‘stabilized’ [297]. However, this was found to produce implausibly high rates of mortality, especially in the context of birth testing. In the new version of Thembisa, we have therefore estimated these mortality rates directly from South African ART programmes participating in the International Epidemiology Databases to Evaluate AIDS (IeDEA) collaboration [310]. The rate of AIDS mortality in children starting ART in early disease is calculated as $\psi(x) = \beta P^x$, where β is the HIV mortality rate that applies at age 0, and P is the factor by which the AIDS mortality rate is reduced per year of age. These parameters have been set to 0.06 and 0.2 respectively, based on attempts to fit the model to IeDEA data (for a more detailed explanation, see Appendix D).

Although the model allows for children to interrupt ART and resume ART (Figure 5.1), there is currently substantial uncertainty around the rates of ART interruption in children, and we therefore assume the same rates of ART interruption and resumption as for adults (see Appendix G). There is also substantial uncertainty regarding the extent to which mortality changes while children are interrupting ART, and we therefore do not attempt to differentiate mortality rates in interrupters from those currently on ART.

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 calculated as

$$S^0(t) = \left(\sum_{s=0}^{1} \left(N_s(0,t)V(0,t)\pi_s(0) + N_s(2,t)V(2,t)\pi_s(2) \right) E_0(t) + N_3(2,t)V(2,t)E_3(t) \right) l, \quad (5.6)$$

where $N_s(x, t)$ is the number of 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; $E_0(t)$ is the fraction of infants in early disease who are eligible to receive ART in year t; $E_3(t)$ is the fraction of children in advanced disease who are eligible to receive ART in year t; and l is the fraction of ART-eligible diagnosed infants who link to ART care soon after diagnosis. As shown in Figure 5.1, stages 0 and 1 correspond to infants in early disease who were antenatally PMTCT-unexposed and PMTCT-exposed respectively, and stage 3 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 [141, 311], adjusted to reflect under-count due to late immunization [312, 313] and over-count due to non-return of test results to caregivers [314-316]. After birth testing was introduced in 2015, birth screening coverage increased to 68.7% in 2015-16 [140, 317], and to around 90% thereafter [318]. Limited information is available on the rate of screening at 10 weeks since the introduction of the new screening policy, but data suggest that screening coverage at 10 weeks may be lower than has historically been observed at 6 weeks [317, 319]. For example, Kalk *et al* [317] found that the fraction of infants receiving HIV testing at 6-10 weeks dropped from 93% in the period before birth testing to 80% after the introduction of universal birth testing. We have assumed 80% coverage from 2015 onward; this is conservative because the model treats the probabilities of birth and 6-10 week testing as independent, when in reality there is a negative association that is likely to result in a high overall fraction on infants screened (either at birth or at 6-10 weeks). 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 [320], assuming that all infants who are tested for HIV would at least have received NVP prophylaxis postnatally [283]. 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 [144], ART eligibility for infants in early disease only became official policy in 2010 [321], with some earlier provision following the 2008 WHO guideline revision [322]. The fraction of eligible, diagnosed infants who link to care and start ART (l) has been allowed to vary in the uncertainty analysis (see Appendix D).

Table 5.3: HIV diagnosis and ART eligibility in HIV-positive children

	Fraction tested at 6 or 10 weeks ($V(2,t)$)	Fraction tested at birth ($V(0,t)$)	Early ART eligibility			Late ART eligibility ($E_3(t)$)
			Infants ($E_0(t)$)	Ages 1-4 ($E_1(t)$)	Ages 5-12 ($E_2(t)$)	
Pre-2004	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
2004-2006	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%
2006-2007	8.5%	0.0%	0.0%	0.0%	0.0%	100.0%
2007-2008	19.1%	0.0%	0.0%	0.0%	0.0%	100.0%
2008-2009	29.5%	0.0%	20.0%	0.0%	0.0%	100.0%
2009-2010	40.1%	0.0%	60.0%	0.0%	0.0%	100.0%

2010-2011	53.0%	0.0%	100.0%	0.0%	0.0%	100.0%
2011-2012	60.8%	0.0%	100.0%	0.0%	0.0%	100.0%
2012-2013	68.9%	0.0%	100.0%	100.0%	0.0%	100.0%
2013-2014	84.8%	0.0%	100.0%	100.0%	0.0%	100.0%
2014-2015	92.0%	0.0%	100.0%	100.0%	0.0%	100.0%
2015-2016	92.0%	68.7%	100.0%	100.0%	0.0%	100.0%
Post-2016	80.0%	90.0%	100.0%	100.0%	100.0%	100.0%

The model also makes provision for other HIV testing in children (independently of the screening programmes at birth and 6-10 weeks) and resulting ART initiation. The number of children who start ART in month *t* as a result of this other HIV testing is calculated as

$$S^1(t) = \left[\sum_{s=0}^{2} \left(\sum_{x=18}^{59} N_s(x,t)\,\tau_s(x,t) E_1(t) + \sum_{x=60}^{179} N_s(x,t)\tau_s(x,t)\,E_2(t) \right) + \sum_{x=0}^{179} N_3(x,t)\,E_3(t)\tau_3(x,t) \right] l_3(t) \quad (5.7)$$

where $E_1(t)$ and $E_2(t)$ are the fractions of children in early disease who are eligible to receive ART in year *t*, for the 1-4 and 5-14 age groups respectively (Table 5.3); $\tau_s(x, t)$ is the monthly probability of HIV testing in stage *s* in year *t*; and $l_3(t)$ is the fraction of newly-diagnosed children who link to ART after diagnosis. The $E_1(t)$ and $E_2(t)$ parameters have been set to reflect the changes in ART eligibility criteria in children over time, which in 2012 included children in early disease aged 1-4 [147], and which were extended to all children in 2016. HIV testing rates in older children in early HIV disease ($\tau_s(x, t)$ for $s < 3$ and *x* aged 60 months or older) are assumed to be a constant multiple of those in sexually experienced girls aged 15. A prior distribution has been specified to represent the uncertainty around this ratio (see Appendix B). HIV testing rates in children in advanced HIV disease ($\tau_3(t)$) are assumed to be a constant multiple of those in early disease, i.e. $\tau_3(x, t) = \tau_0(x, t) \times Q$; a uniform (0, 1) prior is specified to represent the uncertainty around the $1/Q$ parameter (see Appendix B). In younger children (aged 19-59 months), the rate of testing is assumed to be 1.8 times that in the 60-179 month age group, based on routine data on total numbers of tests performed in children over the 2015-18 period (Tshepo Molapo, personal communication). In children aged 18 months, it has been policy to conduct HIV screening since 2008 [323], although implementation has been variable, with some provinces conducting universal testing and others limiting testing to HIV-exposed children (Ameena Goga, personal communication). Based on the routine data for the 2015-2018 period, we assume that 20% of children aged 18 months get tested in every year after 2008, although we lack data on the extent of 18-month testing in the period before 2008. Mathematically, the testing rate in children (ignoring screening at birth and 2 months) is

$$\tau_s(x,t) = \begin{cases} \varphi k(t) & \text{for } 60 \le x < 179 \text{ and } s < 3 \\ \varphi k(t) Q & \text{for } 60 \le x < 179 \text{ and } s = 3 \\ \varphi k(t) J & \text{for } 18 < x < 60 \text{ and } s < 3 \\ \varphi k(t) JQ & \text{for } 0 \le x < 179 \text{ and } s = 3 \\ F(t) & \text{for } x = 18 \\ 0 & \text{for } x < 18 \text{ and } s < 3 \end{cases} \quad (5.8)$$

where $k(t)$ is the rate of HIV testing in sexually-experienced non-pregnant girls aged 15, φ is the relative rate of testing in virgins, J is the relative rate of testing at ages 19-59 months (relative to 60-179 months) and $F(t)$ is the fraction of children who are tested for HIV at 18 months in year t. Because HIV testing in children under the age of 18 months requires a PCR test rather than a standard rapid test, and because PCR testing is more complex logistically, HIV testing below age 18 months is assumed to occur only if there is a clinical suspicion of HIV (i.e. the child is in advanced disease, as reflected in equation 5.7) or because the child receives HIV screening at the standard birth/2 month screening (equation 5.6).

Due to lack of information on rates of paediatric linkage to ART after diagnosis, outside of the context of early infant diagnosis, the rates of linkage soon after diagnosis ($l_3(t)$) are assumed to be a constant multiple of those assumed for newly diagnosed adults with OIs (see Appendix E). If children do not initiate ART at the time of HIV diagnosis, the model allows for later ART initiation, provided they are eligible. 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 immediately after diagnosis. Similar to equation (3.6),

$$S(t) - S^0(t) - S^1(t) \approx \rho(t) \sum_{x=0}^{179} N_7(x,t) + \rho(t) \times \delta \times \sum_{s=4}^{6} \left(\sum_{x=0}^{11} N_s(x,t) E_0(t) + \sum_{x=12}^{59} N_s(x,t) E_1(t) + \sum_{x=60}^{179} N_s(x,t) E_2(t) \right) \quad (5.9)$$

where $S(t)$ is the total number of children (aged <15) starting ART in month t; stages 4-7 correspond to the HIV-diagnosed but ART-naïve stages (Figure 5.1); $\rho(t)$ is the monthly probability of ART initiation in month t, in children who are in late disease; and δ is the relative rate of ART initiation in early disease compared to advanced disease. The relative rate of ART initiation in early disease compared to advanced disease is uncertain, and a prior distribution has therefore been assigned to represent the uncertainty in this parameter (see Appendix D). By rearranging the terms in equation (5.8), $\rho(t)$ can be estimated 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 3.4 for each year up to mid-2018 (monthly numbers are calculated by dividing these annual totals by 12).

In the period after mid-2018, 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 2013-18 period the average treatment delay for children with advanced disease ($1/\rho(t)$) was approximately 8 months (Table 3.4), and this same parameter value has been assumed in the post-2022 period. (In the period between 2018 and 2022, the $\rho(t)$ parameter is interpolated linearly between the estimated rate in 2016/17 and the assumed ultimate rate of 1/8 per month). The short average treatment delay relative to adults (around 22 months in women and 30 months in men, as discussed in section 3.3.5) suggests more rapid linkage to care after diagnosis in children than in adults.

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 [298]. This means that on reaching age 10, children who are in the late HIV stage and ART-naïve get moved into the CD4 <200/μl category, and children who are ART-naïve and in early disease on reaching age 10 are divided equally between the CD4 500+, 350-499 and 200-349 categories. HIV survival in 10-14-year olds is modelled according to the disease progression and mortality assumptions specified for adults, although the model of ART initiation in 10-14-year olds remains consistent with that in children under the age of 10. For the sake of simplicity, equations (5.7) and (5.9) do not reflect the changes in HIV disease stage definitions that occur after age 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 national model [324].

6.2 Fertility

Total fertility rates (TFRs) for the 12 months prior to each census (1996, 2001 and 2011) and Community Survey (CS, 2007 and 2016) 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 [325], 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/surveys 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/surveys. These estimates were then replaced by estimates for the period following the 2001 census as described below.

For the period 2002 to 2016, the approach was to derive the fertility rates from the best estimate of the number of births in each year. The best estimates were produced by averaging estimates derived from several sources. The first, covering the years from 2002 onwards, were derived by applying estimates of under-reporting to correct the vital registration birth statistics. These estimates of under-reporting were originally estimated by comparison of the numbers of registered births to those implied by the numbers counted in the 2011 census and/or the school enrolment numbers in 2011 if the various sources produced significantly different estimates. The second, covering the years from 2004 onwards, were derived from births recorded by the DHIS, plus 20% to allow for those not captured by the system (estimated from a comparison with the estimates from the first source of estimates). The third source were estimates from the CARe_3.2 projection model[1], which applies estimates of fertility derived from the responses to the fertility questions in the censuses and community surveys.

The average of these estimates (the first up to 2003, the first and second from 2004 to 2010, and all three after that) were then used to measure the completeness of the registration of births by duration since birth. These estimates were adjusted to ensure (to the extent that it is possible) that the completeness of the births reported up to and including a given year of registration was plausible.

[1] The CARe workbook is a simplified model, with the same demographic assumptions as the Thembisa model, which concentrates on the demographic impact of HIV/AIDS.

These numbers were converted into fertility rates by assuming that the proportion of births at each age remained constant at the levels estimated from the 2011 census and 2017 CS data.

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) for the period prior to 2002, and from the calendar year after that.

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 removed 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, 2011 and 2015 were derived from the proportions attributable to five-year age groups reported by women in each census and the 2007 and 2016 Community Surveys 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 2016, age-specific fertility rates are assumed to decline to a 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

$$F(x,t)\Gamma(s)^q, \qquad (6.1)$$

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 ≥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 [326, 327]. 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

$$F(x,t)Y(1,s,d)^q \qquad (6.2)$$

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, 258, 328, 329].

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

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

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 [330]. 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. Following this, 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(-3.985$_4m_1$)/[(1-q_2)(1-q_3)(1-q_4)], where m_0 and $_4m_1$ were the rates derived from the NBD estimates.

Rates for 2011 to 2015 were set as those projected using the CARe_3.2.xls model.

Probabilities of death for 1985 were set to those from the ASSA2008 model, and for 1986 to 1996, the probabilities of death were determined by linear interpolation between the estimates

for 1985 and 1997. Beyond 2015, 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 [331]. These numbers were derived from the change in the numbers of people by place of birth (province or outside South Africa) between censuses, less 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 [332].

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 five-year age groups before adjustment from the census count in these age groups. ${}_5M_{x-5}$ was set to $({}_5P^c_x - {}_5P_x)/10$, ${}_5M_0$ to $({}_5P^c_5 - {}_5P_5)/5$ and M_{85+} to ${}_5M_{80}$, where ${}_5P_x$ represents the number of people in the population aged between x and x+5, the superscript c represents the census count and ${}_5M_x$ 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 asymptotically to zero at a rate of 4.5% per annum.

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 adult HIV prevalence data and mortality data, using a Bayesian approach. The sections that follow describe the different steps in more detail. The model is also calibrated separately to paediatric HIV prevalence data, routine HIV testing data and key population prevalence data, as described in the appendices (see section 1 for an overview of the calibration process).

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 [333], it is unlikely that HIV prevalence in women aged 15-49 in 1985 would have been more than 0.04% (0.0076×1.8^{-5}), since antenatal HIV prevalence tends to exceed prevalence in the general female population [334]. Since we assume that 25% of women are in the high-risk group, this suggests an upper limit of 0.16% on the initial HIV prevalence in the high risk group (0.0004/0.25). The initial HIV prevalence in 15-49 year old females in the high risk group has therefore been assigned a uniform (0, 0.002) prior. The initial ratio of male prevalence to female prevalence, as well as the initial age distribution of HIV, is set to be consistent with patterns of infection observed in the early stages of the epidemic in KwaZulu-Natal in 1991 [335].

Table 7.1: Prior distributions

	Prior distribution	Prior mean, std deviation	Ref.
Sexual mixing parameter	Beta (11.50, 12.46)	0.48, 0.10	2.5
Degree of reversal in condom use	Uniform (0, 1)	0.50, 0.29	2.8
Reduction in unprotected sex after HIV diagnosis	Beta (21.9, 14.6)	0.60, 0.08	2.10
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 10-year increase in age	Gamma (9, 50)	0.18, 0.06	3.1
Reduction in mortality* per unit increase in rate of ART initiation (at CD4<200) over last 3 years	Gamma (4.59, 0.612)	7.5, 3.5	3.4
Female-to-male transmission probability in short-term/ non-spousal partnerships	Beta (7.05, 874)	0.008, 0.003	4.1
Male-to-female transmission probability in short-term/ non-spousal partnerships	Beta (5.68, 468)	0.012, 0.005	4.1
Initial HIV prevalence in high-risk women, ages 15-49	Uniform (0, 0.002)	0.001, 0.00058	7.1

* 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 2015 (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). Although no antenatal survey was conducted in 2016, the survey was repeated in 2017, and these data have also been included in the model calibration. We include HIV prevalence estimates for 5 age groups (15-19, 20-24, 25-29, 30-34 and 35-39).

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

$$H_{x,t}(\boldsymbol{\varphi}) = 1 - \frac{\sum_{j=x}^{x+4} F(j,t) N^{1}_{0,0,0}(j,t)}{\sum_{j=x}^{x+4} \overline{F}(j,t) \sum_{i,a,s,d} N^{i}_{a,s,d}(j,t)}. \qquad (7.1)$$

The corresponding prevalence of HIV actually measured in the antenatal survey is represented by $y_{x,t}$. It is assumed that if $\boldsymbol{\varphi}$ is the true set of parameter values, then the difference between the logit-transformed model estimate and the logit-transformed observed prevalence is normally distributed. The mean of this normal distribution represents the extent of antenatal bias, which arises due to the exclusion of women receiving private antenatal care from the sample and other behavioural factors. The variance of the distribution is assumed to be composed of a 'survey error' term (representing the uncertainty around the survey estimate due to binomial variation and cluster variation in the survey) and a 'model error' term (representing the error that may arise due to the assumption that the antenatal bias is constant over time and constant with respect to age). More formally, it is assumed that

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

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 $\boldsymbol{\varphi}$, the antenatal bias parameter is estimated using the formula

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

(The 100 in the denominator corresponds to the total number of observations, i.e. 5 age-specific HIV prevalence measures for each of 20 surveys.) The $\sigma^2_{x,t}$ values are estimated from the 95% confidence intervals that have been published for the various survey estimates. Once these $\sigma^2_{x,t}$ values have been obtained, the σ^2_m parameter is estimated using the formula

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

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

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

where $\mathbf{y}$ represents the matrix of $y_{x,t}$ values, across age bands 15-19 to 35-39, and across calendar years 1997-2015 and 2017.

7.2.2 Likelihood definition for household survey data

The model is calibrated to HIV prevalence data from four nationally-representative household surveys conducted by the Human Sciences Research Council (HSRC) in 2005 [14], 2008 [15], 2012 [118] and 2017 [119], as well as HIV prevalence data from the 2016 Demographic and Health Survey (DHS) [336]. HIV prevalence levels in each HSRC survey are estimated by 5-year age group (from 15-19 up to 55-59) and by sex (age bands are defined differently in the DHS report). The approach adopted in defining the likelihood function in respect of the HSRC and DHS 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 [337, 338], in which it is assumed that household prevalence data provide an unbiased estimate of HIV prevalence in the general population. The model error term is omitted because it is not necessary if the survey estimates are truly unbiased. However, even if the household survey estimates were biased, the 95% confidence intervals around the household prevalence estimates are very wide, relative to the confidence intervals around the antenatal survey estimates, and the model error would therefore be small relative to the survey error.

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 2016 [339]. 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 [340], 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 $\Theta_{g,x,t}(\boldsymbol{\varphi})$ 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 $\boldsymbol{\varphi}$ 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 $\boldsymbol{\varphi}$ is the true set of parameter values, then the difference between the log-transformed model estimate of the number of reported deaths ($\Theta_{g,x,t}(\boldsymbol{\varphi})\gamma_{g,x,t}$) 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

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

where $\varepsilon_{g,x,t} \sim N\left(0, \sigma_d^2\right)$. 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* [341] 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 [342-344]. 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 [345].

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 [345], 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.

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

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

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

$$\hat{\sigma}_d^2 = \frac{1}{320}\sum_g\sum_x\sum_{t=1997}^{2016}\left[\log\left(R_{g,x,t}\right)-\log\left(\Theta_{g,x,t}(\boldsymbol{\varphi})\gamma_{g,x,t}\right)\right]^2, \qquad (7.7)$$

where 320 is the total number of observations (20 years, 8 age groups, for men and women separately). The likelihood in respect of the reported death data is then calculated based on the assumed normality of the error terms:

$$L(\mathbf{R}\mid\boldsymbol{\varphi}) = \prod_g\prod_x\prod_{t=1997}^{2016}\left(2\pi\hat{\sigma}_d^2\right)^{-0.5}\exp\left(-\frac{\left(\log\left(R_{g,x,t}\right)-\log\left(\Theta_{g,x,t}(\boldsymbol{\varphi})\gamma_{g,x,t}\right)\right)^2}{2\hat{\sigma}_d^2}\right), \quad (7.8)$$

where **R** represents the matrix of reported death data.

7.3 Posterior simulation

The posterior distribution was simulated numerically using Incremental Mixture Importance Sampling (IMIS) [346]. Following the recommendations of Raftery and Bao [346], 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.

7.4 Combining uncertainty from different analyses

In the presentations of the posterior model estimates in sections 8.1-8.3, posterior means and confidence intervals represent only the uncertainty in the 10 parameters listed in Table 7.1. However, for the purpose of representing uncertainty in other sections, and for the purpose of representing uncertainty in the Thembisa model estimates on the Thembisa website, it is helpful to extend these ranges to reflect the sources of uncertainty described in Appendices B-E. For example, the 95% confidence interval around the published estimate of paediatric HIV prevalence should reflect not only the uncertainty about adult HIV transmission probabilities and HIV disease progression rates, but also the uncertainty around mother-to-child transmission rates and paediatric HIV disease progression.

To achieve this, the 1000 parameter combinations obtained in section 7.3 are combined with the 1000 sets of parameter combinations generated in each of Appendices B, C and E to generate 1000 distinct combinations of 39 parameter values (10 corresponding to parameters in Table 7.1, 13 in Table B7, 3 in Table C1 and 13 in Table E1). For each combination of 39 parameters, the model is run. After the 1000 sets of results have been generated, means, 2.5 and 97.5 percentiles are calculated from the distributions of model results.

8. Results of model calibration

8.1 Comparison of prior and posterior distributions

Table 8.1 compares the prior and posterior means for the 10 parameters that are allowed to vary when fitting the model to the adult HIV prevalence data 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. The extent of the reversal in condom use in recent years is substantial (0.606), implying that the model fits the HIV prevalence trends in recent years significantly better when it is assumed that there have been substantial reductions in condom use.

Table 8.1: Comparison of prior and posterior distributions

	Prior distribution (mean, 95% CI)	Posterior distribution (mean, 95% CI)
Sexual mixing parameter	0.480 (0.287-0.676)	0.457 (0.425-0.488)
Reduction in unprotected sex after HIV diagnosis	0.600 (0.439-0.751)	0.610 (0.562-0.657)
Degree of reversal in condom use	0.500 (0.025-0.975)	0.606 (0.415-0.797)
Average survival in absence of ART (years)	12.00 (10.12-14.04)	11.78 (11.45-12.10)
RR of HIV disease progression in women	0.960 (0.864-1.060)	0.931 (0.906-0.956)
Increase in HIV disease progression per 10-year increase in age	0.180 (0.082-0.315)	0.241 (0.219-0.265)
Reduction in mortality* per unit increase in rate of ART initiation (at CD4<200) over last 3 years	7.50 (2.29-15.76)	9.55 (8.02-11.11)
Female-to-male transmission probability in short-term/ non-spousal partnerships	0.0080 (0.0032-0.0149)	0.0064 (0.0062-0.0067)
Male-to-female transmission probability in short-term/ non-spousal partnerships	0.0120 (0.0043-0.0236)	0.0207 (0.0198-0.0215)
Initial HIV prevalence in high risk women, ages 15-49	0.100% (0.005-0.195%)	0.158% (0.138-0.175%)

* On a natural log scale.

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 does not match the marked decline in HIV prevalence in young women (15-24) in 2017, a trend that is inconsistent with the results from the HSRC survey.

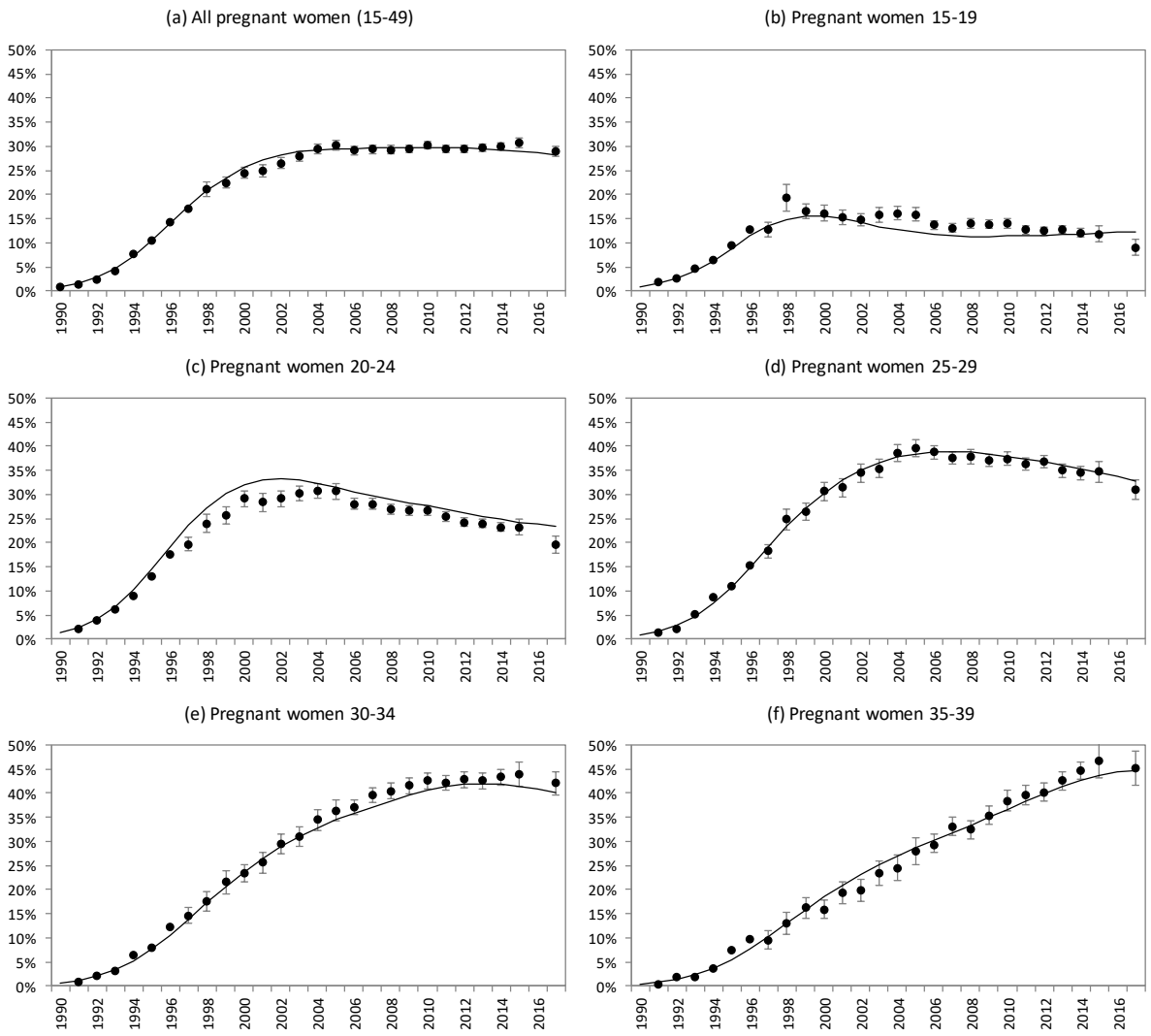


Figure 8.1: HIV prevalence levels in pregnant women attending public antenatal clinics
Dots represent HIV prevalence levels reported in surveys conducted from 1990-2015 and 2017 (the 1998 data were adjusted to correct an error in the provincial weights in that year). Solid lines represent the posterior 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.

The model provides a reasonably good fit to the HSRC prevalence survey data (Figure 8.2). The model fits the 2017 survey data reasonably well, although the model tends to slightly under-estimate the levels of HIV prevalence observed in women over the 25-49 age range.

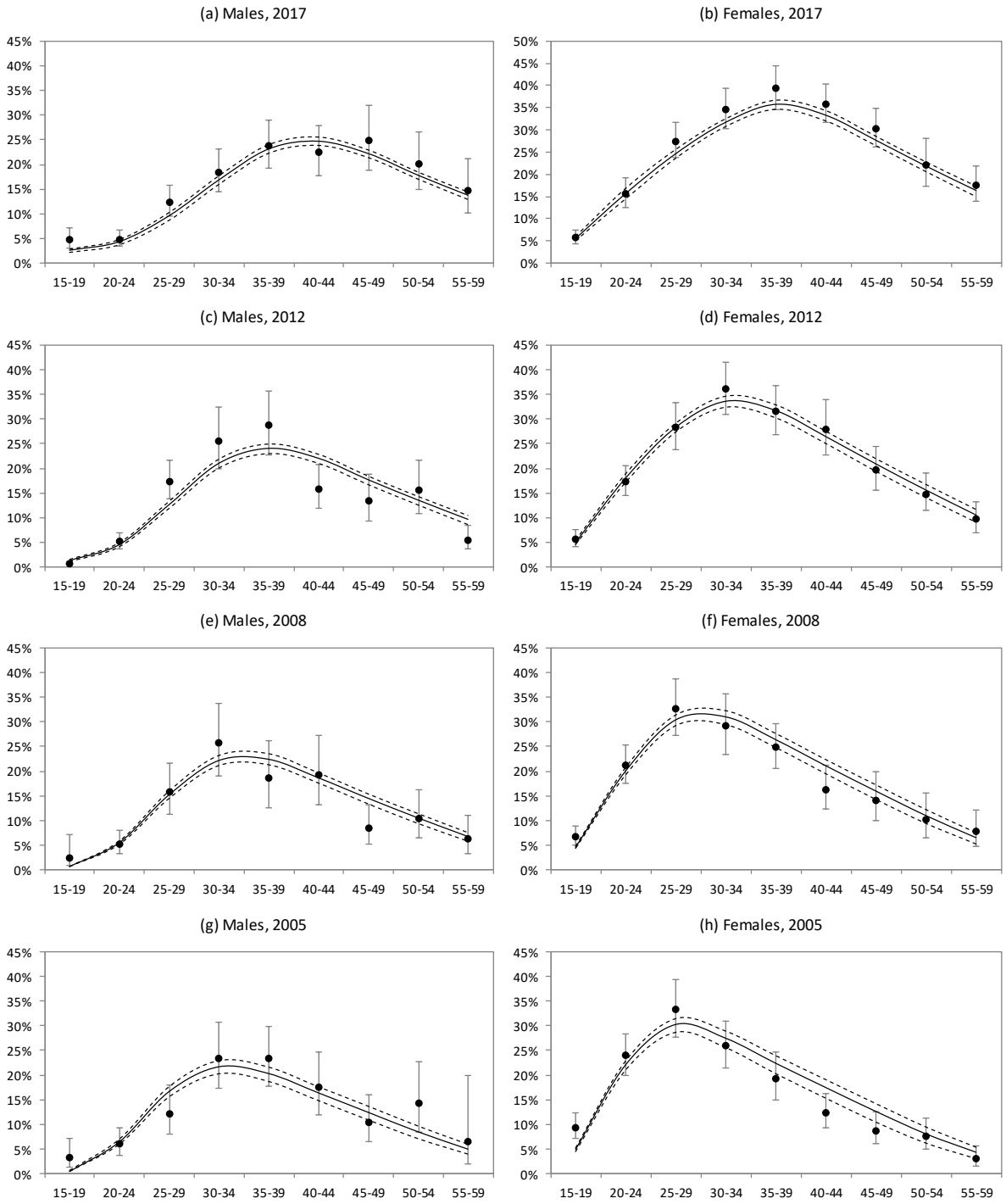


Figure 8.2: HIV prevalence levels in the general population

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.

Figure 8.3 shows the model fit to the 2016 DHS data. Although the model estimates of HIV prevalence appear roughly consistent with the male HIV prevalence data, the model tends to estimate a lower HIV prevalence in women aged 25-44 than that observed in the survey, similar to the discrepancy observed when comparing the model to the 2017 HSRC survey.

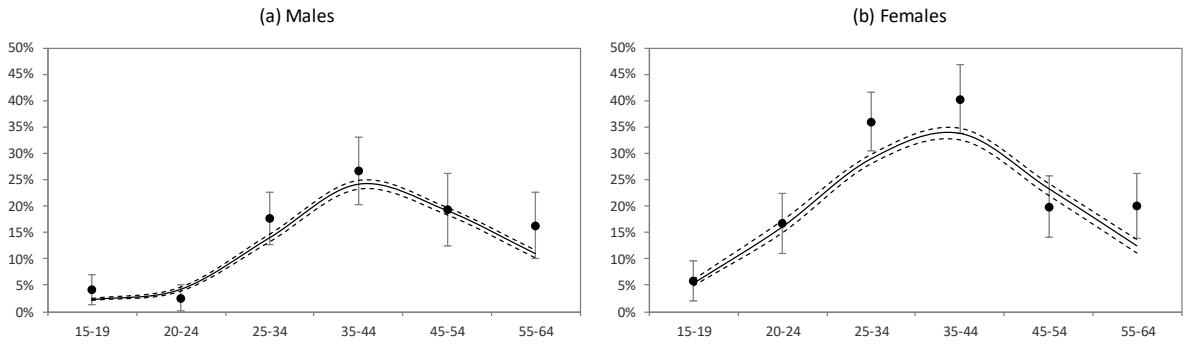


Figure 8.3: HIV prevalence levels in the general population in 2016
Dots represent DHS prevalence estimates, together with 95% confidence intervals (confidence intervals for the survey have not been published and were approximated here based on an assumed design effect of 1.6). Solid lines represent the posterior mean model estimates of HIV prevalence, and dashed lines represent the 95% confidence intervals around these estimates.

Figure 8.4 shows that the model also matches the household survey prevalence trends over time, although the most recent HSRC and DHS survey results suggest a more substantial increase in HIV prevalence in recent years than the model suggests. A possible explanation for the unexpectedly high prevalence in the two most recent surveys is differential non-response by socio-economic status: in the 2016 DHS, for example, the fraction of household members who were interviewed and tested for HIV ranged between 39% in the highest wealth quintile and 69% in the lowest wealth quintile, and HIV prevalence was inversely associated with wealth quintile [336]. To the extent that this under-sampling of higher socio-economic status groups is not corrected for by the survey weights, HIV prevalence could be over-stated.

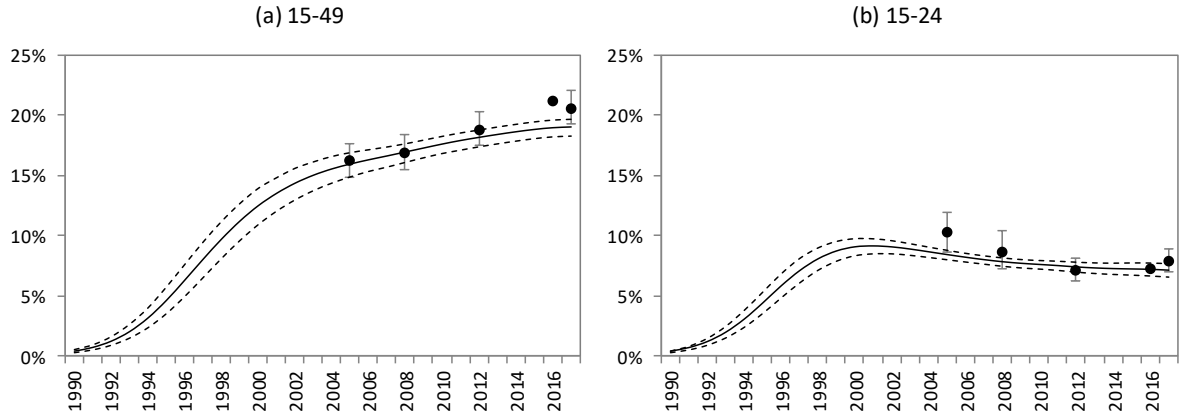


Figure 8.4: HIV prevalence trends in the general population
Dots represent HSRC and DHS survey prevalence estimates, together with 95% confidence intervals (confidence intervals have not yet been published for the 2016 DHS). Solid lines represent the posterior mean model estimates of HIV prevalence, and dashed lines represent the 95% confidence intervals around these estimates.

The model has also been calibrated to HIV prevalence data from HIV testing services (Appendix B), surveys of sex workers and MSM (Appendix C), and household survey estimates of prevalence in children (Appendix E). The model matches levels of HIV prevalence observed in individuals attending HIV testing services (Figure B2). The model

also matches the key population HIV prevalence data roughly, but because none of the survey estimates are nationally representative, there is substantial variation in survey estimates of prevalence, and consequently wide confidence intervals around the model estimates of prevalence in key populations (Figure C1). Model estimates of HIV prevalence in children are consistent with survey data in 2008 and 2012, but the model estimates lower levels of paediatric HIV prevalence than observed in the 2005 and 2017 surveys (Figure E1).

8.3 Calibration to adult mortality data

Figure 8.5 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 (2016), possibly as a result of late death registrations. The model also over-estimates the numbers of recorded deaths in women in 2005. Similar patterns are observed when age-specific comparisons are performed (Figure 8.6). 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.

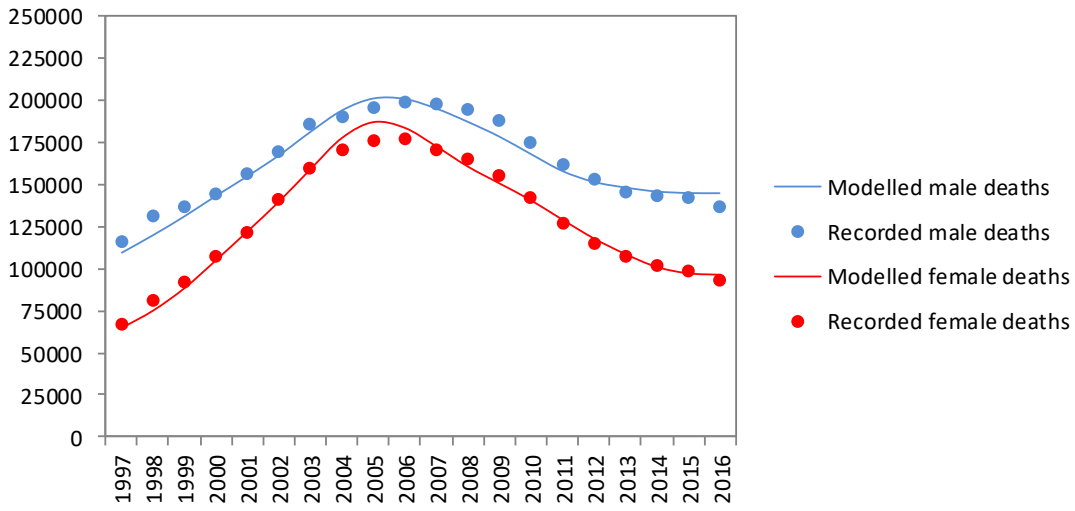


Figure 8.5: Numbers of deaths in adults aged 20-59
Dots represent recorded numbers of deaths, after adjusting for incomplete registration. Solid lines represent the posterior mean model estimates.

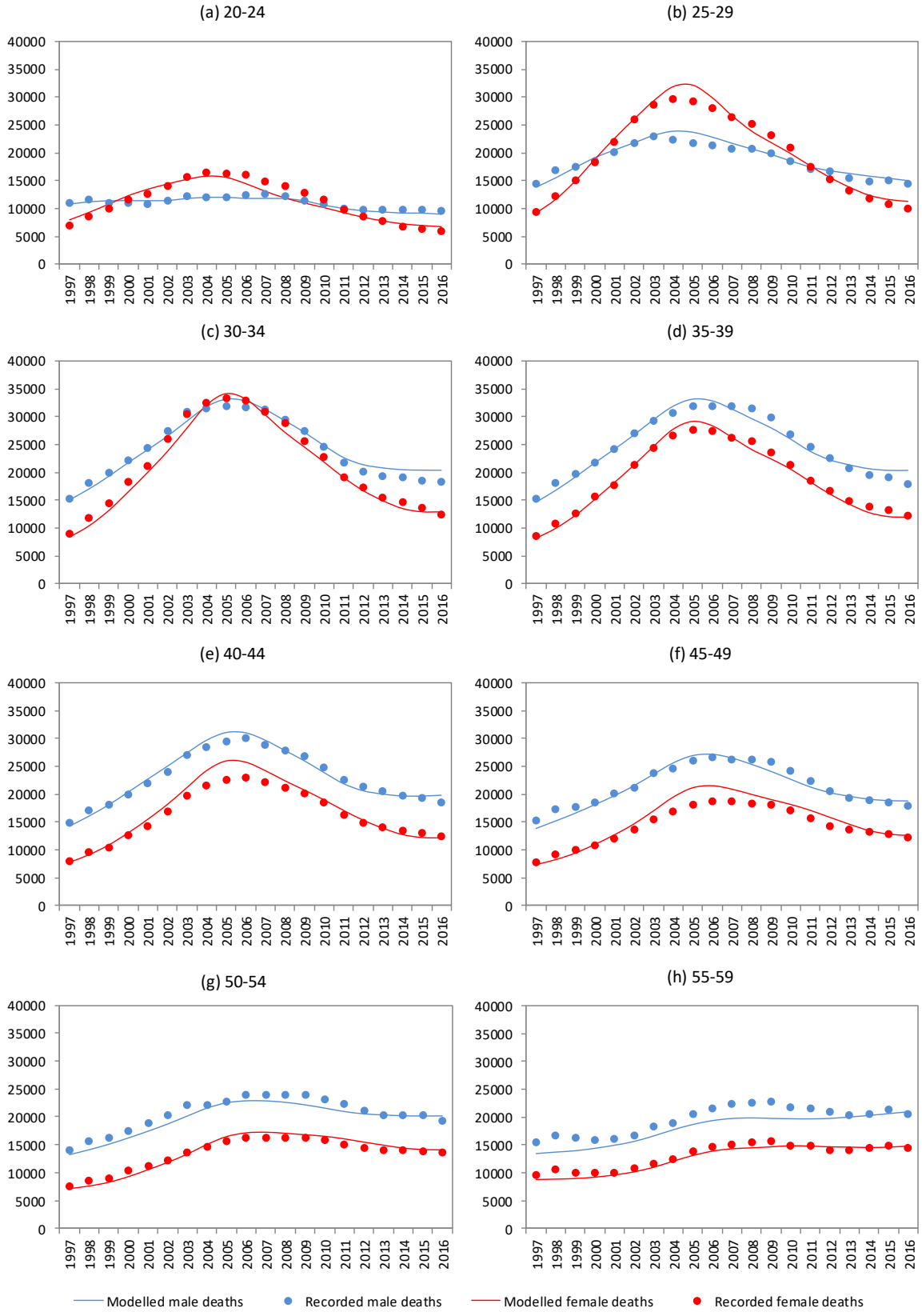


Figure 8.6: Numbers of deaths in adults, by five-year age group

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

8.4 Validation against HIV incidence estimates

Figure 8.7 compares the model estimates of HIV incidence in 15-49 year olds with estimates published by the HSRC [119, 347]. The first three estimates were obtained using a synthetic cohort approach, and model estimates are roughly consistent with these estimates, although the confidence intervals around these estimates are very wide. The two most recent estimates were obtained using a multi-assay testing algorithm based on the LAg avidity assay. The model estimate in 2011-12 is somewhat lower than the survey estimate. This may be because the LAg avidity assay was assumed to produce no false recent reactions; in an alternative analysis in which a false recent rate of 0.5% was assumed, the HIV incidence rate estimated using the multi-assay testing algorithm declined to 1.31% [347], very similar to the model estimate of 1.33% (95% CI: 1.26-1.40%). The model estimate of HIV incidence in 2016-17 is 0.97% (95% CI: 0.89-1.05%), slightly higher than that estimated in the 2017 survey (0.79%). Details regarding the assumptions made in producing the 2017 survey estimate have not yet been published.

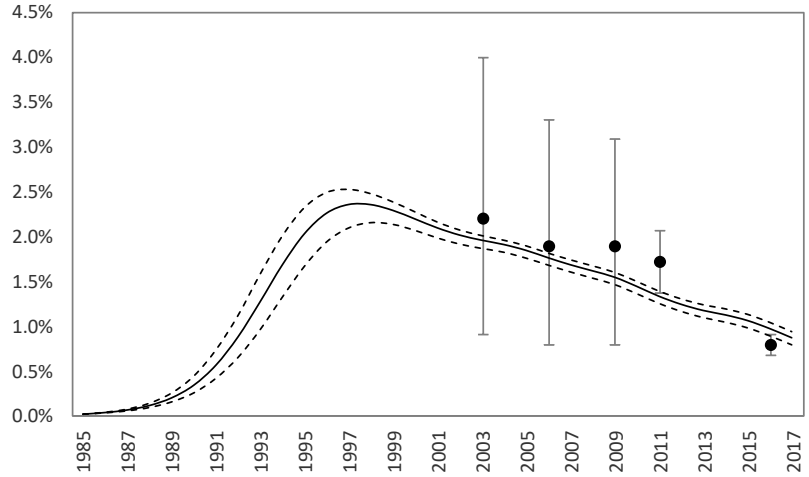


Figure 8.7: HIV incidence in 15-49 age group
Dots represent estimates derived directly from HSRC survey data. Solid lines represent the posterior mean model estimates and dashed lines represent 95% confidence intervals.

Figure 8.8 compares the model estimates of mother-to-child transmission rates from recent routine infant testing data and surveys with corresponding model estimates. Model estimates of perinatal mother-to-child transmission rates are reasonably close to routine data sources (Figure 8.7(a)), which include the District Health Information System (DHIS) [348] and the National Health Laboratory Service (NHLS) [311]. However, these estimates of perinatal transmission are under-estimates 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%) [349]. Our model estimates are consistent with this survey (Figure 8.7(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. The reported transmission rates have not been adjusted for possible false-positive PCR results, which may lead to reported transmission rates exaggerating true transmission rates [350]. Reported rates have also not been adjusted for likely false-negative PCR results in PMTCT-exposed infants [320], and lower rates of screening in mothers who have not received ART antenatally [317, 319, 351], both of which may lead to reported transmission rates under-estimating true transmission rates.

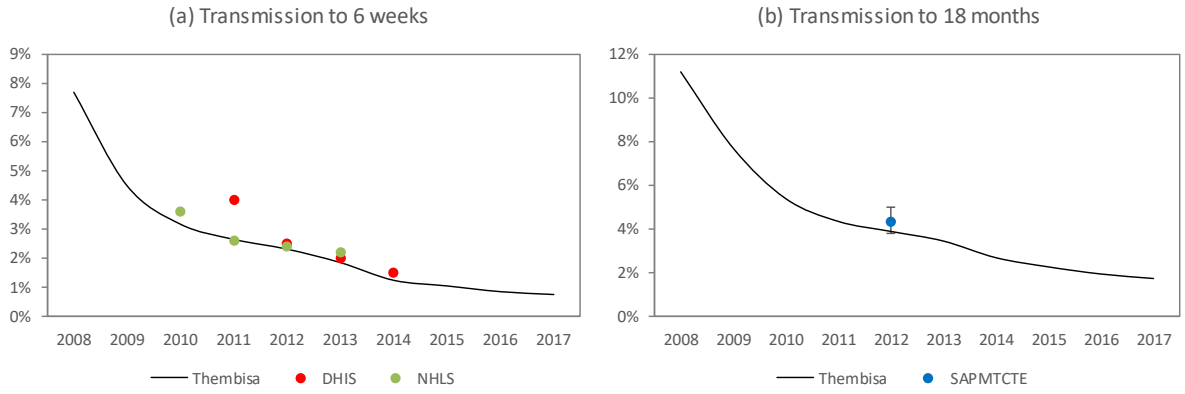


Figure 8.8: Mother-to-child transmission rates

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 Validation against reported ART data

Figure 8.9 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 cumulative enrolment. Thereafter public sector statistics were reported as 'current enrolment', although it is suspected that many clinics were still reporting cumulative enrolment. From 2012 onward, model estimates of current enrolment are more consistent with the reported 'current enrolment' data than the model estimates of cumulative enrolment, reflecting the gradual transition to reporting of current enrolment that started in late 2009. The only estimate of cumulative enrolment in recent years is the estimate of 4.2 million in March 2015, based on viral load data from the NHLS [352]. The model estimate of cumulative enrolment is roughly consistent with this estimate, suggesting that the model assumptions about rates of ART interruption and ART resumption (described in Appendix G) are plausible.

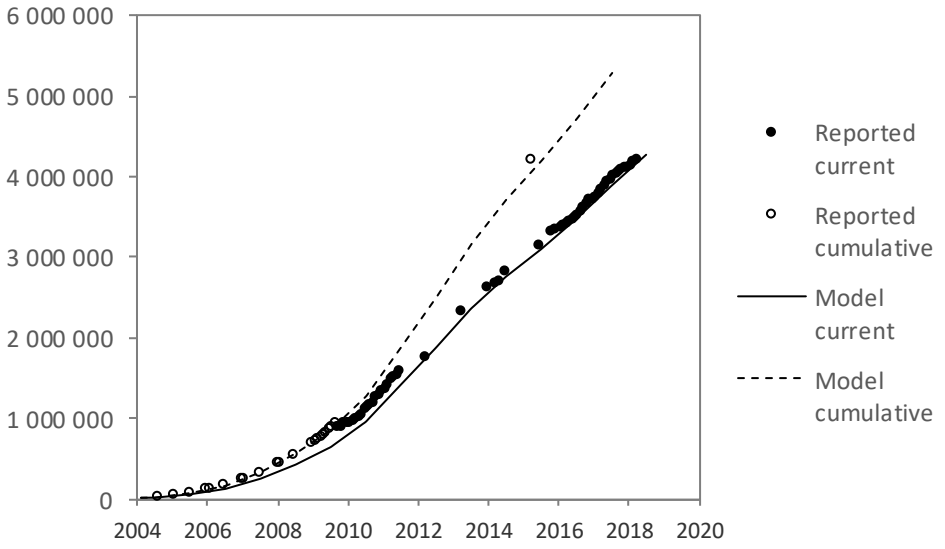


Figure 8.9: ART enrolment in the South African public sector
Dots represent reported numbers receiving ART in the public sector. Solid and dashed lines represent the posterior mean model estimates of numbers currently and cumulatively enrolled on the ART programme, respectively.

Figure 8.10 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 [353].

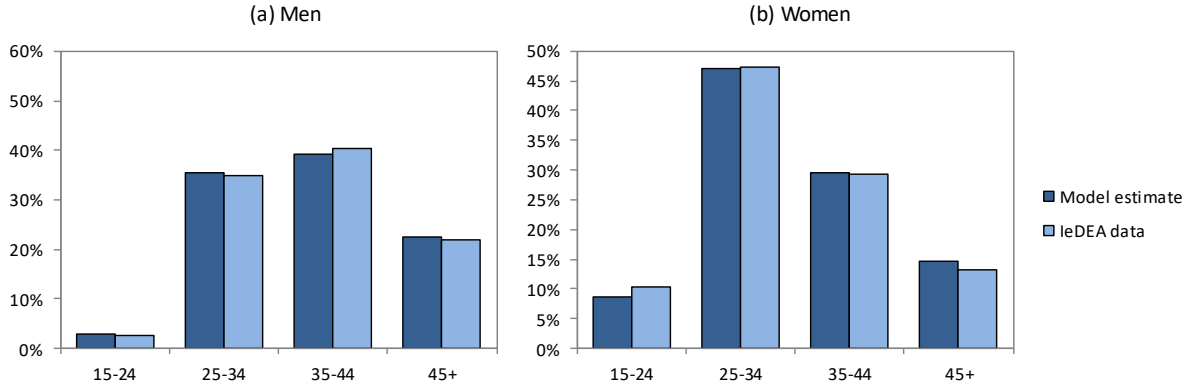


Figure 8.10: Fraction of adult age patients starting ART in different age groups

9. Discussion

Several important changes have been made to the Thembisa model. Most significantly, the paediatric component of the model has been revised in order to ensure a better model fit to recorded numbers of deaths in children. Previous versions of the Thembisa model were calibrated only to adult mortality data [91], due to uncertainty regarding levels of completeness of death recording in children. Our revised model provides a reasonably good fit to the recorded death data in children, and the model estimates of AIDS deaths in children are also remarkably consistent with estimates from the South African Burden of Disease study [354], which is based on analyses of cause-of-death data (Appendix E). Previous versions of the Thembisa model appear to have under-estimated the rates of HIV disease progression and mortality in untreated HIV-positive children at young ages, but over-estimated the extent of untreated HIV mortality in older children. Previous versions of the Thembisa model were also too conservative in their estimates of the effect of ART in child mortality; our new model incorporates mortality data from the IeDEA Southern Africa collaboration, which suggests significantly lower mortality than assumed previously in children who start ART in early HIV infection (Appendix D). Previous versions of the model also did not take into account that as rates of ART initiation in children increase, the profile of 'advanced disease' changes; taking into account this dynamic has also led to the model producing lower estimates of AIDS deaths in children in recent years (Appendices D and E). Finally, the revised paediatric model allows for higher rates of HIV testing in younger children, with special screening at 18 months, in contrast to the previous version of the model, which assumed that rates of antibody testing in children were unrelated to age (see Appendix B).

Although there have been several major advances in the modelling of paediatric HIV, there remain a few limitations. Most significantly, the model does not provide a good fit to recorded deaths in the 10-14 age group (especially for males). This is because the 10-14 disease progression and mortality assumptions are the same as those in adults (not children), and it is therefore difficult to get the model to fit these data by varying only the paediatric disease progression and mortality assumptions. Secondly, there remains significant uncertainty regarding antibody testing rates in children prior to 2015, which in turn implies significant uncertainty regarding the fraction of HIV-positive children who are diagnosed. We hope to incorporate data from the Child Problem Identification Programme [355], which include information on HIV diagnosis at death, in order to improve the accuracy of our estimates. Another limitation is that we currently assume that boys and girls have the same rates of HIV disease progression and mortality, although there is growing evidence to suggest that boys progress more rapidly than girls [299, 356], consistent with differences observed between HIV-positive men and women [88, 89].

Another significant change to the new version of Thembisa has been in the way in which viral suppression on ART is modelled. The previous version of Thembisa was calibrated only to DHIS data on viral suppression, and assumed a linear change in rates of viral suppression over time; the model also assumed that the DHIS data were (on average) unbiased by missing data on viral suppression. In the new version of Thembisa, we allow for more flexibility regarding trends in viral suppression over time, and calibrate to DHIS as well as NHLS data (Appendix F). The new model also includes more recent DHIS data, and the regression model

fitted to the available data suggests a negative relationship between the fraction of patients with viral load measurements and reported levels of viral suppression. This implies that estimates of viral suppression based on very incomplete data are likely to be biased towards overstating the true rates of viral suppression. Our revised estimates of viral suppression in the early years of the ART programme are therefore lower than estimated previously, but in more recent years the new version of Thembisa estimates rates of viral suppression similar to or higher than estimated in the previous version of Thembisa, largely because of the inclusion of significant amounts of recent data (from 2017-18). Another major change to the model of viral suppression is the assumption of differences in viral suppression between adults and children; consistent with recent studies [357, 358], the new model estimates substantially lower rates of viral suppression in children than in adults.

Despite these improvements, many aspects of the viral suppression model remain speculative and uncertain. It is not clear, for example, what explains the apparent significant rise in viral suppression rates in recent years (Appendix F), nor is it obvious that patients with unrecorded viral load measurements are less likely to be virologically suppressed. Although we have included some NHLS data in the calibration of the viral suppression model, where we believed that the data had been successfully adjusted to remove duplicate measurements in the same patients [359], there are also several NHLS estimates that we have not included, due to concern that there was only partial de-duplication (i.e. virologically failing patients, who are supposed to have more regular measurements, are over-represented). Despite this, the model appears roughly consistent with the NHLS data that have not been used in calibration. For example, the NHLS data suggest that in 2018 87.5% of adults on ART had viral loads of less than 1000 copies/ml (Gayle Sherman, personal communication), similar to the Thembisa model estimate of 88.4% (95% CI: 86.3-90.5%). Further research is currently being conducted using IeDEA South African viral load testing data to better understand the effect of incomplete recording of viral loads, and to validate the current Thembisa estimates of recent increases in viral suppression. Data from the African Heath Research Initiative are also being analysed to better understand the difference between rates of viral suppression estimated from routine monitoring systems and those estimated from population-level surveys. As these new analyses yield results, and as new data become available, we hope to be able to estimate rates of viral suppression in South African with greater confidence.

The revised model has been calibrated to HIV prevalence data from the 2016 DHS, which was not available at the time of the previous Thembisa. The HIV prevalence levels in the 2016 DHS are similar to those in the 2017 HSRC survey, and a continuing concern is that the Thembisa model produces a lower estimate of HIV prevalence in 2016-17 than both surveys suggest (Figure 8.4). As noted previously, this could be due to non-response bias in the recent surveys, with response rates being lower in the higher socio-economic groups, which also have lower HIV prevalence – this would suggest a bias towards under-estimation of prevalence. The high levels of HIV prevalence in 2017, and the substantial growth in prevalence between 2012 and 2017, appear to be at odds with the low HIV incidence in the 2017 survey – low relative to the 2012 survey estimate, and low relative to Thembisa (Figure 8.7). Further work is required to better understand the higher-than-expected HIV prevalence levels in the 2016 DHS and 2017 HSRC survey.

Although the revised estimates of HIV incidence prior to 2017 are generally not more than 5% different from those estimated in the previous version of Thembisa, the estimate of the total number of new infections in 2017-18 is 249 000 (95% CI: 231 00-266 000), 10% less

than the estimate from the previous version of Thembisa (275 000, 95% CI: 255 000-293 000). This difference is in part because of the substantially higher rate of viral suppression, as described previously. In addition, the new model produces a slightly greater estimate of ART coverage in 2018 than was previously projected (4.57 million versus 4.45 million). Some of the reduction in HIV incidence is also attributable to changes in the modelling of MMC: previously it was assumed that MMC uptake was independent of views on traditional male circumcision (i.e. that there would be some reduction in traditional male circumcision due to increasing uptake of MMC). Recent unpublished data suggest that this is not the case, and the new model therefore assumes instead that demand for MMC and traditional circumcision are mutually exclusive. This leads to a greater modelled benefit of MMC, and a greater increase in male circumcision prevalence over time, more consistent with recent survey data [336].

The model of HIV testing and diagnosis has also been modified slightly, with the new version of Thembisa allowing for changes over time in the extent of retesting in previously-tested individuals. The previous model assumed that the rates of testing in previously tested and diagnosed individuals were fixed multiples of those in individuals who had never been tested, with these multiples remaining constant over time. The new model estimates that the multiples have generally increased over time as testing volumes have increased (see Appendix B), i.e. HIV testing has become relatively less efficient because there has been a tendency to repeat testing in the same individuals at high rates, rather than extend testing services to people who have never tested previously. This change was made to the model in order to achieve greater consistency with the 2017 HSRC HIV testing history data (Edmore Marinda, personal communication), which were not included in the calibration of the previous version of Thembisa. Despite these structural changes and the inclusion of new data, the model estimates of the fraction of HIV-positive individuals who are diagnosed are only fractionally lower than those estimated in the previous version of Thembisa; the statistic in 2017, for example, was 90.0% (95% CI: 89.2-90.6%) in the previous version of Thembisa and is 89.1% (95% CI: 88.6-89.7%) in the new version of Thembisa.

As in the previous version of Thembisa, we have found that it is only possible to fit the model to observed trends in HIV prevalence if it is assumed that there have been substantial reductions in condom use in recent years. This is a major cause for concern, as it suggests that the HIV prevention gains from expanding HIV diagnosis and ART coverage are being offset to some extent by reductions in condom use.

Acknowledgements

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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

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

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 $f_{g,l}(y \mid x)$ 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

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

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

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

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

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

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

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

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

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

where ε is the assortativeness parameter described in section 2.5, 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:

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

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

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

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

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 $q^{A}_{g,j,i}(y,t)$ 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

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

where (3 – *g*) is the sex opposite to *g*. Similarly, we define $q^{N}_{g}(y,t)$ 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

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

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 $\exp\left(-\delta_g(x)\right)$. 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

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

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* [30] 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 $f_{1,3}(y \mid x)$ 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 [30] 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 [30, 360], with an age offset of 10 years to prevent implausible levels of sexual activity in very young boys. The $f_{1,3}(y \mid x)$ 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 $\int N(x) f_{1,3}(y \mid x) dx$ values roughly consistent with the distribution of $N(y)$ values (Figure A1).

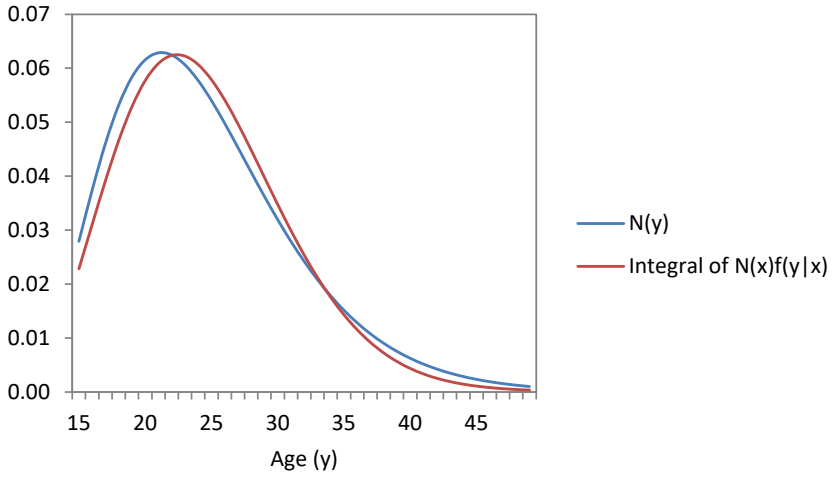

Figure A1: Age distribution of sexual activity in South African MSM

Appendix B: Calibration to HIV testing data

A multi-parameter evidence synthesis approach has been used to estimate rates of HIV testing and diagnosis in South Africa. This involves triangulating self-reported levels of testing, total numbers of HIV tests and HIV prevalence levels in individuals seeking HIV testing, within a Bayesian framework. The sections that follow describe the data sources (sections B.1-B.4), the mathematical structure of the model (sections B.4-B.6), the Bayesian procedure (sections B.7 and B.8) and the comparison of the model estimates with the data (sections B.9 and B.10).

B.1 Numbers of HIV tests performed

Our approach to estimating the total number of HIV tests performed in South Africa is to aggregate estimates from four different sources: the public health sector, private medical schemes, insurance companies (tests performed on individuals applying for life insurance) and other private providers (tests performed by employee wellness programmes and workforce programmes that are independent of medical schemes). Of these four sources, the most significant are the public sector and the insurance industry, both of which have supplied data for several years. However, data are missing or incomplete for some years, and data from other sources are very limited. Our approach is therefore to estimate total numbers of HIV tests in South Africa for each of the years for which public sector data are available, then to use linear interpolation and extrapolation to estimate the totals for the other years. The data sources up to the 2011-12 year have been described previously in the supplementary material of a previous paper on adult HIV testing [117].

A significant limitation of the historic data is that it is often unclear whether the reported numbers of tests are for adults or for adults and children combined. Almost all HIV testing performed in the first 18 months of life relies on PCR testing, not antibody testing, and it is assumed that this PCR testing is not included in the reported totals. In the case of the insurance industry data, it would be rare to take out insurance on a child's life, and it can therefore be assumed that all of the insurance industry testing is done in adults. Tests performed as part of employee wellness programmes are also done almost exclusively in adults. In the case of the public sector data, reporting is inconsistent and sometimes contradictory. Some government reports indicate that the quoted numbers of tests are for 15-49 year olds [223, 224, 226], but some state that the reported totals are for ages 5 and older (Tshepo Molapo, personal communication), and most do not specify the age range for the reported statistics. Only in the three most recent reporting years (2015-16 to 2017-18) is a detailed age breakdown given. In the years prior to this, we assume that all reported numbers of HIV tests relate to the age group 15 and older. This assumption is intended as a compromise between the bias that would arise if the reported tests were for adults and children combined and the bias that would arise if the reported totals related only to 15-49 year olds.

Table B1 shows the assumed annual numbers of HIV tests performed in adults in each year. Assumptions for the period up to 2011/12 are the same as presented previously [117]. More recent public sector statistics were obtained from the Department of Health (Tshepo Molapo, personal communication), while medical scheme estimates were obtained by scaling up

previous estimates for 2011 in proportion to the size of the medical scheme beneficiary population [361]. Due to lack of recent data on HIV testing by the insurance industry and other private sector organizations, annual testing numbers in these sectors are assumed to have remained unchanged. Although this assumption is unrealistic, the private sector contributes relatively little to total testing volumes in recent years (7%), and any bias introduced by these assumptions is therefore unlikely to distort the overall estimates substantially.

Table B1: Assumed numbers of HIV tests performed in South African adults (in thousands)

Year	Public sector	Medical schemes	Insurance industry	Other private	Total
2002-03	691000	285897	432268	75798	1484963
2003-04	821238	285897	432268	75798	1615201
2004-05	951476	285897	432268	75798	1745439
2005-06	1376582	290102	432268	75798	2174750
2006-07	1610755	298510	432268	75798	2417331
2007-08	1923430	315328	432268	75798	2746824
2008-09	2591441	327941	432268	75798	3427448
2009-10	6770000	336350	432268	75798	7614416
2010-11	9523400	344758	432268	75798	10376224
2011-12	8772000	353167	432268	75798	9633233
2012-13	8978177	361576	432268	75798	9847819
2013-14	7334942	365780	432268	75798	8208788
2014-15	8636033	369985	432268	75798	9514084
2015-16	11324134	369985	432268	75798	12202185
2016-17	12465313	374189	432268	75798	13347568
2017-18	11902403	374189	432268	75798	12784658

In the period prior to 2002, there is almost no data to guide assumptions about annual numbers of HIV tests performed. Given the lack of data prior to 2002, our approach is to assume that annual numbers of HIV tests in adults increased linearly from zero in 1990 to 1 484 963 in 2002.

In the case of children, the model does not specify numbers of HIV tests as an input, since these are lacking in all but the most recent years. Instead, rates of HIV testing in children are specified as a multiple of rates in adults, and these multiples are set in such a way that the modelled numbers of HIV tests in children between the age of 18 months and 15 years match those reported in the two most recent years (2015-16 and 2016-17) as closely as possible. For calibration purposes, the reported numbers of children tested in the public sector are increased by 3% in order to make allowance for paediatric HIV testing in medical schemes (since medical schemes are estimated to account for 3% of combined adult public sector and medical scheme testing in the most recent years, and since there is assumed to be no paediatric HIV testing in the insurance industry and in workplace testing programmes). After adjustment, the estimated total numbers of antibody tests performed in children are 880 100 in 2015-16, 1 143 671 in 2016-17 and 1 162 737 in 2017-18.

B.2 HIV prevalence in individuals tested for HIV

Although numbers of HIV tests performed in South Africa are routinely reported, the reporting of the fraction of individuals testing positive has been sporadic. Methods used to estimate the HIV prevalence in individuals testing for HIV have been slightly modified from the method described previously [117] to take into account uncertainty regarding the sensitivity and specificity of the rapid testing, which has been recommended in South Africa since 2003 [362]. In South Africa and other African settings there has been particular concern regarding the accuracy of HIV rapid testing performed by lay health workers [363, 364], and it is therefore appropriate to rely on local estimates of sensitivity and specificity of rapid tests when performed in field settings. Table B2 summarizes the results of African studies that have evaluated the sensitivity and/or specificity of a rapid diagnostic algorithm (i.e. an initial test followed by a confirmatory test in the case of individuals who test positive). The assumed average sensitivity is 93.6% and the assumed average specificity is 99.7%, corresponding to the medians of the estimates in Table B2. In order to model the uncertainty around the reported HIV prevalence levels, it is also necessary to specify a standard deviation around the sensitivity and specificity, which we set to 3.5% and 0.2% respectively.

Table B2: Sensitivity and specificity of rapid testing in South Africa

Study	Location	Years	Sensitivity	n	Specificity	n
Bock *et al* [365]	Western Cape,	2014	51.1%	90	100.0%	1496
	SA	2015	74.4%	117	100.0%	2276
		2016	85.3%	34	100.0%	1375
Jackson *et al* [366]	KZN, SA	2009-11	98.0%	491	99.6%	3505
Wolpaw *et al* [367]	Cape Town, SA	2008-09	91.3%	150	-	
Kufa *et al* [368]	KZN, SA	2015-16	91.1%	326	99.9%	3382
Bassett *et al* [369]	Durban, SA	2007	98.5%	1314	-	
Gray *et al* [370]	Uganda	2003-04	97.7%	170	90.4%	1347
Shanks *et al* [371]	DRC	-	-		98.7%	2568
Bruzzone *et al* [372]	Congo	2005-06	100.0%	200	99.7%	3414
Urassa *et al* [373]	Tanzania	-	95.8%	215	99.7%	1646
Median			93.6%		99.7%	

DRC = Democratic Republic of Congo; KZN = KwaZulu-Natal; SA = South Africa.

Suppose that $\rho(t)$ is the true HIV prevalence among people who test for HIV in year t. The true prevalence is unknown for two reasons: (a) imperfect test sensitivity and specificity, and (b) uncertainty about HIV prevalence among individuals testing for HIV in the private sector. If it is assumed that J is the ratio of HIV prevalence among individuals tested in the private sector to that among individuals tested in the public sector then

$$\rho(t) = Z(t)\big(JR(t) + \big(1 - R(t)\big)\big), \qquad \text{(B1)}$$

where $Z(t)$ is the HIV prevalence among individuals tested in the public sector and $R(t)$ is the fraction of individuals receiving HIV testing in year t who test through the private sector (estimated from the data in Table B1). We can estimate J using data from 2010-11, the year for which we have the most complete HIV testing data. In this year, the HIV prevalence among individuals testing for HIV was 16.21% in the public sector, 1.59% in insurance applicants and 9.51% in workplace programmes. The HIV prevalence among individuals

testing for HIV through medical schemes is unknown, but is generally considered to be lower than in the public sector [374]. If HIV prevalence in medical scheme testers is assumed to be half of that in public sector testers, we estimate J = 0.304, but if we assume the HIV prevalence in medical scheme testers to be 0 or the same as that in public sector testers (likely lower and upper bounds on the true prevalence), the estimated values of J are 0.102 and 0.506 respectively. Based on these calculations, we set E[J] to 0.304 and Var[J] = 0.117^2, on the assumption that J is uniformly distributed on the interval (0.102, 0.506). It follows from equation (B1) that Var[$\rho(t)$] = Var[J] $(R(t)Z(t))^2$.

Now suppose that $\theta(t)$ is the HIV prevalence that we might observe after the sensitivity and specificity of the HIV testing algorithm are taken into account:

$$\theta(t) = \rho(t)(Se + Sp - 1) + 1 - Sp, \tag{B2}$$

where Se and Sp are the sensitivity and specificity respectively. We have previously shown [375] that the mean and variance of this expression are

$$\mathrm{E}[\theta(t)] = \mathrm{E}[\rho(t)](\mathrm{E}[Se] + \mathrm{E}[Sp] - 1) + 1 - \mathrm{E}[Sp] \tag{B3}$$

and

$$\begin{aligned}\mathrm{Var}[\theta(t)] = {} & \mathrm{Var}[Se]\left(\mathrm{Var}[\rho(t)] + \mathrm{E}[\rho(t)]^2\right) \\ & + \mathrm{Var}[Sp]\left(\mathrm{Var}[\rho(t)] + (1 - \mathrm{E}[\rho(t)])^2\right) \\ & + (\mathrm{E}[Se] + \mathrm{E}[Se] - 1)^2 \mathrm{Var}[\rho(t)]\end{aligned} \tag{B4}$$

respectively. Note that E[$\rho(t)$] = $Z(t)$(E[J]$R(t)$ + (1 – $R(t)$)). The only quantity in these equations for which we have not previously calculated values is $Z(t)$), which we take to be the reported HIV prevalence in public sector testers after adjusting for the expected sensitivity and specificity of the testing algorithm. Table B3 shows the calculations of these different quantities over the 2004-2017 period.

Table B3: Estimated HIV prevalence and associated uncertainty in adults testing for HIV

Year	Public sector reported	Public sector adjusted ($Z(t)$)	Private sector proportion ($R(t)$)	Expected total prevalence E[$\rho(t)$]	Variance of total prevalence Var[$\rho(t)$]	Expected unadjusted prevalence E[$\theta(t)$]	Variance of unadjusted prevalence Var[$\theta(t)$]
2004-05	35.57%	37.81%	45.49%	25.84%	$2.01\%^2$	24.41%	$2.09\%^2$
2005-06	34.89%	37.07%	36.70%	27.60%	$1.59\%^2$	26.05%	$1.78\%^2$
2006-07	31.82%	33.78%	33.37%	25.93%	$1.32\%^2$	24.50%	$1.53\%^2$
2007-08	30.14%	31.99%	29.98%	25.31%	$1.12\%^2$	23.92%	$1.38\%^2$
2008-09	28.44%	30.16%	24.39%	25.04%	$0.86\%^2$	23.66%	$1.20\%^2$
2010-11	16.21%	17.05%	8.22%	16.08%	$0.16\%^2$	15.30%	$0.61\%^2$
2015-16	9.45%	9.81%	7.20%	9.32%	$0.08\%^2$	8.99%	$0.38\%^2$
2016-17	8.39%	8.67%	6.61%	8.27%	$0.07\%^2$	8.02%	$0.35\%^2$
2017-18	7.48%	7.70%	6.90%	7.33%	$0.06\%^2$	7.14%	$0.32\%^2$

A similar process is followed in estimating HIV prevalence among children tested for HIV (note again that this excludes PCR testing in children under the age of 18 months. However,

workplace testing and insurance testing are assumed not to account for any HIV testing in children, and this means that only the only private sector HIV testing in children is through medical schemes. Thus J is assumed to be uniformly distributed on the interval (0, 1). In addition, we make a different assumption about the sensitivity of HIV testing in children. Although we have no information on the sensitivity of the rapid HIV testing algorithm when applied to children, it has been shown that low rapid sensitivity is strongly associated with a high fraction of HIV infections that are in the acute stage of HIV infection [376], and therefore it might reasonably expected that if very few HIV-positive children over the age of 18 months are in the acute phase of HIV infection, sensitivity should be very high. We therefore assume optimistically that sensitivity is 100% and the standard deviation of the sensitivity is zero. Table B4 shows the resulting estimates for children.

Table B4: Estimated HIV prevalence and associated uncertainty in children receiving antibody testing for HIV

Year	Public sector reported	Public sector adjusted ($Z(t)$)	Private sector proportion ($R(t)$)	Expected total prevalence E[$\rho(t)$]	Variance of total prevalence Var[$\rho(t)$]	Expected unadjusted prevalence E[$\theta(t)$]	Variance of unadjusted prevalence Var[$\theta(t)$]
2015-16	3.76%	3.47%	3.16%	3.42%	$0.03\%^2$	3.71%	$0.20\%^2$
2016-17	2.60%	2.31%	2.91%	2.28%	$0.02\%^2$	2.57%	$0.20\%^2$
2017-18	1.92%	1.62%	3.05%	1.60%	$0.01\%^2$	1.89%	$0.20\%^2$

B.3 Proportions of adults ever tested for HIV

Estimates of the proportions of adults ever tested for HIV were obtained from four national household surveys, conducted by the Human Sciences Research Council (HSRC) in 2005, 2008, 2012 and 2017 [14, 118, 119, 377]. Estimates were stratified by age group, sex and HIV status, as shown in Table B5; these same data have previously been used in the calibration of the Thembisa model, although previous analyses did not include the most recent 2017 data [2, 117]. Similar data have been collected in the recent 2016 DHS, but these data are not yet available.

Table B5: Proportions of adults reporting having ever tested for HIV

		HIV-negative		HIV-positive	
Year	Age	Males	Females	Males	Females
2005	15-24	11.3% (9.2-13.9)	27.3% (24.1-30.8)	22.4% (9.2-45.1)	37.2% (29.5-45.6)
	25-34	43.4% (34.4-52.7)	48.2% (43.2-53.3)	29.6% (19.9-41.5)	44.1% (35.6-52.9)
	35-44	46.4% (40.3-52.7)	47.3% (42.2-52.4)	34.2% (24.7-45.3)	35.6% (27.0-45.2)
	45-59	36.0% (30.6-41.7)	26.1% (22.7-29.9)	49.4% (31.0-67.9)	25.4% (15.0-39.7)
	60+	17.8% (12.2-25.4)	6.2% (4.2-9.2)	40.6% (11.2-78.8)	3.5% (0.9-12.8)
2008	15-24	25.7% (21.9-29.9)	50.5% (46.8-54.3)	21.2% (8.8-43.0)	73.3% (65.2-80.0)
	25-34	54.8% (48.2-61.2)	80.6% (76.1-84.4)	52.5% (39.9-64.9)	76.4% (68.6-82.7)
	35-44	63.2% (56.4-69.5)	70.7% (66.1-75.0)	63.9% (48.9-76.6)	69.5% (61.4-76.6)
	45-59	59.9% (54.3-65.2)	43.3% (39.1-47.5)	61.2% (44.7-75.5)	57.2% (44.6-69.0)
	60+	28.8% (22.8-35.7)	15.5% (12.3-19.4)	62.7% (32.4-85.5)	26.9% (8.3-59.7)
2012	15-24	38.1% (34.5-41.7)	61.6% (58.4-64.8)	58.9% (46.2-70.6)	78.8% (70.9-85.1)
	25-34	65.3% (60.3-69.9)	91.0% (88.7-92.9)	61.9% (49.8-72.7)	94.1% (91.6-95.9)
	35-44	71.8% (66.1-76.8)	86.3% (83.0-89.0)	75.4% (63.8-84.2)	91.5% (86.0-95.0)
	45-59	71.4% (66.8-75.6)	68.4% (64.8-71.7)	82.4% (70.0-90.4)	77.8% (70.3-83.7)
	60+	46.7% (41.0-52.5)	36.6% (32.6-40.8)	58.2% (36.6-77.0)	57.8% (43.2-71.2)
2017	15-24	50.7% (48.4-53.0)	62.3% (60.2-64.4)	81.3% (71.1-88.4)	90.3% (85.7-93.4)
	25-34	76.3% (73.8-78.7)	93.1% (91.6-94.3)	84.8% (79.1-89.2)	94.9% (92.8-96.4)
	35-44	78.8% (75.7-81.5)	89.9% (87.9-91.6)	87.3% (82.3-91.1)	96.4% (94.4-97.7)
	45-59	79.9% (77.3-82.2)	81.4% (79.5-83.2)	90.1% (85.2-93.6)	95.2% (92.8-96.8)
	60+	63.8% (60.5-67.0)	57.9% (55.3-60.5)	90.6% (79.1-96.1)	89.0% (81.6-93.7)

95% confidence intervals are shown in brackets.

B.4 Rates of HIV testing in patients with opportunistic infections

Published statistics on rates of HIV testing in patients with opportunistic infections are limited, and almost all of the published data relate to HIV testing in tuberculosis (TB) patients specifically. A further problem is that the most recent published data on HIV testing in TB patients (since 2009) do not directly report the fraction of TB patients tested for HIV but rather the fraction of TB patients who know their HIV status (which includes both those tested and those who were previously diagnosed HIV-positive). Another challenge is that even when the reported statistics represent the rate of HIV testing in TB patients who were not previously diagnosed HIV-positive, this represents only testing in the facility in which TB is treated, around the time of treatment. It does not include TB patients who may have been diagnosed with HIV after being referred for HIV testing in other facilities, or TB patients who may have sought HIV testing because their symptoms led them to suspect they may have HIV.

To address these problems, we adjust the reported fractions of TB patients who know their HIV status to take into account these biases, through a two-step process. As in section 3.2, we define $d_i(t)$ to be the fraction of OI patients, with HIV testing history i, who receive HIV testing as a result of their OI, if their OI occurs in year t. (The HIV testing history, i, is 0 if the individual has never been tested for HIV, 1 if the individual has been tested for HIV but not diagnosed positive, 2 if the individual has been diagnosed positive but not started ART, and 3 if the individual has started ART.) We wish to estimate $d_i(t)$ from $\chi_i(t)$, the reported fractions of TB patients who know their HIV status in year t (these reported fractions are shown in Table B6). We also define $\gamma_i(t)$ to be the fraction of OI patients, with HIV testing history i, who receive HIV testing in the facility where they are treated for their OI, if their OI occurs in year t. This differs from $d_i(t)$, which includes all HIV testing resulting from the OI,

regardless of whether it occurs in the health facility where the individual was treated for their OI. The two parameters are assumed to be related to each other by the odds ratio Φ, defined as the ratio of the odds of an OI patient being tested for HIV in the same facility as that in which they are treated to the odds of an OI patient receiving any HIV testing as a result of their OI, i.e.

$$\Phi = \left(\frac{\gamma_i(t)}{1-\gamma_i(t)} \right) \Big/ \left(\frac{d_i(t)}{1-d_i(t)} \right) \tag{B5}$$

In 2009 and subsequent years, the $\chi_i(t)$ and $\gamma_i(t)$ parameters are related to each other by the equation

$$\chi_i(t) = \frac{\sum_s \sum_{i=0}^{1} N_{s,i}(t)\Omega_s \gamma_i(t) + \sum_{s>0} \sum_{i=2}^{3} N_{s,i}(t)\Omega_s}{\sum_s \sum_{i=0}^{3} N_{s,i}(t)\Omega_s} \tag{B6}$$

where $N_{s,i}$(t) is the number of individuals in stage s of HIV infection (s = 0 if the individual is uninfected), with HIV testing history i, at the start of year t, and Ω_s is the annual incidence of opportunistic infections in stage s of HIV infection. (The values of Ω_s for untreated HIV-positive individuals are presented in Table 3.1, and incidence rates for HIV-negative individuals and individuals on ART are set at 0.019 and 0.10 respectively.) This equation represents $\chi_i(t)$ as the proportion of OI patients who have already been diagnosed positive prior to their OI (the second term in the numerator) plus the proportion of other OI patients who are offered HIV testing (the first term in the numerator). From this it follows that

$$\gamma_i(t) = \frac{\chi_i(t) \sum_s \sum_{i=0}^{3} N_{s,i}(t)\Omega_s - \sum_{s>0} \sum_{i=2}^{3} N_{s,i}(t)\Omega_s}{\sum_s \sum_{i=0}^{1} N_{s,i}(t)\Omega_s}. \tag{B7}$$

In the years prior to 2009, it is not clear if the reported proportions are the fractions receiving testing (among those not previously diagnosed positive) or the fractions who know their HIV status (including those who were previously diagnosed). However, early reports tend to suggest the former [128, 134], and hence $\gamma_i(t)$ is set equal to $\chi_i(t)$ in the years before 2009.

Having estimated $\gamma_i(t)$ from $\chi_i(t)$, the next step is to estimate $d_i(t)$ from $\chi_i(t)$, using equation B5. This requires an estimate of Φ, which is unknown. To represent the uncertainty regarding Φ, we assign a vague prior, which is uniform on the interval [0, 1). The posterior analysis (presented in more detail below) yields a posterior estimate of 0.42 for the Φ parameter. Table B6 presents the resulting estimates of the $d_i(t)$, $\gamma_i(t)$ and $\chi_i(t)$ parameters. It is worth noting that in 2010 and subsequent years, the net effect of the two adjustments is relatively small (i.e. there is only a modest difference between $d_i(t)$ and $\chi_i(t)$). However, in the pre-2009 period, $d_i(t)$ is substantially higher than $\chi_i(t)$ because of the assumed change in reporting in 2009 (i.e. the change from reporting the fraction tested to reporting the fraction tested or previously diagnosed).

Table B6: Proportions of OI patients tested for HIV

Year	% of OI patients tested at OI treatment facility or knowing their status ($\chi_i(t)$)		% of OI patients previously undiagnosed, who receive testing at OI treatment facility ($\gamma_i(t)$)	% of OI patients previously undiagnosed, who receive testing as a result of their OI ($d_i(t)$)
	Rate	Sources		
Pre-2004	5%		5%	12%
2004-05	8%	[128]	8%	18%
2005-06	20%	[130]	20%	38%
2006-07	31%	[130]	31%	53%
2007-08	39%	[130, 134]	39%	61%
2008-09	40%	[130, 134]	40%	62%
2009-10	53%	[130]	16%	32%
2010-11	64%	[139] [140]	36%	59%
2011-12	83%	[140]	70%	85%
2012-13	87%	[140]	76%	88%
2013-14	90%	[140]	81%	91%
2014-15	94%	[140]	89%	95%
2015-16	95%*	[140]	90%	96%

* Proportion is assumed to remain constant at 95% in subsequent years.

B.5 Rates of HIV testing in asymptomatic, non-pregnant individuals

Suppose that $G(t)$ is the total number of HIV tests performed in adults aged 15 and older, in year t, as shown in Table B1. As defined in section 3.2, the symbol $\tau_{g,i,s}(x,t)$ is the rate of HIV testing in sexually experienced individuals of age x and sex g, in HIV stage s and with HIV testing history i. The symbol $\tau'_{g,i,s}(x,t)$ is used to represent the corresponding rate of HIV testing in virgins. If $N_{g,i,s}(x,t)$ is the corresponding number of sexually experienced individuals and $V_{g,i,s}(x,t)$ is the number of virgins, at the start of year t, then

$$G(t) \approx \sum_g \sum_i \sum_s \sum_x N_{g,i,s}(x,t)\tau_{g,i,s}(x,t) + V_{g,i,s}(x,t)\tau'_{g,i,s}(x,t). \qquad \text{(B8)}$$

(The relation is not exact because the numbers of individuals in the different strata change over the course of the year, so relying only on the values at the start of the year may lead to some bias – it will later be shown that this bias is very small.) The rate of HIV testing in asymptomatic virgins is assumed to be a multiple φ of the rate of HIV testing in asymptomatic girls aged 15 who are sexually experienced and non-pregnant, i.e.

$$\tau'_{g,i,s}(x,t) = b(t)A_2(15,t)r_i(t)\varphi + \Omega_s d_i(t) \qquad \text{(B9)}$$

where $b(t)$ and $A_g(x,t)$ are the base testing rate and age-specific adjustment factor respectively (see section 3.2). Substituting equations (3.3) and (B5) into equation (B4), we obtain the following estimate for the base HIV testing rate in year t:

$$\hat{b}(t) = \frac{G(t) - \sum_g \sum_i \sum_s \sum_x N_{g,i,s}(x,t)\left\{\Omega_s d_i(t) + F_{g,s}(x,t)v_i(t)\right\} + V_{g,i,s}(x,t)\Omega_s d_i(t)}{\sum_g \sum_i \sum_s \sum_x N_{g,i,s}(x,t)A_g(x,t)r_i + V_{g,i,s}(x,t)A_2(15,t)r_i\varphi}.$$

This approximation to $b(t)$ is calculated at the start of each year, and is substituted into equation (3.3). Estimates of the $N_{g,i,s}(x,t)$ population totals are updated at monthly time steps, with the estimated values of $b(t)$ being held constant over the course of each year.

The above approach is used to calculate rates of HIV testing at ages 10 and older. In children between the ages of 5 and 10 years, the same equation (B9) is used to calculate the HIV testing rate, except that the second term (representing HIV testing in OI patients) is omitted in children who are either HIV-negative or in the early stage of HIV disease. For children who are in the advanced stage of HIV disease and not yet on ART, this testing rate is multiplied by a factor Q, as the incidence of opportunistic infections in children is not simulated directly. As described in section 5.3, rates of HIV testing in children aged 19-59 months are assumed to be higher than those at 5-10 years (by a factor of J), and the fraction of children tested at 18 months is assumed to have been constant at 20% since 2009. The same formula (adjusted by the factors J and Q) is used to model the rate of PCR testing in children under the age of 18 months who have advanced HIV infection, but no provision is made for PCR testing in children who are HIV-negative or in the early stage of HIV infection, except in the context of early infant diagnosis.

B.6 Model estimates of numbers of HIV tests and HIV prevalence in HIV testers

For individuals aged 15 and older, the total number of HIV-negative test results over the course of year t is calculated as

$$T_0(t) = \sum_{m=1}^{12}\sum_{g=0}^{1}\sum_{i=0}^{1}\sum_{s=0}^{1}\sum_{x=15}^{90} N_{g,i,s}\left(x, t+\frac{m-1}{12}\right)\tau_{g,i,s}(x,t) + V_{g,i,s}\left(x, t+\frac{m-1}{12}\right)\tau'_{g,i,s}(x,t),$$

and the total number of HIV-positive test results is

$$T_1(t) = \sum_{m=1}^{12}\sum_{g=0}^{1}\sum_{i=0}^{3}\sum_{s=2}^{5}\sum_{x=15}^{90} N_{g,i,s}\left(x, t+\frac{m-1}{12}\right)\tau_{g,i,s}(x,t) + V_{g,i,s}\left(x, t+\frac{m-1}{12}\right)\tau'_{g,i,s}(x,t).$$

The latter sum excludes individuals in the acute stage of HIV infection (s = 1), as the model assumes that HIV is (on average) not detectable during the acute phase of HIV infection. The model thus makes an implicit allowance for the sensitivity of the rapid test, assuming that the sensitivity is strongly related to the fraction of testers who are in the acute phase of HIV infection, as has been shown in a recent meta-analysis [376]. However, this sensitivity adjustment is not necessarily equivalent to that described in section B.2, hence the importance of allowing for uncertainty in the latter when calibrating the model to routine HIV testing data. The model estimate of the fraction of adults testing for HIV in year t who test positive is

$$P(t) = \frac{T_1(t) + T_0(t)\left(1 - \mathrm{E}[Sp]\right)}{T_0(t) + T_1(t)},$$

where E[Sp] is the same specificity parameter as in section B.2 (0.997). A similar approach is used to calculate the number of antibody tests performed in children under the age of 15, and the HIV prevalence in children tested for HIV. However, as the model does not consider acute HIV infection in children (it would be rare in HIV-positive children over the age of 18

months), there is no exclusion of acutely-infected children, and thus the model implicitly assumes that rapid testing in children has 100% sensitivity.

B.7 Likelihood definition

The likelihood function is defined with respect to four data sources: the proportions of individuals who report having ever tested for HIV in three national household survey (see section B3), the empirically-derived estimates of the HIV prevalence in individuals tested for HIV in six years (see section B2), the estimated numbers of HIV tests performed in children (see section B1) and the total number of children on ART. Although it is not strictly necessary to include the last of these data sources in the model calibration, we found that if the paediatric ART data were not included, the model produced estimates of the fraction of HIV-positive children diagnosed that were lower than the independently-estimated fractions of HIV-positive children on ART. Including the likelihood in respect of the paediatric ART data prevents such inconsistencies.

Considering first the likelihood in respect of the household survey data, we define $E_{g,x,h}(t)$ to be the model estimate of the proportion of the population ever tested, in individuals of sex g and HIV status h (0 = negative, 1 = positive), in age group x, at time t. The corresponding survey estimate is denoted by $\zeta_{g,x,h}(t)$. For the purpose of calibration, the data are grouped into five age categories: 15-24, 25-34, 35-44, 45-59 and 60+. The likelihood is calculated on the assumption that the differences between the logit-transformed survey estimates and the logit-transformed model estimates are normally distributed with mean U_h. (The logit transformation is used as it helps to ensure that the assumption of normally-distributed error terms is not violated.) In mathematical terms, we assume

$$\log\left(\frac{\zeta_{g,x,h}(t)}{1-\zeta_{g,x,h}(t)}\right)=\log\left(\frac{E_{g,x,h}(t)}{1-E_{g,x,h}(t)}\right)+U_h+\eta_{g,x,h}(t)+\varepsilon_{g,x,h}(t)$$

where U_h is a reporting bias parameter, $\eta_{g,x,h}(t)$ is a model error term and $\varepsilon_{g,x,h}(t)$ is the survey error term, which is assumed to follow a N(0, $\sigma^2_{g,x,h}(t)$) distribution. The variable $\mathrm{K}_h \equiv \exp(U_h)$ is defined as the odds ratio comparing reported prior testing to actual prior testing. The U_h parameter is estimated using the standard maximum likelihood formula,

$$\hat{U}_h=\frac{1}{45}\sum_g\sum_x\sum_t\log\left(\frac{\zeta_{g,x,h}(t)}{1-\zeta_{g,x,h}(t)}\right)-\log\left(\frac{E_{g,x,h}(t)}{1-E_{g,x,h}(t)}\right),$$

and the $\sigma^2_{g,x,h}(t)$ parameter is estimated from the 95% confidence intervals shown in Table B3. The model error term is assumed to follow a N(0, σ^2_E) distribution, with the variance of the model error being estimated as

$$\hat{\sigma}^2_E=\frac{1}{90}\sum_g\sum_x\sum_t\sum_h\left(\log\left(\frac{\zeta_{g,x,h}(t)}{1-\zeta_{g,x,h}(t)}\right)-\log\left(\frac{E_{g,x,h}(t)}{1-E_{g,x,h}(t)}\right)-\hat{U}_h\right)^2-\sigma^2_{g,x,h}(t).$$

The likelihood function in respect of the household survey data is then

$$\prod_{g}\prod_{x}\prod_{t}\prod_{h}\left(2\pi\left(\hat{\sigma}_E^2+\sigma_{g,x,h}^2(t)\right)\right)^{-0.5}\exp\left[-\frac{\left(\text{logit}\left(\zeta_{g,x,h}(t)\right)-\text{logit}\left(E_{g,x,h}(t)\right)-\hat{U}_h\right)^2}{2\left(\hat{\sigma}_E^2+\sigma_{g,x,h}^2(t)\right)}\right].$$

Secondly, for the purpose of defining the likelihood function in respect of the HIV prevalence data, suppose that $\theta(t)$ represents the empirically-derived estimate of HIV prevalence in adults tested for HIV in year *t*. It is again assumed that the difference between the model estimate and the empirical estimate is normally distributed on the logit scale. In mathematical terms, we assume

$$\log\left(\frac{\theta(t)}{1-\theta(t)}\right)=\log\left(\frac{P(t)}{1-P(t)}\right)+\varepsilon_\theta(t)$$

where $\varepsilon_\theta(t)$ is the error associated with the empirical derivation (due to incorrect assumptions regarding HIV prevalence in data sets for which prevalence information is missing, and incorrect test specificity assumptions). The $\varepsilon_\theta(t)$ term is assumed to follow a N(0, $\sigma_\theta^2(t)$) distribution, with $\sigma_\theta(t)$ being estimated from the upper and lower limits on the empirically-derived prevalence estimates (Table B2). In the case of the HIV prevalence data, we do not make provision for a model error term, as there are relatively few HIV prevalence data points, and the inclusion of a model error would lead to the HIV prevalence data being given very low weight relative to the household survey data. The likelihood function in respect of the HIV prevalence data is

$$\prod_{t}\left(2\pi\sigma_\theta^2(t)\right)^{-0.5}\exp\left[-\frac{\left(\text{logit}\left(\theta(t)\right)-\text{logit}\left(P(t)\right)\right)^2}{2\sigma_\theta^2(t)}\right].$$

The same approach is adopted in defining the likelihood for the HIV prevalence in children tested for HIV.

The final component in the likelihood definition is the likelihood in respect of the reported number of HIV tests. If *T'*(*t*) is the model estimate of the total number of antibody tests in children in year t, and *G'*(*t*) is the corresponding empirical estimate, then the difference between the two, on a log scale, is assumed to be normally distributed with zero mean and standard deviation σ_G. Model estimates of the number of HIV tests in children (as a fraction of the number of tests in adults) are constrained to be reasonably stable in recent years because of the assumption that testing rates in children can be expressed as multiples of the testing rates in adults. The variance of the error term is therefore calculated by assessing the extent to which the fraction of HIV tests in children varies over the 2015-2018 period. The ratio of the number of HIV tests in children to that in adults (considering only the available public-sector statistics) is 0.075 in 2015-16, 0.089 in 2016-17 and 0.095 in 2017-18 (average 0.086, standard deviation 0.010). Given that the model is constrained to produce a fairly stable value of this ratio, we should tolerate a similar 'error' in model estimates, i.e. the coefficient of variation in *G'*(*t*) values should be 0.010/0.086 = 0.116 for the purpose of calculating the likelihood. Mathematically,

$$\sigma_G^2 = \mathrm{Var}\left[\log\left(G'(t)\right)\right] \approx \frac{1}{G'(t)^2}\mathrm{Var}\left[G'(t)\right] = 0.116^2 .$$

The total likelihood is the product of the likelihood in respect of the household survey data, the likelihood in respect of the HIV prevalence data, and the likelihood in respect of the reported numbers of paediatric HIV tests.

B.8 Prior distributions

Table B7 summarizes the parameters included in the uncertainty analysis, the prior distributions assigned to these parameters, and the data sources on which these prior distributions are based. Most of these prior distributions are the same as in our previous analysis of HIV testing rates up to 2012 [117]. Most of the parameters have been defined in this appendix, although some have been defined previously in section 3.2. Gamma distributions are used to represent the uncertainty for the first six parameters and the r_1 and r_2 parameters, while a beta distribution is assigned to represent the uncertainty around the φ parameters, and uniform (0, 1) prior distributions are assigned to the remaining parameters.

Table B7: Prior distributions

Parameter	Symbol	Mean	SD	Data source
Mean age of testing: men*	α_0 / λ_0	42	7	Based on fitting gamma functions to age profile of individuals tested for HIV in Mpumalanga [120], using the provincial age profile [324]
Mean age of testing: women*	α_1 / λ_1	24	4	
SD of age of testing: men*	$\sqrt{\alpha_0} / \lambda_0$	30	5	
SD of age of testing: women*	$\sqrt{\alpha_1} / \lambda_1$	24	4	
Ratio of male to female test uptake at age 25 in 2002	$B_0(2002)$	0.8	0.1	2006 National Communication Survey [121]
Ratio of male to female test uptake at age 25 in 2010	$B_0(2010)$	0.8	0.1	-
HIV test history adjustment:				
Never previously tested	r_0	1	-	Definition of base rate
Previously tested negative	$r_1(0)$	1.5	0.4	[48, 122, 123]
Previously tested negative	$r_1(max)$	1.5	0.7	[48, 122, 123]
Diagnosed HIV+, pre-ART	r_2	0.5	0.30	[371, 378-380]
ART-experienced	r_3	0.5	0.29	[371, 378-380]
OR for HIV testing in OI treatment facility	Φ	0.5	0.29	Vague prior
Relative rate of testing in virgins	φ	0.2	0.1	Unpublished data (Franziska Meinck)
Ratio of testing rate in early vs late paediatric HIV	$1/Q$	0.5	0.29	Vague prior

OI = opportunistic infection. OR = odds ratio. SD = standard deviation.

* For a hypothetical population with uniform age distribution. The actual distribution of HIV testing ages differs when the function is applied to the population pyramid in South Africa.

B.9 Comparison of prior and posterior distributions

Posterior distributions were simulated using Incremental Mixture Importance Sampling [346]. The resulting posterior estimates of the model parameters are presented in Table B8. Consistent with our previous analysis, and consistent with a recent study showing high rates of retesting in recently diagnosed sex workers [381], results suggest a high rate of retesting in individuals who have previously been diagnosed HIV-positive, although retesting appears to be substantially less frequent after ART initiation. The results also suggest a low rate of HIV testing in children and youth who are not yet sexually experienced, although the rate of testing in HIV-positive children is estimated to increase dramatically once they have progressed to advanced disease.

Table B8: Prior and posterior distributions

Parameter	Prior distribution (mean, 95% CI)	Posterior distribution (mean, 95% CI)
Mean age of testing: men*	42.0 (29.4-56.8)	39.5 (34.7-45.6)
Mean age of testing: women*	24.0 (16.8-32.5)	23.1 (18.8-27.3)
SD of age of testing: men*	30.0 (21.0-40.6)	28.3 (21.4-34.5)
SD of age of testing: women*	24.0 (16.8-32.5)	22.4 (18.9-27.3)
Ratio of male to female test uptake in 2002	0.80 (0.62-1.01)	0.80 (0.72-0.91)
Ratio of male to female test uptake in 2010	0.80 (0.62-1.01)	0.74 (0.64-0.86)
HIV test history adjustment:		
Previously tested negative (baseline)	1.50 (0.82-2.38)	2.24 (1.49-3.06)
Previously tested negative (maximum)	1.50 (0.46-3.12)	5.08 (3.21-7.17)
Diagnosed HIV+, pre-ART	0.50 (0.09-1.24)	1.38 (0.87-1.89)
ART-experienced	0.50 (0.025-0.0975)	0.26 (0.16-0.40)
OR for HIV testing in OI treatment facility	0.50 (0.025-0.0975)	0.42 (0.23-0.63)
Relative rate of testing in virgins	0.20 (0.03-0.43)	0.11 (0.08-0.14)
Ratio of testing rate in early vs late paediatric HIV	0.50 (0.025-0.0975)	0.06 (0.03-0.08)

OI = opportunistic infection. OR = odds ratio. SD = standard deviation.
* For a hypothetical population with uniform age distribution. The actual distribution of HIV testing ages differs when the function is applied to the population pyramid in South Africa.

The posterior estimates of the θ_0 and θ_1 parameters are 1.53 (95% CI: 1.39-1.68) and 0.74 (95% CI: 0.66-0.83) respectively. This suggests that HIV-negative individuals tend to over-report their past HIV testing, while HIV-positive individuals tend to under-report their past HIV testing. A more detailed discussion of these reporting biases is provided elsewhere [117].

B.10 Comparison of model estimates with data

Figure B1 compares the model estimates of the fraction of adults ever tested for HIV with the household survey data (after adjusting the model estimates to take account of the reporting biases noted previously). Although the model is in good agreement with the data from the 2005 and 2012 surveys, the model tends to under-estimate the reported levels of past testing in the 2008 survey and tends to over-estimate the reported levels of past testing in the 2017 survey (especially in women).

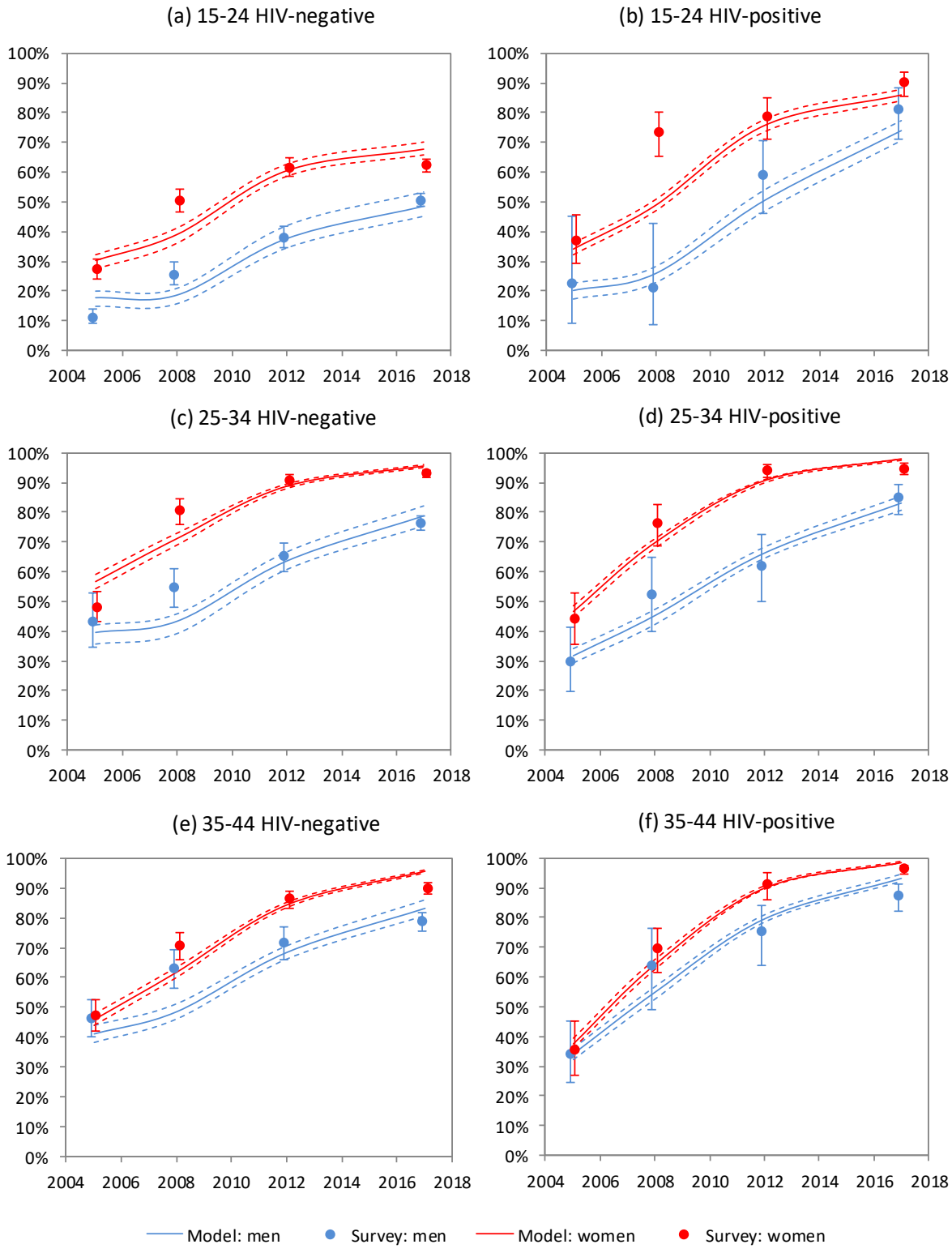

Figure B1: Proportions of adults who report having ever been tested for HIV

Model estimates have been adjusted to reflect expected reporting bias. Dashed lines represent 95% confidence intervals around average model estimates (solid lines), while vertical lines represent 95% confidence intervals around survey estimates (dots).

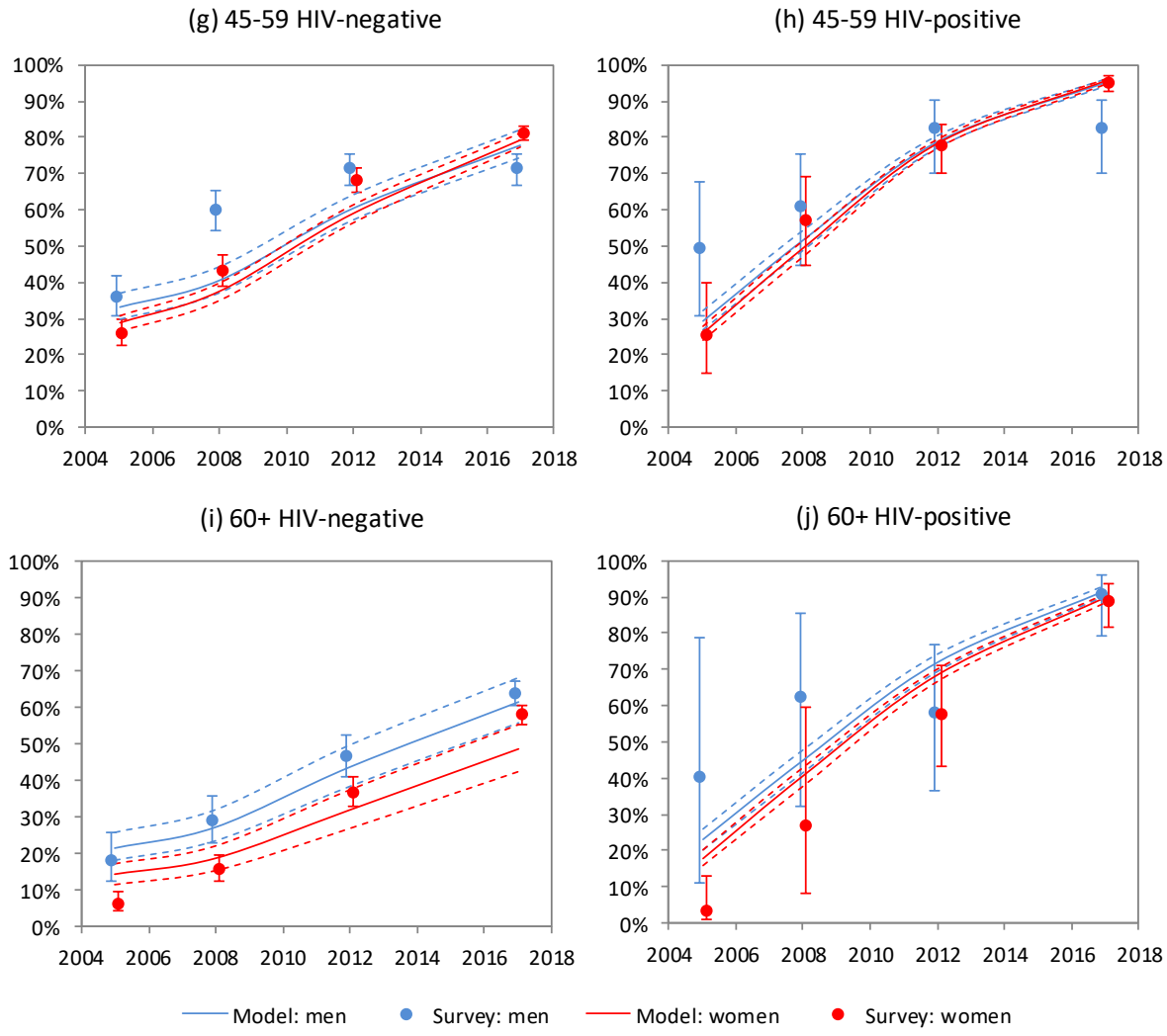

Figure B1 (continued): Proportions of adults who report having ever been tested for HIV
Model estimates have been adjusted to reflect expected reporting bias. Dashed lines represent 95% confidence intervals around average model estimates (solid lines), while vertical lines represent 95% confidence intervals around survey estimates (dots).

Figure B2 compares the model estimates of HIV prevalence in individuals tested for HIV with the corresponding empirically-derived estimates. The model matches the routine testing reasonably closely. For both adults and children, the model estimates an increase in prevalence up to 2006-7, reflecting the increasing HIV prevalence in the general population. Thereafter, the model estimates a steady decline in HIV prevalence, in part because of rising levels of diagnosis and ART coverage (since previously diagnosed and treated individuals are less likely to get tested again than those who test negative). In children, the steep decline after 2007 is also due in part to the success of the PMTCT programme, which dramatically reduced paediatric HIV incidence rates. However, the paediatric estimates are highly uncertain, due to the lack of paediatric HCT data before 2015. Ramirez-Avila *et al* found a high HIV prevalence (17%) among children receiving HIV testing in Durban in 2010 [382], but this study was not included in the model calibration because it was not nationally representative.

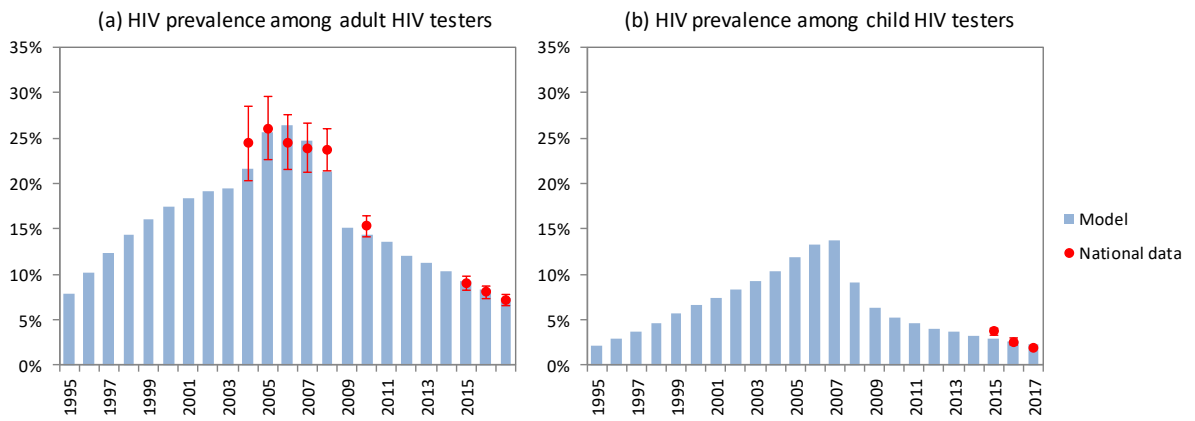

Figure B2: HIV prevalence in individuals tested for HIV

Figure B3 compares the model estimates of the total numbers of HIV tests with the empirically-derived totals. In the case of adults, there is close agreement between the modelled totals and the empirical estimates, suggesting that any bias due to the assumption of a constant population profile over the course of a year is likely to be minimal. Numbers of HIV tests have been high since the start of national HIV testing campaigns in 2009/10, but the numbers of tests conducted in children are small relative to the numbers in adults.

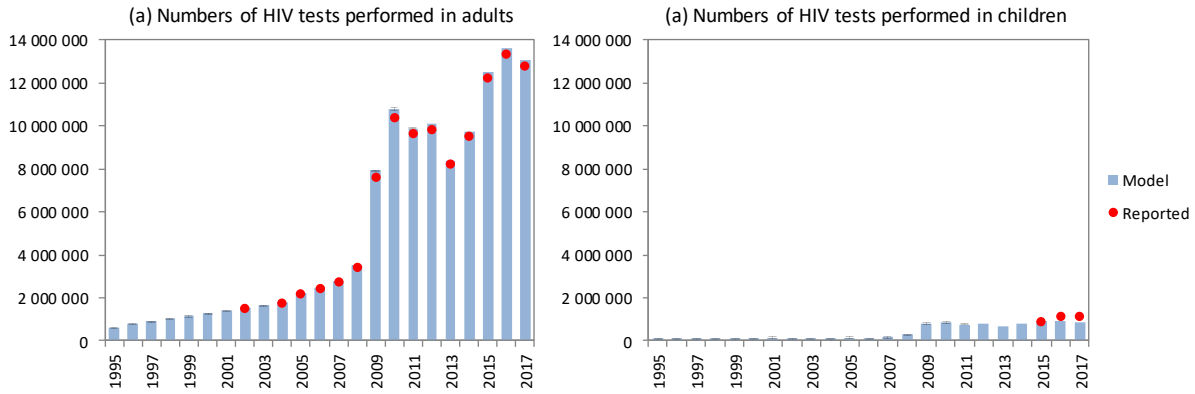

Figure B3: Annual numbers of HIV tests

Finally, Figure B4 shows the model estimates of the fraction of HIV-positive testers who are in the acute phase of infection (which is equivalent to 1 – the assumed test sensitivity). In the early phases of the epidemic, this fraction declines over time as HIV incidence declines, but the model estimates that as HIV testing efforts intensify and there is an increasingly high fraction of HIV-positive adults diagnosed, the fraction of HIV-positive testers in the acute phase of infection increases in the more recent years. The fraction in the acute phase of infection ranges between 2.4% and 4.5% over the 2000-2017 period, slightly lower than the rate of 4.7% of positive testers in the acute phase of HIV infection in low-income countries (4.7%) but slightly higher than the false negative rate in low-income countries (2.3%) in the meta-analysis of Tan *et al* [376].

Figure B4: Fraction of HIV-positive testers in the acute phase of HIV infection
Solid line represent model mean; dashed lines represent 95% confidence intervals.

Appendix C: Calibration to HIV prevalence data from key populations

The Thembisa model is fitted to HIV prevalence data from sex workers and MSM, using a Bayesian approach.

C.1 Prior distributions

Prior distributions are assigned to represent the uncertainty in three key parameters. Table C1 summarizes these prior distributions.

The first of these parameters is the male-to-female transmission probability per sex act in sex worker-client interactions. Few studies have estimated the probability of HIV-1 transmission from an infected client to a susceptible sex worker, in African settings. In a study of Senegalese sex workers, Gilbert *et al* estimated that the average probability of HIV-1 transmission per act of sex with an infected client was between 0.00031 and 0.00056, depending on the approach to dealing with missing data on numbers of clients [383]. A similarly low probability of transmission per unprotected sex act with an infected client, 0.00063, was estimated in a cohort of Kenyan sex workers [200]. Data from a South African study of sex workers in KwaZulu-Natal (KZN) can also be used to estimate the probability of transmission per sex act. In this study, an HIV incidence rate of 14.7 per 100 person years was observed [167] in sex workers who reported an average of 23.3 sex acts with clients per week, of which 20.3 were protected [168]. HIV prevalence in truck driver clients was estimated to be 56% [35]. If β is the probability of transmission per act of unprotected sex, and condoms are assumed to reduce this transmission probability by 90% [191], we can crudely estimate the average weekly rate of HIV acquisition as

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

Setting this expression to 0.147/52 and solving for β yields a β estimate of 0.00100. However, the true HIV prevalence in clients is unknown, as truck driver clients might not be typical of clients generally. In a systematic review of HIV risk factors in sub-Saharan Africa, Chen *et al* [384] estimated an average HIV prevalence in sex worker clients of 35%. If the true prevalence in KZN sex worker clients were closer to this average, the estimate of β would be substantially higher. To represent the uncertainty regarding β, we assign a beta prior with a mean of 0.001 (the same as the value from the estimated from the KZN study) and a standard deviation of 0.0005. This prior distribution has a 2.5 percentile of 0.0003 (consistent with the lowest estimate of Gilbert *et al*) and a 97.5 percentile of 0.0022 (a likely upper bound around the transmission probability in the KZN sex worker study).

The second parameter that is allowed to vary in the model calibration is the effect of HIV diagnosis on women's entry into commercial sex. One might expect that a woman who has been diagnosed HIV-positive would be less likely to begin sex work than an HIV-positive woman who is undiagnosed, due to fear of transmitting HIV to others or due to greater concern for her own health. South African studies estimate lower probabilities of HIV diagnosis in HIV-positive sex workers [37, 385] compared to HIV-positive women generally [117], which could be due to a reduced probability of starting sex work following an HIV

diagnosis (though other explanations are possible, such as confounding by age and difficulties sex workers may experience in accessing HIV testing). Given the uncertainty regarding the proportionate reduction in the rate of entry into commercial sex after diagnosis, we assign a vague prior, which is uniform on the interval [0, 1), to represent the uncertainty around the reduction.

The third parameter for which a prior distribution is assigned is the male-to-male transmission probability per sex act. The only published estimates of these male-to-male transmission probabilities are from high-income settings [173-175], and as heterosexual transmission probabilities in developing countries tend to be higher than those in high-income settings [115], we have chosen a prior distribution for the South African setting with a mean higher than that observed (mean 0.020, standard deviation 0.005). The model does not distinguish transmission probabilities according to the type of sex act.

Table C1: Prior distributions

Parameter	Prior distribution	Mean, standard deviation
Client-to-sex worker transmission probability*	Beta (3.995, 3991)	0.001, 0.0005
Proportionate reduction in rate of entry into sex work following an HIV diagnosis	Uniform (0, 1)	0.5, 0.29
Male-to-male transmission probability*	Beta (15.66, 767.3)	0.02, 0.005

* Per act of unprotected sex.

C.2 Likelihood definitions: sex worker survey data

Table C2 summarizes the HIV prevalence data from surveys of sex workers, which have been used in model calibration. The surveys of commercial sex workers have been conducted in specific communities, and cannot be considered representative of sex workers nationally. It is therefore necessary to allow for potential heterogeneity in HIV prevalence between commercial sex workers surveyed in different communities, using different sampling techniques. We use the notation t_i, n_i and p_i to represent the time of the i^{th} survey, the sample size of the i^{th} survey and the HIV prevalence measured in the i^{th} survey respectively.

Table C2: Studies of HIV prevalence in South African sex workers

Study	Location	Year (t_i)	Sample size (n_i)	Prevalence of HIV (p_i)
Ramjee *et al* [167]	Truck stops between Durban and Johannesburg	1996	416	50%
Dunkle *et al* [42]	Johannesburg	1996	295	46.4%
Leggett *et al* [386]	Johannesburg, Durban, Cape Town	1998*	249	42.6%
Williams *et al* [12]	Carletonville	1998	121	68.6%
Ndhlovu *et al* [387]	Carletonville	2001	101	78%
van Loggerenberg *et al* [45]	Durban	2004	775	59.6%
Luseno & Wechsberg [48]	Pretoria	2005	276	59.1%
Greener *et al* [388]	Durban	2012	349	66.9%
USCF [37]	Johannesburg	2013	764	71.8%
	Cape Town	2013	650	39.7%
	Durban	2013	766	53.5%
Schwartz *et al* [389]	Port Elizabeth	2014	410	61.5%

* The study date was not stated, and has been assumed to be three years prior to the date of publication, based on average publication delays in other STI prevalence surveys [390].

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

$$\log\left(\frac{p_i}{1-p_i}\right) = \log\left(\frac{C(t_i, \boldsymbol{\varphi})}{1-C(t_i, \boldsymbol{\varphi})}\right) + r_i + \varepsilon_i, \qquad \text{(C1)}$$

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

$$\hat{\sigma}_i^2 = \frac{1}{n_i p_i (1-p_i)}. \qquad \text{(C2)}$$

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

$$\hat{\sigma}_r^2 = \frac{1}{12}\sum_{i=1}^{12}\left(\log\left(\frac{p_i}{1-p_i}\right) - \log\left(\frac{C(t_i, \boldsymbol{\varphi})}{1-C(t_i, \boldsymbol{\varphi})}\right)\right)^2 - \frac{1}{n_i p_i (1-p_i)}. \qquad \text{(C3)}$$

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

$$L(\mathbf{p} \mid \boldsymbol{\varphi}) = \prod_{i=1}^{12}\left(2\pi\left(\hat{\sigma}_r^2 + \hat{\sigma}_i^2\right)\right)^{-0.5} \exp\left[-\frac{\left(\text{logit}(p_i) - \text{logit}(C(t_i, \boldsymbol{\varphi}))\right)^2}{2\left(\hat{\sigma}_r^2 + \hat{\sigma}_i^2\right)}\right], \qquad \text{(C4)}$$

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

C.3 Likelihood definitions: MSM survey data

Table C3 summarizes the HIV prevalence data from surveys of men who have sex with men (MSM), which have been used in model calibration. Only studies that used respondent-driven sampling (RDS) have been used for calibration (i.e. excluding venue-based sampling studies, which tend to be biased towards recruitment of higher-risk MSM). Since none of the surveys are nationally representative, the approach used in defining the likelihood function is the same as for sex worker HIV prevalence data, i.e. based on a random effects model to represent heterogeneity between studies. The only difference is that the model estimates of HIV prevalence have been adjusted so that each model estimate of HIV prevalence in MSM is age-standardized to correspond to the age profile in the survey of MSM (as represented by the fraction of sampled MSM who are aged 18-24, shown in the last column of Table C3). This age standardization is necessary because South African surveys of MSM appear to be

biased toward younger MSM, and without appropriate age adjustment, this may lead to the model under-estimating HIV prevalence in MSM [391].

Table C3: Studies of HIV prevalence in South African MSM

Study	Location	Year (t_i)	Sample size (n_i)	Prevalence of HIV (p_i)	% aged 18-24
Cloete *et al* [4]	Cape Town	2012	286	22.3%	67.3%
	Durban	2012	290	48.2%	27.0%
	Johannesburg	2012	349	26.8%	52.1%
Lane *et al* [5]	Gert Sibande district	2012	307	29.4%	29.6%
	Ehlanzeni district	2012	298	15.9%	28.0%
Lane *et al* [6]	Soweto	2008	363	13.6%	31.0%
Rispel *et al* [392]	Johannesburg	2008	202	49.5%	33.3%
	Durban	2008	69	27.5%	33.3%
Sandfort *et al* [360]	Pretoria	2011	480	30.1%	41.0%
Kufa *et al* [393]	Johannesburg	2015	546	43.4%*	45.2%*
	Bloemfontein	2015	525	17.3%*	71.6%*
	Mafikeng	2015	474	14.6%*	71.2%*
	Polokwane	2015	358	22.4%*	59.7%*
Fearon *et al* [394]	Johannesburg	2017	300	37.5%	48%

* Unpublished data. RDS-weighted estimates are not yet available (although an RDS design was used), so only the unweighted estimates are used. Variance estimates were calculated using the RDS design effects described previously.

C.4 Model results

Table C4 compares the prior and posterior estimates of the model parameters. The posterior estimates of the HIV transmission probabilities are both substantially higher than the corresponding prior estimates. The Bayesian analysis also suggests that HIV-diagnosed women are on average 79% less likely to begin sex work than HIV-positive women who are undiagnosed.

Table C4: Comparison of prior and posterior distributions

Parameter	Prior distribution (mean, 95% CI)	Posterior distribution (mean, 95% CI)
Client-to-sex worker transmission probability per sex act	0.001 (0.0003-0.0022)	0.0015 (0.0009-0.0019)
Proportionate reduction in rate of entry into sex work following an HIV diagnosis	0.500 (0.025-0.975)	0.790 (0.188-0.987)
Male-to-male transmission probability per sex act	0.020 (0.011-0.031)	0.029 (0.023-0.036)

Figure C1 compares the model estimates of HIV prevalence in sex workers and MSM with the levels of HIV prevalence measured in South African surveys. As none of the key population surveys is nationally representative, some degree of divergence between model estimates and survey estimates is to be expected. Survey estimates of HIV prevalence are highly variable, reflecting variation in geographic locations and sampled populations. Due to the absence of any HIV prevalence surveys amongst MSM in the early stages of South Africa's HIV epidemic, confidence intervals around the model estimates of HIV prevalence in MSM during the 1990s are very wide.

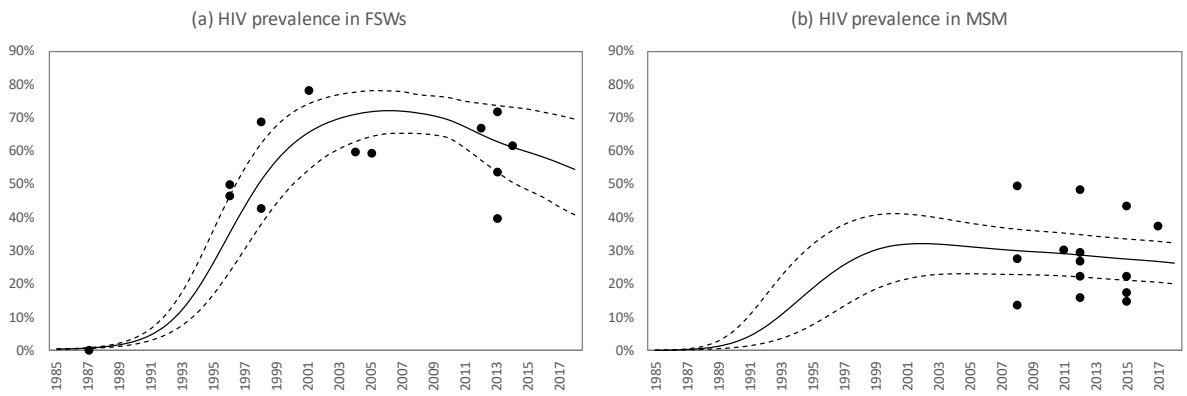

Figure C1: HIV prevalence in key populations

Dots represent survey prevalence estimates (the 1987 data point shown in panel (a) was not included in the definition of the likelihood as the survey found no HIV in sex workers [395], and the likelihood for this observation was thus undefined). Solid lines represent the posterior mean model estimates of HIV prevalence, and dashed lines represent the 95% confidence intervals around these estimates.

Appendix D: The impact of ART on mortality in children

Section 5.3 sets out the general structure of the model of paediatric HIV disease progression, mortality and ART. This appendix provides more detail on two aspects of the model parameterization: the effects of changes over time in rates of ART initiation in late disease (section D.1) and the estimation of mortality rates in children who start ART in early disease (section D.2).

D.1 Modelling the effect of ART on mortality in late disease

A limitation of the Thembisa model is that it groups HIV-positive children with advanced disease into a single state, and does not allow for the possibility that there may be significant heterogeneity in mortality within this state. This becomes particularly problematic when modelling the impact of ART on mortality, as changes in ART uptake lead to changes in the CD4 distributions of untreated children as well as changes in the CD4 distributions of children starting ART. This in turn means that mortality rates in ART-naïve and treated children change as ART uptake increases. To address this challenge, we develop a simple heuristic to adjust the base model assumptions to take account of the effect of ART. This heuristic procedure is very similar to the approach developed for adults, as described previously (see Appendix A of the Thembisa analysis of adult mortality trends in South Africa [91]).

To describe pre-ART mortality at CD4 percentages below 15% (which we will use here as a rough approximation to 'advanced disease'), we assume that the untreated HIV mortality rate in children with CD4 % x is

$$\mu(x) = a\left(b^{x}\right), \qquad \text{(D1)}$$

where a is the mortality rate we would expect in an untreated individual with a CD4 % of zero, and b is the factor by which the mortality rate decreases for a 100% increase in the CD4 % (i.e. ab is the theoretical mortality rate at a CD4 % of 100%). The b parameter is estimated by fitting regression models of the form given in equation (D1) to average mortality levels reported over different CD4 ranges, in different age groups, as reported in a meta-analysis of paediatric survival studies conducted in resource-limited settings prior to the availability of ART [308]. The resulting model fits to the data are shown in Fig D1. Estimates of the b parameter are higher at the younger ages (0.0000305 and 0.0000292 at ages 1-2 and 3-4 respectively) than at the older ages (0.0000005 and 0.0000006 at ages 5-6 and 7 or older, respectively). We set the b parameter in our model at the average of these values, 0.0000153.

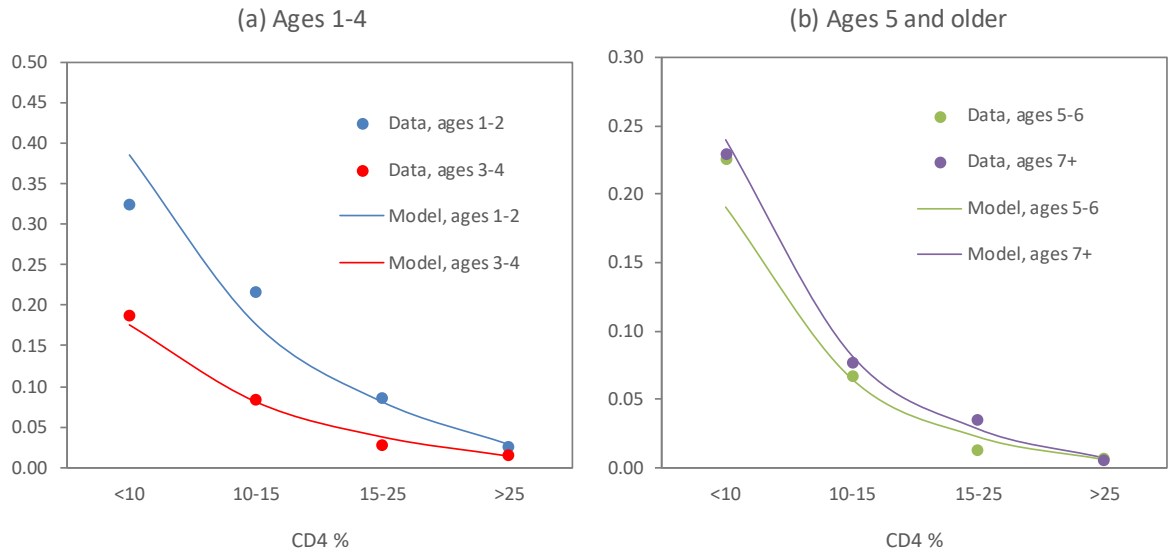

Fig D1: Effect of CD4 count on mortality in the absence of ART

For the purpose of fitting the models to the data points, the average mortality rates reported over different ranges have been taken to apply at the midpoints of the relevant ranges. Mortality data from the >15% CD4 range have been included in order to increase the statistical confidence in the fitted parameters.

Further suppose that $f(x)$ is the distribution of CD4 percentages in a theoretical ART-naïve population, in children who have progressed to advanced disease (which we approximate as CD4 <15% for the sake of simplicity). We assume $f(x) = ke^{\lambda x}$, for $0 \leq x \leq 0.15$, where k is a constant that must satisfy the condition

$$\int_0^{0.15} ke^{\lambda x} dx = 1, \qquad \text{(D2)}$$

from which it follows that $k = \lambda(e^{\lambda \times 0.15} - 1)^{-1}$. In order to estimate the λ parameter, we need to know something about the distribution of CD4 percentages in untreated children with advanced HIV disease. From the same meta-analysis described previously [308], we estimate that roughly 55% of all children who have CD4 percentages <15% have a CD4 <10%. From this it follows that

$$0.55 = \frac{e^{0.1\lambda} - 1}{e^{0.15\lambda} - 1}, \qquad \text{(D3)}$$

and solving this equation gives an estimate of $\lambda = 6.79$.

Having estimated the distribution of CD4 percentages in an ART-naïve population of children with advanced HIV disease, it is possible to estimate the average mortality rate, q_0, as

$$\begin{aligned} q_0 &= \int_0^{0.15} f(x) a b^x dx \\ &= \frac{\lambda a \left(\left(e^{\lambda} b \right)^{0.15} - 1 \right)}{\left(\lambda + \ln(b) \right) \left(e^{0.15\lambda} - 1 \right)}. \end{aligned} \qquad \text{(D4)}$$

Now suppose that q_t is the annual mortality rate in untreated children with CD4 <15%, in year t (this is analogous to the $\mu(x)$ parameter in section 5.3, although for the purpose of this description we are ignoring age effects on mortality). Further suppose that $q_{\min}$ is the minimum mortality rate that we would expect if rates of ART initiation were at their maximum. We would expect q_t to decline as the rate of ART initiation increases, as high rates of ART initiation imply that few individuals will progress to very low CD4 values without starting ART. In modelling q_t we assume it is exponentially related to r_{t-}, the average rate of paediatric ART initiation over the previous three years, subject to the maximum of q_0 and the minimum of $q_{\min}$:

$$q_t = q_{\min} + (q_0 - q_{\min})\exp(-mr_{t-}), \tag{D5}$$

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

$$A_t = \frac{q_{\min}}{q_0} + \left(1 - \frac{q_{\min}}{q_0}\right)\exp(-mr_{t-}), \tag{D6}$$

where $A_t \equiv q_t / q_0$ is an adjustment factor applied to the mortality rate that would be expected in the absence of any ART rollout. The ratio $q_{\min}/q_0$ can be estimated by noting that untreated mortality is at a minimum when all children start ART soon after their CD4 drops below 15%, i.e. $q_{\min} = ab^{0.15}$. From this it follows that

$$\frac{q_{\min}}{q_0} = \frac{b^{0.15}(\lambda + \ln(b))\left(e^{0.15\lambda} - 1\right)}{\lambda\left(\left(e^{\lambda}b\right)^{0.15} - 1\right)}. \tag{D7}$$

Substituting λ = 6.79 and b = 0.0000153 into this equation gives a $q_{\min}/q_0$ estimate of 0.45, which is slightly higher than the corresponding value of 0.31 previously estimated for adults [91].

The m parameter in equation (D6) is difficult to quantify precisely, so a Bayesian approach is adopted to reflect the uncertainty regarding this parameter. Given the lack of information for children, we assign the same prior distribution to this parameter as assumed for adults, viz. a gamma distribution with a mean of 7.5 and a standard deviation of 3.5.

So far we have considered only mortality in untreated children. A similar approach is adopted in modelling the effect of ART-related changes in CD4 distributions on mortality during the first 6 months after starting ART. Suppose that v_t is the annual mortality rate in adults during their first 6 months after starting ART (with baseline CD4 <15%), in year t (this is analogous to $\Phi_0\mu(x)$ in section 5.3, although this is defined for the first 3 months after ART initiation and is age-dependent). Further suppose that v_0 is the corresponding mortality rate that would have been expected in the very early stages of the ART rollout, when rates of ART initiation were very low, and that $v_{\min}$ is the minimum mortality rate that we would expect if rates of ART initiation were at their maximum. We would expect v_t to decrease as the rate of ART rollout increases, as higher rates of ART rollout should lead to higher baseline CD4 counts. As before, we assume a relationship of the form

$$B_t = \frac{v_{\min}}{v_0} + \left(1 - \frac{v_{\min}}{v_0}\right)\exp\left(-mr_{t-}\right), \qquad \text{(D8)}$$

where $B_t \equiv v_t / v_0$. Note that the *m* parameter is assumed to be the same as that in equation (D6), although one could argue that the relationship with the rate of ART initiation may differ depending on whether one is considering pre-ART mortality or treated mortality. (In the interests of obtaining a parsimonious model fit, we use the same parameter value in equations (D6) and (D8), but the model does allow for different values to be assumed.)

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

$$v(x) = z\left(h^x\right). \qquad \text{(D9)}$$

We fit this model to data from a pooled analysis of paediatric ART programmes in South Africa, collected at a relatively early stage in the paediatric ART rollout [310]. After controlling for age, the mortality risk was found to reduce by a factor of 0.895 for each percentage point increase in the baseline CD4 count; this suggests an *h* value of 0.895^{100} = 0.0000144. Of children starting ART with CD4 <15%, 25% had a CD4 <5%, 33% had a CD4 of 5-9% and 42% had a CD4 of 10-14%. Taking this to be the baseline CD4 distribution that would be expected in the early stages of the paediatric ART rollout (i.e. when rates of ART uptake are low), and assuming a roughly uniform distribution of CD4 values within each CD4 category, we can approximate the ratio $v_{\min}/v_0$ as

$$\frac{v_{\min}}{v_0} = \frac{zh^{0.15}}{z\left(0.25h^{0.025} + 0.33h^{0.075} + 0.42h^{0.125}\right)}. \qquad \text{(D10)}$$

Substituting *h* = 0.0000144 into this equation gives a $v_{\min}/v_0$ estimate of 0.43, similar to the estimate of 0.39 previously obtained using adult data [91].

Finally, we define $w(x)$ to be the mortality rate that would be expected at durations >6 months after ART initiation, in children who started ART with a CD4 count <15% (this is analogous to $\Phi_1\mu(x)$ in section 5.3). Similar to the approach adopted with $v(x)$, we assume $w(x)$ can be related to the baseline CD4 % by the equation $w(x) = p(s^x)$, and we estimate the *s* parameter by fitting a regression model to the same paediatric ART dataset as described previously [310]. After controlling for age and ART duration, this regression model estimates that the mortality rate reduces by a factor of 0.938 for each percentage point increase in baseline CD4 %. This is equivalent to an *s* value of 0.938^{100} = 0.00175.

We define w_t to be the annual mortality rate in children in year *t*, who have been on ART for durations >6 months, having started ART with an initial CD4 <15%. As with v_t, we would expect this rate to decline with respect to *t* as rates of ART initiation increase. However, we would expect the decline in w_t to be more moderate than that in v_t, since mortality at longer ART durations is not as strongly related to baseline CD4 count as mortality at early ART durations. We define a relation between w_t to and r_{t-} similar to that in equation (D5):

$$w_t = w_{\min} + (w_0 - w_{\min})\exp(-mr_{t-}), \quad \text{(D11)}$$

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

$$C_t = \frac{w_{\min}}{w_0} + \left(1 - \frac{w_{\min}}{w_0}\right)\exp(-mr_{t-}). \quad \text{(D12)}$$

For the purpose of estimating the ratio $w_{\min}/w_0$, we use the same baseline CD4 distribution as before for the scenario in which there is limited ART rollout:

$$\frac{w_{\min}}{w_0} = \frac{ps^{0.15}}{p\left(0.25s^{0.025} + 0.33s^{0.075} + 0.42s^{0.125}\right)}. \quad \text{(D13)}$$

Substituting s = 0.00175 into this equation gives a $w_{\min}/w_0$ estimate of 0.63, close to the value of 0.61 previously estimated using adult data [91].

A limitation of the approach described above is that it considers only the uncertainty in the m parameter. There is also uncertainty regarding the $q_{\min}/q_0$, $v_{\min}/v_0$ and $w_{\min}/w_0$ ratios.

D.2 Modelling mortality after ART initiation in early disease

To assess the mortality rates in children who start ART in early disease, we analysed data from the South African ART programmes that participate in the International epidemiology Databases to Evaluate AIDS (IeDEA) collaboration. Patients were included if they had a recorded date of starting triple-drug ART, were aged less than 15 years at the time of ART initiation, had a baseline CD4 count or CD4 percentage at the time of ART initiation (within 6 months before and 1 weeks after ART initiation), were in the 'early' phase of HIV disease at the time of ART initiation, and met the immunological criteria for defining ART eligibility at the time they started ART. Children were considered to be in the early phase of HIV disease if (to be consistent with the model definition in section 5.3) they did not meet any of the criteria for defining ART eligibility in the WHO 2006 paediatric ART guidelines [298], i.e. they were not in WHO clinical stage IV, and were either aged older than 2 years with a baseline CD4% ≥15%, aged 1-2 years with a baseline CD4% ≥20%, or aged <1 year with a baseline CD4% ≥25%. (In cases where only an absolute baseline CD4 count was available, children were instead classified as being in early disease if they were either aged older than 4 years with a baseline CD4 count of ≥200 cells/μl, aged 3-4 years with a baseline CD4 count of ≥350 cells/μl, aged 1-2 years with a baseline CD4 count of ≥750 cells/μl or aged <1 year with a baseline CD4 count of ≥1500 cells/μl.) The exclusion of children who did not meet the immunological criteria for defining ART eligibility at the time they started ART meant the exclusion of all children who started ART before 2008 (since children starting ART before this time only qualified for ART if they were in 'late' disease), the exclusion of children who started ART before 2012 if they were older than 1 year at ART initiation (since South African guidelines changed to allow for early ART initiation in children under the age of 5 in 2012 [146]), and the exclusion of children who started ART before 2016 if they were older than 5

years (since the South African guidelines changed to recommend universal ART eligibility in 2016).

Children were classified as dead if there was a death and date of death recorded. In a subset of children for whom civil ID numbers were available, patient records were linked to the National Population Register (NPR), and children were also recorded as dead if a death was recorded on the NPR (in cases where dates of death were recorded on both the NPR and the patient record system, the date of death on the NPR was taken to be the 'true' date of death). For children in whom no death was recorded, follow-up was censored at the time of the last patient contact or (in the case of children who transferred out of the service), the date of transfer.

After applying the exclusion criteria, 2 828 children were included in the analysis. Table D1 summarizes the characteristics of these children at the age of ART initiation. Relatively few of the children included in the analysis started ART in the 5-14 age group, as guidelines only changed to recommend early ART initiation in this group in 2016.

Table D1: Baseline characteristics of children starting ART in early disease

	%	n
Age at ART initiation		
0-4	85.4%	2414
5-9	6.2%	175
10-14	8.5%	239
Sex		
Male	45.9%	1299
Female	54.1%	1529
Year of ART initiation		
2008-2011	23.4%	662
2012-2015	55.4%	1566
2016-2017	21.2%	600
Prior MTCT drug exposure		
Yes	15.9%	449
No	72.1%	2036
Not recorded	12.0%	340
Baseline CD4%		
15-24%	14.0%	395
25-34%	36.4%	1028
35-44%	16.3%	462
45% or more	9.0%	255
Not recorded	24.3%	688

In total, 51 deaths were recorded over 5814 person years of follow-up, implying a mortality rate of 0.88 per 100 person years (Table D2). The mortality rate was highest in the first year of life (4.57 per 100 person years), and lower in the 1-4 and 5-9 age groups (0.41 and 0.16 per 100 person years, respectively). No deaths were observed in children aged 10-14. Since cause of death was not reliably recorded for most children, and since non-HIV causes are likely to account for a substantial fraction of the deaths (especially in infants), we fit a function of the following form to the recorded death data:

$$\psi(x) = \mu_0(x) + \beta P^x,$$

where $\psi(x)$ is the all-cause mortality rate at age x (in years), $\mu_0(x)$ is the non-HIV mortality rate at age x, β is the HIV-related mortality rate that applies immediately after birth, and P is the factor by which the HIV-related mortality reduces per year of age (as defined in section 5.3). Non-HIV mortality rates are taken from the Thembisa model (using the model assumptions for 2010, and averaging across the male and female rates). The equation is used to calculate the expected number of deaths, for the relevant number of person years, at each age in months. With values of β = 0.06 and P = 0.2, this model produced estimates of mortality roughly consistent with the IeDEA data (Table D2). With these parameters, the model estimates that most deaths in infants who started ART in early disease are HIV-related, but at ages 1 year and older, most of the deaths in children who started ART in early disease are due to non-HIV causes.

Table D2: Mortality rates in children starting ART in early disease

Age group	Person years	Deaths	Mortality rate (per 100 PY)	Modelled mortality rate (per 100 PY)		
				Non-HIV	HIV	Total
0	743.8	34	4.57	1.66	2.53	4.20
1-4	3694.7	15	0.41	0.25	0.22	0.47
5-9	1278.2	2	0.16	0.09	0.00	0.09
10-14	96.9	0	0.00	0.06	0.00	0.06
Total	5813.6	51	0.88	0.39	0.47	0.86

A limitation of this approach is that it does not allow for possible under-reporting of deaths in the IeDEA cohorts. Analyses of adult mortality data from IeDEA cohorts have shown that mortality rates may be substantially under-estimated in the absence of linkage to data from vital registration systems [345]. Since ID numbers were only available for a subset of children, our estimates may therefore under-estimate the true mortality rates in children on ART. However, we have also shown that child mortality does not appear to be under-estimated as substantially as adult mortality in the absence of vital registry linkage [345], and the bias may therefore be small. Another limitation is that the average duration of follow-up is relatively short (2 years), which may lead to mortality rates being over-estimated (since mortality tends to decline as treatment duration increases). The relatively small sample size also prevents the estimation of mortality rates with a high degree of precision, especially in older HIV-positive children.

Appendix E: Calibration to paediatric HIV data

The model is calibrated to HIV prevalence and all-cause mortality data in order to ensure that assumptions about mother-to-child transmission and HIV survival are plausible. The model is also calibrated to data on the age distribution of children starting ART. In the previous version of Thembisa, we calibrated to paediatric HIV prevalence data and the age distribution of children of children starting ART in two separate steps, but in the new version of the model, the calibration to these two data sources is fully integrated. The integration of the all-cause mortality data in the calibration is also new to this version of Thembisa.

E.1 Prior distributions

Prior distributions have been specified for 13 of the mother-to-child transmission and paediatric HIV survival parameters. Table E1 summarizes the prior distributions; the justification for the choice of most prior distributions has been presented in section 5. Most of these parameters and prior distributions are the same as described previously [2]. However, we have increased the variance associated with the 'excess' disease progression and mortality parameters in infancy, and we have also allowed for uncertainty regarding the rate at which these excess parameters decline as children age (previously the reduction factors were held constant). In addition, we have allowed for uncertainty regarding the effect of ART on mortality through two additional priors. The model has been extended to allow for the effect of ART rollout on the distribution of CD4 percentages in untreated children with advanced HIV disease, and one of the new priors controls the extent of this effect (for a more detailed explanation, see Appendix D).

Table E1: Prior distributions for parameters considered in calibration to paediatric HIV data

Parameter	Prior distribution	Prior mean, std. deviation
Probability of MTCT from chronically-infected mothers, per year of mixed feeding	Beta (26.83, 164.8)	0.14, 0.025
Probability of MTCT from acutely- infected mothers, per month of mixed feeding	Beta (23.73, 124.6)	0.16, 0.03
Ratio of postnatal transmission risk per month of EBF to postnatal transmission risk per month of mixed feeding	Beta (5.056, 5.056)	0.50, 0.15
Children infected at/before birth		
Annual rate of progression to late disease in older children	Gamma (16.00, 40.00)	0.40, 0.10
Excess annual rate of progression to late disease in neonates	Gamma (16.00, 8.00)	2.00, 0.50
Excess progression reduction factor, per year of age	Beta (4.44, 13.13)	0.25, 0.10
Relative rate of progression to late disease if infected postnatally	Beta (3.189, 5.922)	0.35, 0.15
Children in late disease, untreated		
Annual rate of AIDS mortality in older children	Gamma (16.00, 133.3)	0.12, 0.03
Excess annual rate of AIDS mortality in neonates	Gamma (25.0, 7.14)	3.50, 0.70
Excess AIDS mortality reduction factor, per year of age	Beta (0.188, 3.563)	0.05, 0.10
Relative rate of linkage to ART soon after diagnosis compared to maximum ART linkage	Uniform (0, 1)	0.50, 0.29
Effect of ART on mortality		
Relative rate of mortality in 'stable' ART phase compared to untreated children with late disease	Beta (3.50, 31.50)	0.10, 0.05
Reduction in mortality* (on log scale) per unit increase in rate of ART initiation (in late disease) over last 3 years	Gamma (4.59, 0.612)	7.5, 3.5

ART = antiretroviral treatment; EBF = exclusive breastfeeding; MTCT = mother-to-child transmission.

A source of uncertainty not previously discussed is the fractions of children who start ART immediately after diagnosis (parameters l and $l_3(t)$ in section 5.3). For the sake of setting the priors on the l and $l_3(t)$ parameters, we have first defined likely upper limits, based on the experience of well-functioning programmes, and have then allowed for a scaling down of these factors, by a constant proportion, to take into account the likely poorer linkage to ART in less well-resourced settings. This constant scaling factor, κ, is included in the uncertainty analysis, and is assigned a uniform (0, 1) prior, given the lack of information regarding the likely extent of the difference. For the l parameter (the fraction of infants diagnosed through early infant diagnosis programmes who start ART soon after diagnosis), the upper limit has been set to 0.80, based on a 71% rate of ART initiation in HIV-diagnosed infants in the Western Cape in 2010 [316], an 88% rate of ART initiation in a small sample of 26 HIV-diagnosed infants in Johannesburg [396] and an 86% rate in another small sample of 21 HIV-diagnosed infants in Cape Town [319]. There is a lack of information on the fraction of older HIV-diagnosed children who start ART soon after diagnosis, although a 2011 study in a fee-for-service clinic in Durban found that 69% of children diagnosed HIV-positive started ART soon after HIV diagnosis [382]. The upper bound on the $l_3(t)$ parameter has been set to the assumed fraction of OI patients who initiate ART soon after a diagnosis, which increases from 63% in 2011-12 to 78% in 2015-16 (Table 3.2).

E.2 Likelihood function: HIV prevalence data

The method used to calculate the likelihood in respect of the paediatric HIV prevalence data has been described previously [245], but has been updated to include data from the 2012 and 2017 national household prevalence surveys [118, 119]. As with adults, we have relied on data from the 2005, 2008, 2012 and 2017 household surveys conducted by the HSRC. For each survey year, sex and age group, the difference between the model estimate of prevalence and survey estimate of prevalence, on the logit scale, is assumed to be normally distributed with zero mean and standard deviation calculated from the reported 95% confidence interval. The likelihood calculation is thus similar to that described in section 7.2.1, but with the omission of the bias and model error terms.

E.3 Likelihood function: all-cause mortality data

Suppose that $N_g(x, t)$ represents the model estimate of the number of deaths (due to all causes) in children of sex g, in age group x, in year t. Let $R_g(x, t)$ be the corresponding number of recorded deaths, as reported by Statistics South Africa [339]. In this analysis, we consider four age groups: <1 year (infants), 1-4 years, 5-9 years and 10-14 years. We consider deaths over the 1997-2016 period.

Let $c_g(x, t)$ be the completeness of death recording, i.e. the fraction of deaths that we would expect to be recorded. The completeness rates are assumed to be the same as assumed in the most recent Rapid Mortality Surveillance report [397], and are shown in Table E2. Completeness is assumed to be the same in boys and girls. Completeness has generally increased over time, although in infants there appears to have been a slight deterioration in completeness since 2011. Completeness also tends to be higher in older children than in younger children, though infants are an exception [345, 398]: most of these infant deaths occur in health facilities, and special interventions (such as the Child Healthcare Problem Identification Programme) have been established to improve the recording of these facility-based deaths [399, 400].

Table E2: Assumed fractions of child deaths that are recorded

	Aged < 1 year	Aged 1-4 years	Aged 5-9 years	Aged 10-14 years
1997	53.3%	38.0%	54.4%	71.7%
1998	61.5%	47.3%	61.2%	75.5%
1999	63.2%	46.3%	61.4%	76.8%
2000	62.7%	47.3%	62.0%	70.1%
2001	62.9%	46.7%	63.9%	73.1%
2002	67.3%	49.7%	66.0%	75.7%
2003	71.8%	53.4%	68.0%	78.1%
2004	76.2%	58.0%	70.0%	80.2%
2005	80.6%	60.1%	71.8%	82.3%
2006	85.0%	63.8%	73.6%	84.1%
2007	85.0%	63.0%	75.1%	85.9%
2008	85.0%	63.6%	76.7%	87.5%
2009	85.0%	63.0%	78.1%	88.9%
2010	85.0%	64.6%	79.5%	90.1%
2011	85.0%	64.6%	80.8%	91.0%
2012	82.0%	64.0%	82.0%	92.1%
2013	75.5%	63.6%	83.2%	93.0%
2014	75.5%	63.2%	84.2%	94.0%
2015	75.5%	62.9%	85.3%	94.7%
2016	75.5%	63.4%	86.2%	95.3%

For the purpose of defining the likelihood function, we assume that the difference between the log-transformed recorded number of deaths and the log-transformed model estimate of deaths (after application of the completeness adjustment) is normally distributed with zero mean and a variance of σ^2. More formally,

$$\ln\left(R_g(x,t)\right) = \ln\left(N_g(x,t)c_g(x,t)\right) + \varepsilon_g(x,t)$$

where $\varepsilon_g(x,t) \sim N(0, \sigma^2)$, i.e. similar to the approach adopted in defining the likelihood when the model is calibrated to the adult mortality data (equation 7.6). The calculation of the variance σ^2 is similar to that for adults (equation 7.7).

E.4 Likelihood function: Paediatric ART data

The age profile of children starting ART is important because it provides indirect information about the fraction of children who start ART soon after HIV diagnosis. The data used in the calibration of the model is the reported fraction of children starting ART in each age group, over the 2004-2014 period, obtained from the Tier monitoring system [162]. The data are summarized in Table E3.

Table E3: Fraction of children starting ART in each age group

Age	2004-5	2005-6	2006-7	2007-8	2008-9	2009-10	2010-1	2011-2	2012-3	2013-4
<12 months	10%	9%	8%	11%	12%	14%	15%	16%	18%	21%
1-4 years	45%	44%	40%	38%	35%	35%	32%	29%	30%	32%
5-14 years	44%	47%	51%	51%	53%	51%	53%	56%	51%	46%

For the purpose of defining the likelihood function, $M(x, t)$ is defined as the model estimate of the fraction of children starting ART in year t who are in age group x (0 for <12 months, 1 for 1-4 years and 2 for 5-14 years), and $R(x, t)$ is defined as the corresponding reported fraction from the Tier data (Table E3). The likelihood function is defined on the assumption that the difference between these proportions, on the logit scale, is normally distributed with zero mean, i.e.

$$\log\left(\frac{R(x,t)}{1-R(x,t)}\right) = \log\left(\frac{M(x,t)}{1-M(x,t)}\right) + \varepsilon(x,t)$$

where $\varepsilon(x, t) \sim N(0, \sigma^2)$. Although it might be considered more correct to define the likelihood based on a multinomial likelihood, the normal approximation gives similar results when sample sizes are large, and the purpose of the $\varepsilon(x, t)$ term is to represent the model error rather than the multinomial error. The maximum likelihood estimate of σ^2 is thus

$$\hat{\sigma}^2 = \frac{1}{20}\sum_{x=0}^{1}\sum_{t}\left(\log\left(\frac{R(x,t)}{1-R(x,t)}\right) - \log\left(\frac{M(x,t)}{1-M(x,t)}\right)\right)^2.$$

The definition of the likelihood also takes into account reported numbers of children on ART, as described elsewhere [83]. These data were included in the definition of the likelihood to avoid model fits that yield estimates of numbers of HIV infections less than reported numbers of ART patients.

E.5 Results of calibration

Table E4 compares the prior and posterior means for the 13 parameters that are allowed to vary when fitting the model to the paediatric HIV prevalence data. In several cases the posterior and prior distributions are similar, although the posterior estimate of the annual probability of transmission from breastfeeding mothers (not on ART or in the acute stage of infection) is substantially lower than the prior mean. The rates of mortality and disease progression in older children tend to be lower than those assumed *a priori*, but the extent of the age-related changes in disease progression and mortality are more modest than assumed *a priori*, i.e. the net effect is a lower mortality rate in older children but a higher mortality rate in younger children (in the absence of ART). The effect of ART on mortality also appears to be more substantial than assumed *a priori*.

Figure E1 shows the calibration of the model to the paediatric HIV prevalence data. Since different surveys report HIV prevalence in different age groups, we show the results both for HIV prevalence in children aged 0-14 (panel a) and children aged 2-14 (panel b). The model estimates of HIV prevalence in 2008 and 2012 are consistent with the survey data in these years, but the model estimates of paediatric HIV prevalence in 2005 and 2017 are significantly lower than the corresponding survey estimates.

Table E4: Comparison of prior and posterior distributions for parameters considered in calibration to paediatric data

Parameter	Prior distribution (mean, 95% CI)	Posterior distribution (mean, 95% CI)
Probability of MTCT from chronically-infected mothers, per year of mixed feeding	0.140 (0.095-0.192)	0.088 (0.075-0.103)
Probability of MTCT from acutely- infected mothers, per month of mixed feeding	0.160 (0.106-0.223)	0.153 (0.119-0.188)
Ratio of postnatal transmission risk per month of EBF to postnatal transmission risk per month of mixed feeding	0.500 (0.213-0.787)	0.516 (0.270-0.742)
Children infected at/before birth		
Annual rate of progression to late disease in older children	0.400 (0.229-0.619)	0.277 (0.195-0.384)
Excess annual rate of progression to late disease in neonates	2.00 (1.14-3.09)	2.64 (2.17-3.29)
Excess progression reduction factor, per year of age	0.250 (0.084-0.468)	0.423 (0.300-0.537)
Relative rate of progression to late disease if infected after birth	0.350 (0.096-0.666)	0.283 (0.199-0.383)
Children in late disease, untreated		
Annual rate of AIDS mortality in older children	0.120 (0.069-0.186)	0.095 (0.081-0.107)
Excess annual rate of AIDS mortality in neonates	3.50 (2.27-5.00)	3.31 (2.74-3.94)
Excess AIDS mortality reduction factor, per year of age	0.050 (0.000-0.367)	0.295 (0.262-0.337)
Relative rate of linkage to ART soon after diagnosis compared to maximum ART linkage	0.500 (0.025-0.975)	0.375 (0.151-0.627)
Effect of ART on mortality		
Relative rate of mortality in 'stable' ART phase compared to untreated children with late disease	0.100 (0.025-0.217)	0.058 (0.040-0.080)
Reduction in mortality (on log scale) per unit increase in rate of ART initiation (in late disease) over last 3 years	7.50 (2.29-15.76)	8.52 (4.57-13.31)

ART = antiretroviral treatment; EBF = exclusive breastfeeding; MTCT = mother-to-child transmission.

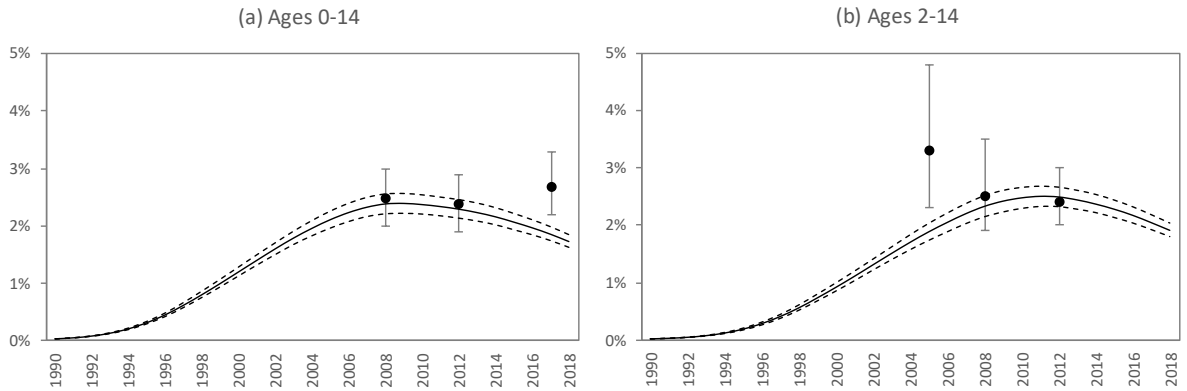

Figure E1: Paediatric HIV prevalence

Solid lines represent posterior means and dashed lines represent posterior 95% confidence intervals. Dots represent HIV prevalence measurements from national household surveys.

Figure E2 shows that the model matches the overall trend in recorded deaths in children quite closely, although the model tends to under-estimate mortality in the 2012-15 period (and the recorded number of deaths in 2016 could be an under-estimate because of late registration, i.e. making the model fit to the data look better than it actually is). When results are disaggregated by age, it appears that the model does not fit the mortality trend well in the 10-14 age group (especially in boys). This is because mortality rates in the 10-14 age group are

determined principally by the adult HIV disease progression and mortality assumptions (which are held fixed for the purpose of this analysis).

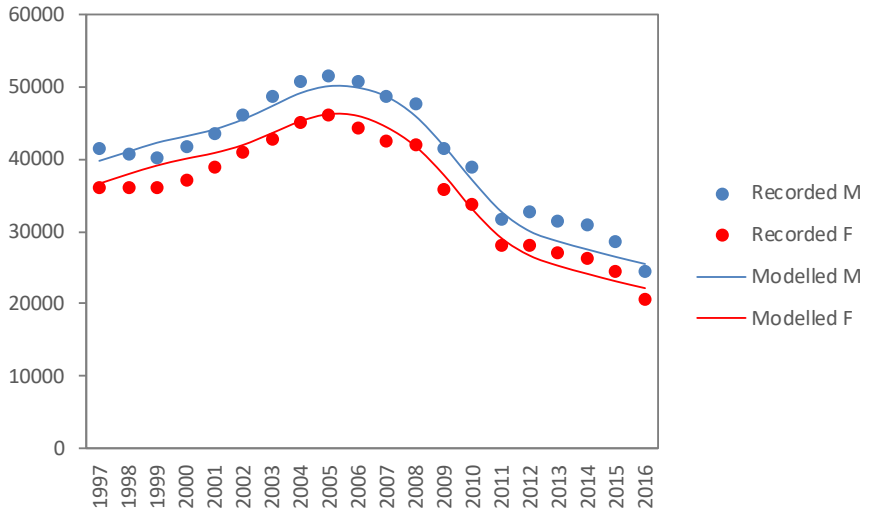

Figure E2: Comparison of modelled deaths and recorded deaths in children aged 0-14 years
Recorded deaths have been adjusted upward based on the completeness assumptions in Table E2.

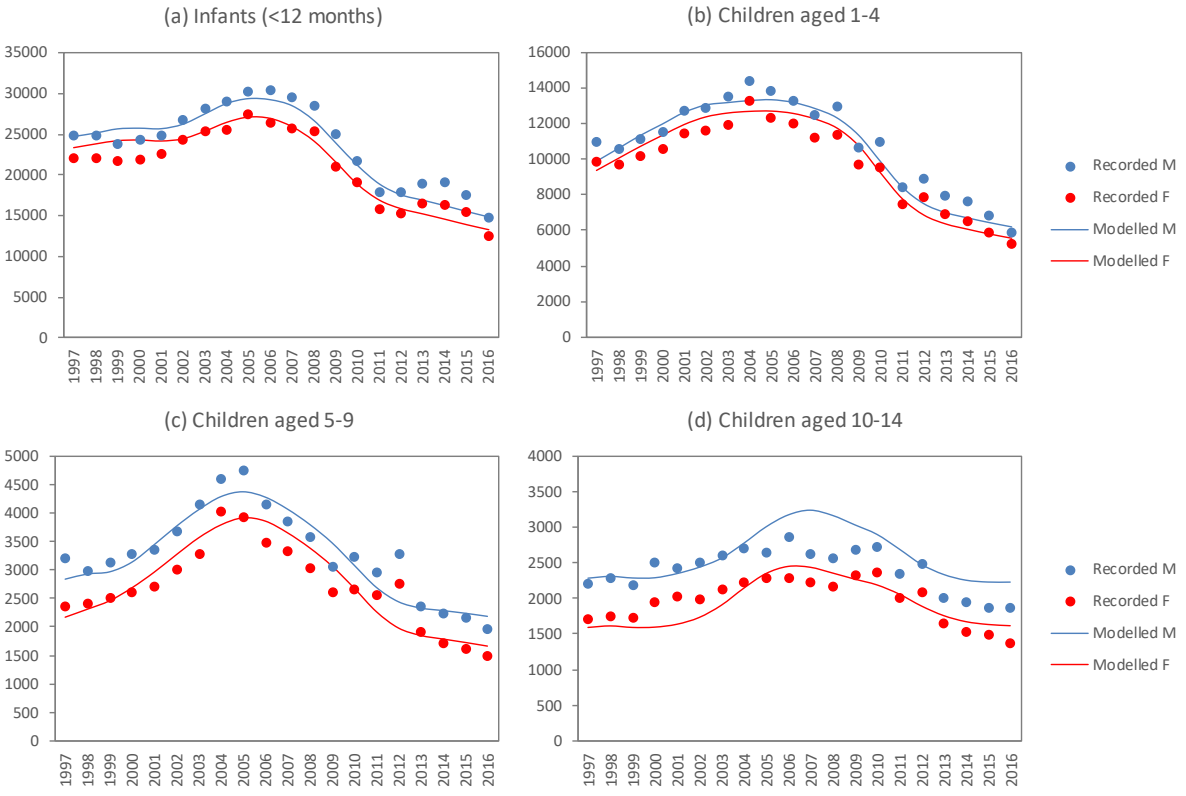

Figure E3: Comparison of modelled deaths and recorded deaths in children, by age
Recorded deaths have been adjusted upward based on the completeness assumptions in Table E2.

Figure E4 shows the model fit to the age distribution of children starting ART over the 2004-2014 period. The model matches the data reasonably well, although slightly over-estimating the fraction of paediatric ART initiations in the 1-4 age group in the 2011-2013 period.

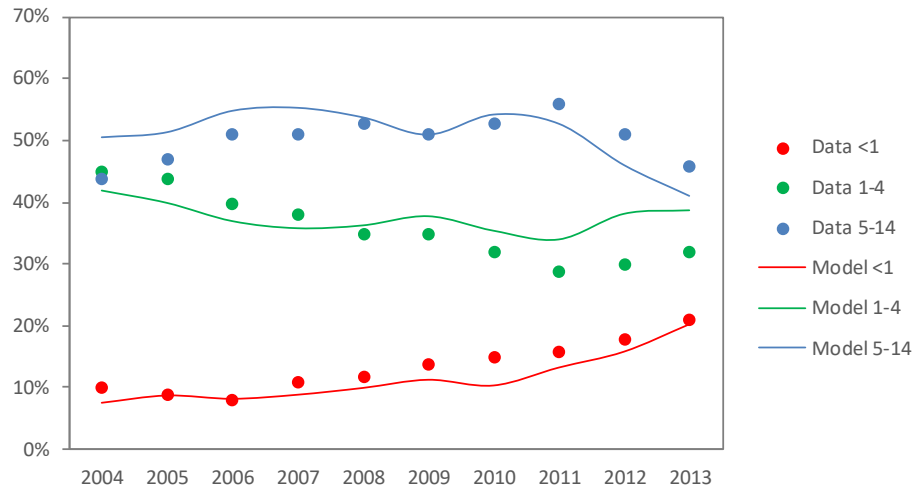

Figure E4: Fraction of children starting ART in different age groups

The model has also been validated against a number of data sources that have not been considered in the definition of the likelihood. Figure E5 shows that the model estimates of perinatal transmission rates (at/before birth) from mothers who are diagnosed positive during pregnancy are consistent with PCR-positive rates in infants tested under the age of 2 months, after 2007 [401]. However, in the period up to 2007, PCR testing was less routine and screening tended to occur more frequently in sick infants who were suspected of having HIV, which may explain why the model tends to under-estimate the PCR-positive rates in this period. The model is nevertheless consistent with early studies that achieved more representative PCR screening of infants born to HIV-positive mothers [402, 403].

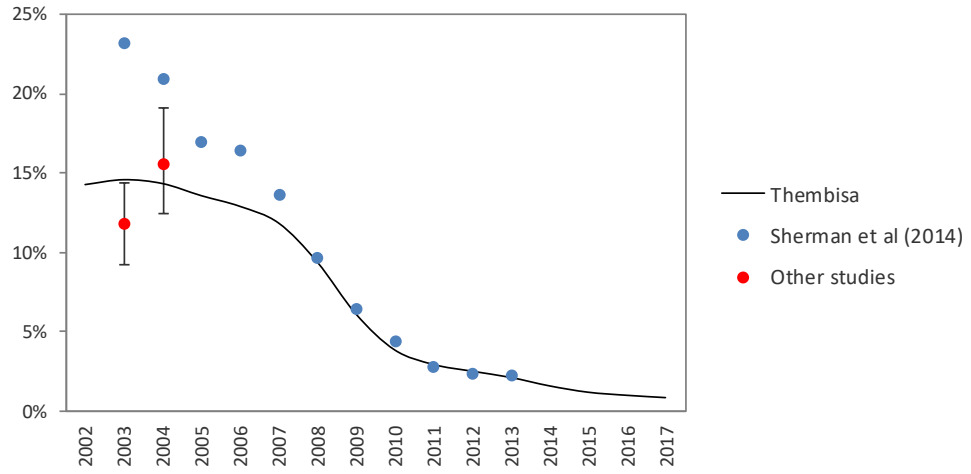

Figure E5: Transmission at/before birth from mothers who have been diagnosed
The data are from routine reporting of PCR screening in the first 2 months of life [401] and from surveys conducted at the time of single-dose nevirapine prophylaxis [402, 403].

The model is also validated against the estimates of the numbers of AIDS deaths from the National Burden of Disease study, which estimated numbers of AIDS deaths based on cause of death statistics, adjusted to take into account mis-reporting of causes of death in individuals dying of HIV-related causes [354]. Figure E6 shows that the model estimates of AIDS deaths in children are very consistent with the estimates from the National Burden of Disease study.

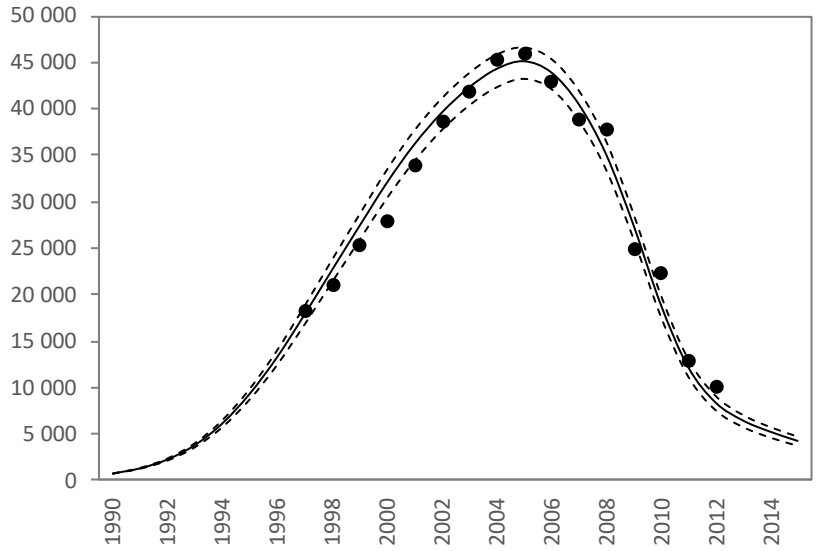

Figure E6: Annual numbers of AIDS deaths in children
NBD estimates are represented by dots. Thembisa estimates are represented by solid lines (means of posterior estimates) and dashed lines (95% confidence intervals).

E.6 Comparison with previous version of Thembisa

In an attempt to calibrate the new version of the Thembisa model to the recorded death data in children, we have made several changes to the paediatric HIV model. It is therefore useful to compare the parameter estimates and results of the new and old versions of the Thembisa model (versions 4.2 and 4.1 respectively). Table E5 compares the posterior estimates of the new model with those from the previous version of Thembisa. Estimates of mother-to-child transmission rates are roughly similar in the two models. However, there are substantial differences in the estimated rates of untreated disease progression, with the new model suggesting substantially higher rates of disease progression in infants and younger children, but lower rates of disease progression in older children. The same is true for untreated mortality rates. The new model also suggests a lower rate of linkage to ART soon after diagnosis than the previous model suggested.

Table E5: Comparison of posterior estimates of paediatric HIV parameters in new and previous versions of Thembisa

Parameter	Thembisa 4.1 (mean, 95% CI)	Thembisa 4.2 (mean, 95% CI)
Probability of MTCT from chronically-infected mothers, per year of mixed feeding	0.107 (0.079-0.144)	0.088 (0.075-0.103)
Probability of MTCT from acutely- infected mothers, per month of mixed feeding	0.154 (0.106-0.212)	0.153 (0.119-0.188)
Ratio of postnatal transmission risk per month of EBF to postnatal transmission risk per month of mixed feeding	0.490 (0.220-0.780)	0.516 (0.270-0.742)
Children infected at/before birth		
Annual rate of progression to late disease in older children	0.423 (0.256-0.637)	0.277 (0.195-0.384)
Excess annual rate of progression to late disease in neonates	2.08 (1.58-2.61)	2.64 (2.17-3.29)
Excess progression reduction factor, per year of age	0.25*	0.423 (0.300-0.537)
Relative rate of progression to late disease if infected after birth	0.352 (0.140-0.591)	0.283 (0.199-0.383)
Children in late disease, untreated		
Annual rate of AIDS mortality in older children	0.125 (0.087-0.165)	0.095 (0.081-0.107)
Excess annual rate of AIDS mortality in neonates	3.57 (2.99-4.20)	3.31 (2.74-3.94)
Excess AIDS mortality reduction factor, per year of age	0.05*	0.295 (0.262-0.337)
Relative rate of linkage to ART soon after diagnosis compared to maximum ART linkage	0.756 (0.425-0.980)	0.375 (0.151-0.627)
Effect of ART on mortality		
Relative rate of mortality in 'stable' ART phase compared to untreated children with late disease	0.100*	0.058 (0.040-0.080)
Reduction in mortality (on log scale) per unit increase in rate of ART initiation (in late disease) over last 3 years	0*	8.52 (4.57-13.31)

* Fixed parameters that were not allowed to vary in the previous model calibration. ART = antiretroviral treatment; EBF = exclusive breastfeeding; MTCT = mother-to-child transmission.

Figure E7 compares estimates of key paediatric HIV indicators in the new and old versions of Thembisa. Estimates of AIDS mortality in children are clearly very different in the new model (higher in the earlier stages of the epidemic but lower in the later stages of the epidemic). However, estimates of annual numbers of new MTCT cases are very similar. As a result of the difference in mortality, the new version of Thembisa produces lower estimates of HIV prevalence in the early stages of the epidemic but a more slowly declining prevalence in recent years, so that by 2017 the two versions produce similar estimates of paediatric HIV prevalence. Because HIV prevalence is lower in the new model, the new model estimates higher levels of paediatric ART coverage.

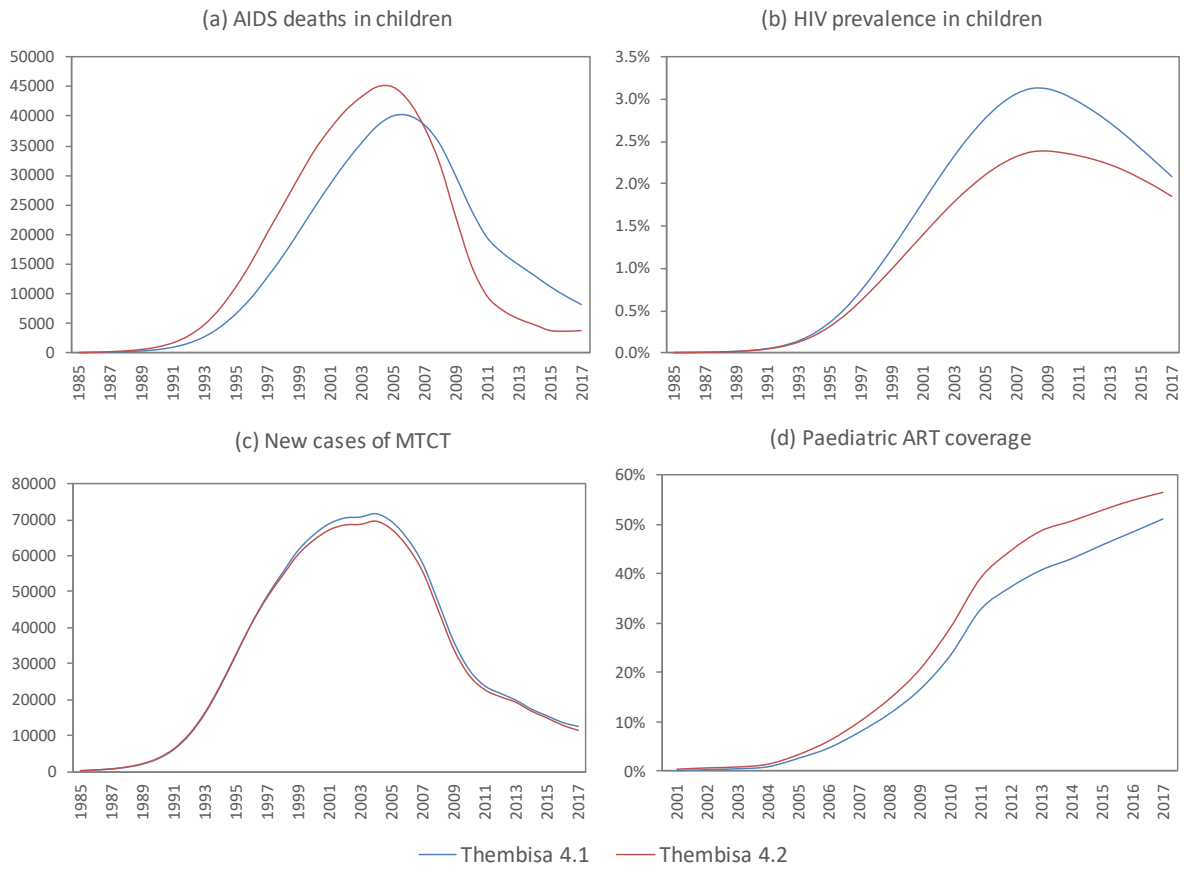

Figure E7: Key paediatric HIV indicators

Appendix F: Estimating rates of viral suppression

In the previous version of Thembisa, it was assumed that rates of viral suppression changed linearly over time, and that viral suppression data were (on average) unbiased in the presence of incomplete reporting of viral suppression [52]. Neither assumption is realistic, and in the revised version of Thembisa we aim to improve on these assumptions. The new model also incorporates more recent viral suppression data, and the greater volume of recent data allows for greater confidence in the estimation of provincial differences in viral suppression.

When interpreting viral suppression data, it is important to consider the bias that may arise due to incomplete data. Typically, viral load data is missing for a substantial fraction of patients. This may be because the viral load test was not done, possibly because the patient's clinic attendance was poor and they did not attend the laboratory monitoring visit (suggesting a bias towards over-estimation of viral suppression if less regular attendance is associated with poorer adherence). It is also possible that a viral load test might be more likely to be performed in a patient who is not doing well clinically, which would suggest a bias in the opposite direction. Finally, many viral load tests are done but results are simply not recorded in patient record systems [404]. It is possible that clinicians might be more likely to record an unsuppressed viral load, since this would necessitate either further monitoring or a change in treatment. This would also suggest a bias towards under-estimation of viral suppression rates [404].

If it is true that there is a significant bias associated with missing viral load data, one would expect to see a correlation between the proportion of patients with viral load data and the proportion of patients whose viral load measurements show viral suppression, across districts/provinces. We previously tested this hypothesis using two datasets: the National Health Laboratory Service (NHLS) database for 2014-15 [359] and the TIER database [152], and found no significant correlation in either case [52]. However, this analysis did not control for other possible predictors of viral suppression. In the updated analysis, we fit a model of the following form to the TIER and NHLS data:

$$\text{logit}(V_i) = \beta_0 + \beta_1 x_i + \beta_2 x_i^2 + \beta_3 x_i^3 + \gamma_i + \delta \ln(d_i) + \lambda_i(1 - d_i),$$

where V_i is the i^{th} reported estimate of viral suppression, x_i is the time (in years after 2000) to which the estimate relates, γ_i is the coefficient representing the effect of the province in which the measurement was taken (if the measurement is a national estimate then $\gamma_i = 0$), d_i is the fraction of the population for which viral load tests were done, and λ_i is a coefficient that applies if the data are from the NHLS (if the data are from TIER then $\lambda_i = 0$). The logit transformation is applied to avoid situations in which the regression model predicts a rate of viral suppression <0% or >100%. The equation shows that we model time trends in viral suppression using a cubic function, instead of the linear function that was used previously. We previously noted that the effects of the fraction of patients with viral loads available (d_i) might be different for the NHLS and TIER databases, and we have therefore included an interaction term (λ_i) to allow for the possibility that the d_i variable may have different effect in the NHLS database. However, one would expect that when $d_i = 1$ there should be no bias due to missing viral load data, and thus the regression model is specified such that the NHLS and TIER terms in the equation equal zero when $d_i = 1$.

The regression model is fitted to a combined dataset pooled from the following sources:

- NHLS estimates of rates of viral suppression in each of the 52 health districts in 2014-15, as well as a national estimate, i.e. a total of 53 data points [359]. In contrast to other published NHLS estimates, these estimates were obtained after an attempt to match records from the same patient probabilistically, to avoid over-estimating the number of patients with viral load information.
- Province-specific viral load data from the TIER database for 2013-14, considering patients who had been on ART for 6 months and 48 months, i.e. a total of 18 data points (information on viral suppression was not available for other years or for other ART durations) [152].
- National viral load data from the TIER database for patients who had been on ART for 6 months (for each year from 2005-2014) and for 48 months (for each year from 2009-2014), i.e. a total of 16 data points [152].
- National viral load data from the TIER database for patients on ART in 2013, reported at 12-month intervals from 12 to 108 months after ART initiation, i.e. a total of 9 data points [162].
- National and provincial viral load data from the TIER database, for patients who had been on ART for 6 months, for each of the four quarters in the 2017-18 year, i.e. a total of 40 data points (Thapelo Seatlhodi, personal communication).

The regression model is thus fitted to a total of 136 data points. Although there is some double-counting when including both national and provincial data points, this is necessary for the purpose of producing viral suppression estimates at both national and provincial levels. Other viral load data are available, but this analysis is limited to those data sources for which there was information on both the proportion of patients with viral load measurements and the proportion of those measurements that were suppressed. Suppression was defined in all cases as a viral load of <400 RNA copies/ml.

Table F1 summarizes the results of the regression model. When considering only the TIER data, there appears to be a significant negative relation between the fraction of patients with viral load measurements and the fraction virally suppressed, but the same is not true for the NHLS data.

Table F1: Predictors of viral suppression (on logit scale)

Variable	Symbol	Coefficient (95% CI)
Year	β_1	0.90 (-0.05 to 1.86)
Year^2	β_2	-0.10 (-0.18 to -0.02)
Year^3	β_3	0.003 (0.001 to 0.005)
Eastern Cape	γ_1	-0.13 (-0.40 to 0.13)
Free State	γ_2	0.43 (0.16 to 0.71)
Gauteng	γ_3	-0.13 (-0.41 to 0.15)
KwaZulu-Natal	γ_4	0.47 (0.22 to 0.73)
Limpopo	γ_5	-0.35 (-0.62 to -0.08)
Mpumalanga	γ_6	-0.04 (-0.33 to 0.25)
Northern Cape	γ_7	-0.45 (-0.72 to -0.17)
North West	γ_8	-0.04 (-0.32 to 0.24)
Western Cape	γ_9	0.14 (-0.13 to 0.41)
Fraction with viral load measurements (log scale)	δ	-0.48 (-0.76 to -0.19)
Fraction without viral load measurements (NHLS data only)	λ_i	-0.56 (-1.18 to 0.06)
Constant	β_0	-1.10 (-4.53 to 2.33)

Figure F1 shows the fit of the logistic regression model to national viral suppression data. For the sake of comparison we compare the logistic regression model predictions for two scenarios: one in which we assume 100% recording of viral loads (i.e. the 'true' level of viral suppression) and one in which we assume 50% recording of viral loads (close to the average fraction of patients with viral load measurements in the TIER datasets). In the latter case we set $d = 0.5$ and $\lambda = 0$ (i.e. so that the model returns the rate of viral suppression we would expect to observe in the TIER database, since this accounts for almost all of the national viral suppression data points). The figure shows that the second scenario is reasonably consistent with the routine data, which suggest moderate rates of viral suppression in the 2005-2010 period, dropping to relatively low levels between 2011 and 2015, then returning to high levels in recent years. However, the 'true' rate of viral suppression (dashed line) is somewhat lower than the reported rate. The second scenario is also roughly consistent with TIER data from 2016 (not included in the calibration dataset because of missing information on the fraction of patients with viral load measurements).

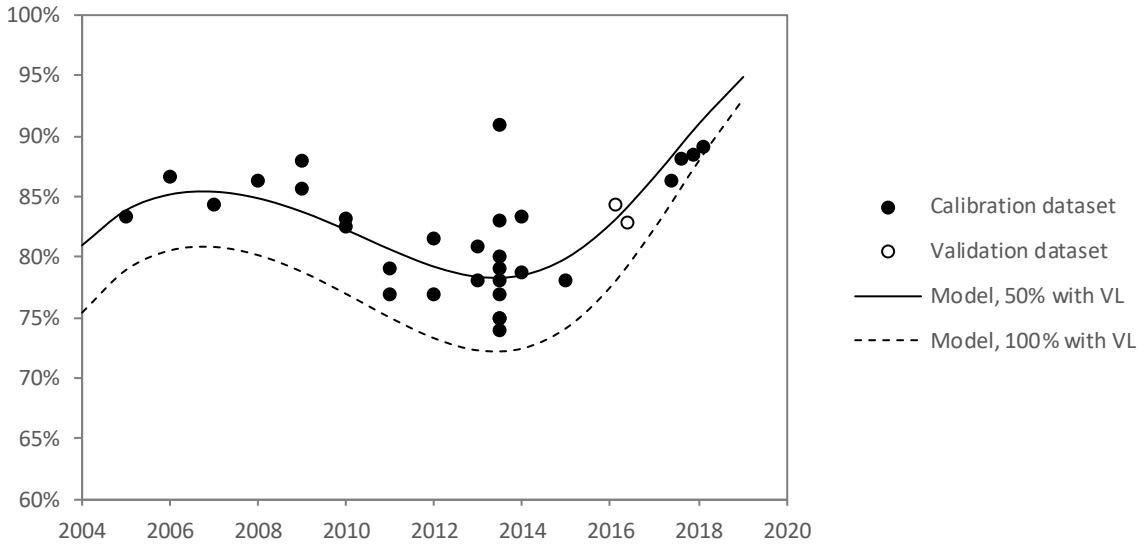

Figure F1: Fraction of South Africa ART patients who are virologically suppressed

Table F2 shows the levels of bias estimated by the model for different fractions of patients with viral load measurements; the bias is expressed as the ratio of the odds of viral suppression in the patients with viral load measurements to the true odds of viral suppression (in all patients). As anticipated, the odds ratio approaches one as the fraction with viral load measurements increases to 100%. However, the bias is more significant in the case of the TIER data than in the case of the NHLS data, suggesting that there is minimal bias in the NHLS data, even at relatively low levels of viral load testing.

Table F2: Effect of fraction with viral load measurements on rate of viral suppression

Fraction with VL (d)	0.4	0.5	0.6	0.7	0.8	0.9	1.0
OR for VS, TIER data ($\delta\ln(d)$)	1.55	1.39	1.27	1.18	1.11	1.05	1.00
OR for VS, NHLS data ($\delta\ln(d) + \lambda(1 - d)$)	1.10	1.05	1.02	1.00	0.99	0.99	1.00

OR = odds ratio; VL = viral load; VS = viral suppression.

As a further validation of the model, we consider an NHLS estimate of the fraction of patients who were virally suppressed in 2012: 73.7% [181]. This was not included in the model calibration as information on the fraction of patients with viral load measurements was missing, but Table F2 suggests that the true rate of viral suppression should be relatively insensitive to the fraction with viral load measurements in the NHLS dataset. The logistic regression model estimate of the fraction virologically suppressed in 2012 is 73.2%, close to the NHLS estimate.

A disadvantage of including the NHLS data in the regression model is that the NHLS data do not include treatment duration, and it is thus not possible to include a treatment duration effect in the regression model. However, when we considered a regression model fitted only to the TIER data, the effect of duration was not statistically significant: the increase in the log odds of viral suppression, for each additional month after ART initiation was 0.001 (95% CI: -0.002 to 0.004). In a recent analysis of 244 000 South African ART patients with viral load measurements, duration effects were found to be non-linear, with the odds of viral suppression being highest in individuals who had been on ART for between 1 and 5 years

[358]. Our data were not consistent with this pattern when we considered a more detailed model of duration effects.

A limitation of this approach is that it does not allow for the possibility of differences in trends between provinces, i.e. the odds ratio representing the effect of province is the same for all years. Although it would be possible to extend the regression model to include interactions between the time and province variables, the relative lack of data at a provincial level makes it difficult to infer differences in trends between provinces with any degree of precision. As more data become available in future, such an approach should be feasible.

The reasons for the changes in viral suppression nationally are unclear. The levels of completeness have not changed substantially over time, and the change in viral suppression is therefore unlikely to be attributable to changes in the completeness of viral load recording. It is possible that the declining levels of viral suppression in the period up to 2015 may be due in part to rising levels of drug resistance [405], or increasing frequency of drug stock outs [406, 407]. It is also possible that this represents a selection bias: the clinics that introduced ART in the early stages of the ART rollout may have been better equipped to provide ART, and the individuals who started ART in the early stages of the rollout may have been more motivated (or more intensively counselled) to adhere to treatment.

In the period from the middle of 2019 onward, rates of viral suppression are assumed to increase as a result of the introduction of dolutegravir to replace efavirenz and nevirapine in first-line ART regimens, although the timing and extent of the introduction of dolutegravir is currently unclear. A recent network meta-analysis estimates that patients receiving dolutegravir are significantly more likely to achieve viral suppression than patients receiving efavirenz (OR 1.87, 95% CI: 1.34-2.64) [182]. We have used this odds ratio to determine the rates of viral suppression in 2019 and subsequent periods, since efavirenz has been the main first-line antiretroviral drug in South Africa up to 2018. However, it is not yet clear if and when dolutegravir will replace efavirenz.

Table F3 summarizes the assumed rates of viral suppression in each year. The model assumptions are specified for patients who start ART with a CD4 count <200 cells/µl, but the previously quoted estimates of viral suppression are for all ART patients, regardless of baseline CD4 count. Because viral suppression is typically poorer in the patients who start ART at low CD4 counts than in patients starting ART at higher CD4 counts [188, 357, 358], it is necessary to adjust the assumed rates of viral suppression downward in order to take into account the lower rates that would be expected in patients starting ART at CD4 <200 cells/µl. The rates shown in Table F3 are calculated by multiplying the previously-specified assumed probabilities by the ratio of the assumed rates of viral suppression in patients starting ART at CD4 <200 cells/µl to the modelled rate of viral suppression in all ART patients, both quantities in the ratio being taken from the previous version of Thembisa (version 4.1). The ratios are shown in the last column of Table F3: the ratio is close to 1 in the early phases of the ART rollout, but declines over time as relatively more patients have started ART at CD4 counts above 200 cells/µl.

Table F3: Assumed annual proportions of patients who are virally suppressed, among patients who started ART with CD4 <200 cells/µl

Year	% suppressed	Relative suppression at CD4 <200
2000-01	0.787	0.9979
2001-02	0.787	0.9979
2002-03	0.787	0.9978
2003-04	0.787	0.9977
2004-05	0.787	0.9978
2005-06	0.787	0.9976
2006-07	0.803	0.9972
2007-08	0.805	0.9970
2008-09	0.798	0.9968
2009-10	0.784	0.9965
2010-11	0.766	0.9961
2011-12	0.745	0.9940
2012-13	0.725	0.9902
2013-14	0.713	0.9868
2014-15	0.713	0.9843
2015-16	0.726	0.9790
2016-17	0.756	0.9753
2017-18	0.800	0.9711
2018-19	0.851	0.9671
2019-20*	0.901	0.9671

* Rates of viral suppression are assumed to remain constant after 2019-20.

For children, we lack reliable data on rates of viral suppression. Although NHLS data have suggested rates of viral suppression in children of 65.4% in 2015, 64.1% in 2016, 65.1% in 2017 and 66.7% in 2018 (Kimberley Perez, personal communication), there are two problems with these NHLS data for children. The first is that they relate to a viral suppression threshold of 1000 RNA copies/ml, not 400 RNA copies/ml, and are thus likely to over-estimate the fraction virally suppressed according to the Thembisa definition. The second is that (unlike the adult NHLS data), these data have not been de-duplicated to remove repeat viral load tests in children experiencing virological failure; this may have led to some under-estimation of the fraction virally suppressed. The two sources of bias probably offset one another to some extent, so that the overall direction of the bias is unclear. In an analysis of 11 000 children receiving ART in four South African provinces, Joseph Davey *et al* [358] estimated the fraction virally suppressed in 2016 (at a threshold of <400 copies/ml) to be 68.2%, significantly lower than the rate of 86% in adults (OR 0.41, 95% CI: 0.39-0.43). This estimate of 68.2% is likely to be an over-estimate of the true rate of viral suppression, given the bias in the TIER data (Figure 3.3), although the authors did not report the proportion of patients with missing viral load measurements. Trends in viral suppression are also unclear. Although the NHLS data cited previously suggest little change in rates of viral suppression over the 2015-18 period, data from the IeDEA collaboration suggest that viral suppression in South African infants initiating ART before 12 weeks of age has deteriorated over the 2006-2016 period [408], and similar deterioration is seen in adolescents starting ART over the 2004-2016 period [409]. These trends observed in the IeDEA data are roughly consistent with the trends we have estimated for adults and children combined in the period up to 2015 (Figure F1), although our trend estimates relate to the period of viral load measurement rather than the period of ART initiation. Factors such as age and disease severity influence rates of

viral suppression in children [357, 410], and thus some change in rates of viral suppression over time might be expected as the age distribution of treated children and baseline disease stage changes [410]. However, given the lack of local paediatric data, we do not attempt to model the contribution of these age and disease severity effects in children. Instead we assume that the odds of viral suppression in treated children is 0.41 times that in adults in all years up to 2018 (based on the analysis of Joseph Davey *et al* [358]), and that there is no change in viral suppression after 2018 (since dolutegravir is unlikely to be introduced in children).

A limitation of this analysis is that it does not consider the possible bias that may be introduced by delays in viral load testing (test performance deteriorates when there are delays in plasma separation and/or testing). Data from the Western Cape province suggest that viral suppression rates may have appeared relatively high in 2009 and 2015 because test turnaround times were relatively long in these years [411]. Further research is required to assess whether similar problems occurred in earlier years and in other provinces.

Appendix G: Modelling treatment interruptions

This appendix describes the approach used to estimate the frequency of treatment interruption and treatment resumption after an interruption. Figure G1 presents an overview of the theoretical model that we apply to South African data sources. Patients are assumed to disengage from care at a constant rate λ, but only a proportion θ of these disengagements are assumed to be true ART interruptions. The reasons for other disengagement will vary from study to study, depending on the methods used to classify patients 'lost to follow-up' (LTFU), but will most commonly include patients who have transferred to other ART services (so-called 'silent transfers') and patients who have died without their death being recorded by the clinic at which they were receiving ART. The patients who interrupt ART are assumed to resume ART at a constant rate ρ, with a proportion ϕ_1 of these patients resuming ART at a different clinic within the same province, a proportion ϕ_2 resuming ART in a different province, and the remainder resuming ART at the same clinic at which they originally received ART. For the sake of simplicity, we do not consider mortality while interrupting ART, as studies suggest that after excluding the deaths that occur soon after LTFU (which in most cases represent failure to record mortality rather than mortality after a treatment interruption) this is a relatively infrequent occurrence [412, 413].

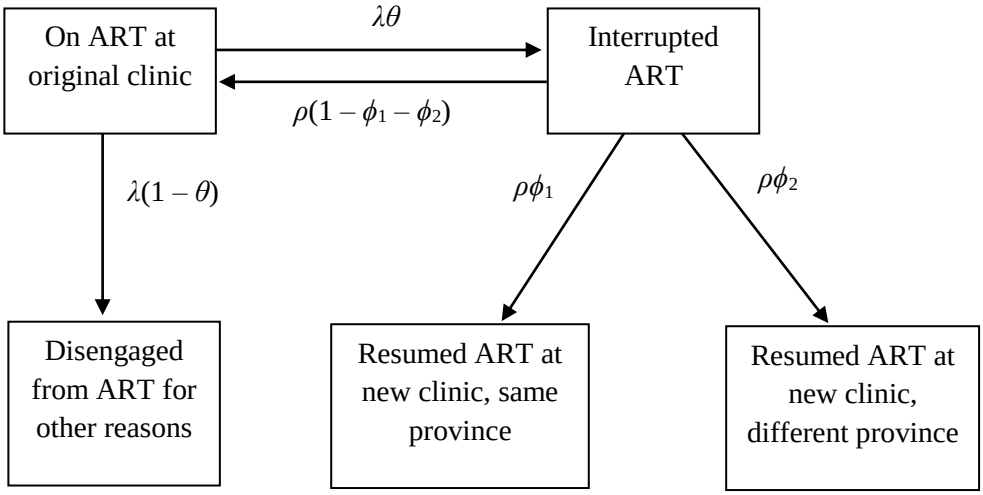

Figure G1: Model of ART interruption and return to care

We attempt to estimate the parameters of this model using data from different studies. Three South African studies were identified that estimated either rates of treatment interruption or rates of treatment resumption [413-415]. Each study follows a different design, and no single study estimates all of these parameters, but by drawing on the estimates from different studies it is possible to determine plausible ranges for the parameters. Of primary interest are the parameters λ, θ and ρ. The sections that follow describe each of the studies and the process followed in estimating the model parameters. The findings of the different studies are then synthesized in the final section.

G.1 Patients on ART in Khayelitsha (Western Cape)

Kaplan *et al* [413] conducted the largest and most recent of the three studies. Patients were included in the study population if they were receiving ART in Khayelitsha clinics between 2013 and 2014. Patients who were lost to follow-up (more than 6 months without a visit and no documented transfer or death) were tracked to determine if they had received ART elsewhere in the province (by linking their patient ID to the provincial patient record system) or had died (by linking their civil ID to the vital registration system). Disengagement from care was defined as a gap of more than six months in receiving ART, without the patient receiving ART or dying within the 6-month window. The definition of disengagement therefore excludes silent transfers (where the patient received ART at another service within 6 months of dropping out of ART care) and unrecorded deaths. The resulting estimates of the treatment interruption rate, which varied between 0.10 and 0.12 per annum, are thus directly comparable with the modelled quantity $\lambda\theta$. This rate of treatment disengagement was found to be roughly constant with respect to the time since ART engagement, after controlling for baseline covariates. This rate of treatment disengagement is probably an under-estimate, since individuals who disengaged from ART but returned to the same clinic at which they were previously treated are not included in the definition of treatment interrupters.

The study found that cumulative rates of return to care after a treatment interruption increased from 27% 1 year after the interruption to 50% by 2.5 years after the interruption (Table G1). However, it is important to note that this represents only patients who returned to other ART facilities within the Western Cape, and (as noted in the previous paragraph) individuals who returned to care at the original ART clinic were not included in the definition of treatment interrupters. It is also important to note that because of the 6-month window used to define LTFU, the quoted durations of follow-up after interruption are 6 months longer than the period in which individuals could actually return to care (if they had returned to care within 6 months then they would not have met the study definition of an interrupter). The model quantity that should be compared to the 27% rate of return after 1 year is thus

$$\frac{\phi_1}{\phi_1 + \phi_2} \exp\left(-\rho / 2\right),$$

and similar equations are defined at the other durations of follow-up shown in Table G1. We adopt a Bayesian approach in estimating these quantities. A vague prior (uniform on the interval [0, 1]) is assigned to represent the uncertainty in the quantity $\exp(-\rho)$. The quantity $\phi_1/(\phi_1 + \phi_2)$ can be estimated approximately from a similar study conducted in Gauteng [415], which found that out of 103 patients who resumed ART at a different ART clinic after interrupting treatment, 69% did so in the same province and the remaining 31% started ART in a different province. Although the rates of clinic movement might be different in Gauteng and the Western Cape, both are predominantly urban provinces, and some similarity would therefore be expected. We therefore assign a beta prior to represent the uncertainty in the quantity $\phi_1/(\phi_1 + \phi_2)$, with mean 0.69 and standard deviation 0.046 (consistent with the sample size of 103).

A likelihood function is defined with reference to the data in Table G1, assuming that the data are drawn from a normal distribution with the mean given by the model and a standard deviation calculated assuming a coefficient of variation of 0.1 around the data (standard

deviations were not reported in the Kaplan study and the coefficient of variation of 0.1 is therefore taken from another study conducted in the Western Cape, the Kranzer study described below [414]). The posterior estimates were generated by drawing a sample of 10 000 parameter combinations from the prior distributions, calculating the likelihood values for each parameter combination, and then drawing a second sample of 1000 parameter combinations from the original set of parameter combinations using the likelihood values as weights (i.e. a sampling importance resampling procedure [416]). Table G1 shows that the resulting model estimates of the fraction returning to care are roughly consistent with the data.

Table G1: Proportions of ART interrupters returning to care at different clinics in the Western Cape

Months after interruption	Observed % returned to care	Standard deviation (assumed)	Posterior model mean (95% CI)
12	27%	2.7%	23.7% (20.5-27.7%)
18	38%	3.8%	38.7% (34.8-43.0%)
24	45%	4.5%	48.3% (44.4-52.4%)
30	50%	5.0%	54.3% (49.4-58.9%)

The posterior estimate of the quantity $\phi_1/(\phi_1 + \phi_2)$ is 0.66 (95% CI: 0.57-0.75), roughly consistent with the prior mean. The posterior estimate of the ρ parameter is 0.92 (95% CI: 0.67-1.32).

As noted previously, the $\lambda\theta$ estimates of 0.10-0.12 are likely to be under-estimates because interrupters who return to the same clinic are not included in the definition of interruption. However, they are also likely to be under-estimates of the true rates because interrupters who resume ART at a different clinic within 6 months of an interruption are also excluded from the definition. Having estimated $\rho = 0.92$, it is possible to estimate the fraction of interrupters who do not resume ART within 6 months, which is $\exp(-\rho/2) = 0.63$, and thus the reported rates of interruption should be inflated by factors of 1/0.63 in order to obtain corrected estimates (0.16-0.19).

G.2 Patients on ART in Masiphumelele (Western Cape)

Kranzer *et al* [414] measured rates of ART interruption and return to care in the Masiphumelele community. This study differed from the previous study in a number of important respects. Treatment interruptions were defined as periods of more than 30 days without a pharmacy refill visit, but individuals who returned to the original clinic were not excluded from the definition of treatment interrupters. Using this definition yielded an incidence of treatment interruption of 0.128 per annum (95% CI: 0.114-0.144).

The study was limited in its ability to isolate 'true' interrupters; patient records were not linked to other health facilities and there was no linkage to the vital registration system to determine whether the patient had died. However, three attempts were made to contact patients who were late in collecting their pharmacy refills, and in addition, home visits were made in the case of half of the LTFU cases to determine whether the patient had died or left the area (such patients were censored at the date of death or migration in the calculation of rates of ART resumption). We define θ to be the fraction of LTFU patients who remained in the same community (Masiphumelele) after stopping treatment and who were not LTFU due

to death (i.e. θ is the fraction of interrupters who could reasonably resume ART in Masiphumelele). Although the θ parameter is unknown, a recent systematic review of studies that had traced patients LTFU after starting ART in sub-Saharan Africa estimated the proportion of individuals not on ART (as distinct from dead or transferred to other ART services) to be 29% (estimates varied between 4% and 82% across studies) [417]. The 29% is probably an under-estimate of the θ parameter, considering that (a) some attempts were made by Kranzer *et al* to trace patients who were LTFU and thus exclude unrecorded deaths and transfers/migrations, and (b) the tracing studies included in the systematic review would mostly not have included patients who interrupted ART but returned to their original clinic in their definition of LTFU. We therefore assign a beta prior to represent the uncertainty around the θ parameter, with mean 0.55 and standard deviation 0.15. The 2.5 and 97.5 percentiles of this distribution are 0.25 and 0.83 respectively. The mean and standard deviation have thus been chosen such that the lower limit is close to the 29% average (which we consider a likely lower bound) and the upper bound is close to the maximum of 82% estimated in the studies included in the systematic review.

Our model estimates that of individuals who interrupted ART, the proportion who resumed ART at their original clinic within t years is $\theta \exp(-\rho(t - 1/12))$, where ρ is defined as the rate of ART resumption within the Masiphumelele community, among the individuals who were still alive and untreated in the Masiphumelele community. The 1/12 adjustment is included to represent the 1-month window used to define interruption. The parameters θ and ρ can be estimated roughly by fitting the model to the observed cumulative proportions of patients who resumed ART (Table G2). As in the previous section, we assign a vague prior to the $\exp(-\rho)$ quantity. We define a likelihood function based on the assumption that the data are drawn from a normal distribution with the means given by the model and the standard deviations calculated from the published confidence intervals around the data. The posterior distribution is simulated in the same way as in the previous section.

Table G2: Proportions of ART interrupters returning to care in Masiphumelele

Months after interruption	Observed % returned to care (95% CI)	Standard deviation (assumed)	Posterior model mean (95% CI)
12	26.7% (21.7-32.7%)	2.8%	25.8% (21.0-31.5%)
24	37.1% (31.1-43.9%)	3.3%	37.5% (33.4-41.4%)
36	42.1% (35.2-49.7%)	3.7%	42.5% (36.6-48.5%)

The resulting posterior estimates of the θ and ρ parameters are 0.47 (95% CI: 0.37-0.65) and 0.94 (95% CI: 0.46-1.65) respectively. The estimate of the rate of ART resumption is thus similar to that estimated in the previous section (0.92). However, the estimate of the quantity $\lambda\theta$ is 0.06 (0.128×0.47), which is substantially lower than the estimates of 0.16-0.19 obtained using the Kaplan study data. This is probably because the patients included in the Kranzer study were followed much more intensively (as noted before, three attempts were made to contact patients if they were late in returning for pharmacy refills), and a subset of the patients were enrolled in a clinical trial. In addition, the estimate of 0.06 per annum excludes individuals who moved out of the study area (who may have been more likely to interrupt ART).

G.3 Pregnant women in Gauteng

Clouse *et al* [415] attempted to trace women who were classified lost to follow-up after initiating ART during pregnancy. Patient records were linked to the National Health Laboratory Service (NHLS) database to identify instances where women had initiated ART at other facilities (outside of the facility at which ART had been initiated during pregnancy), but the definition of treatment resumption excluded women who returned to the same clinic at which they originally resumed ART. Of 274 women who were LTFU, 103 (37.6%) were found to have received ART at other sites. However, it is not clear how many of the women died (since there was no linkage of civil identifiers to the vital registration system), which is a concern, as some of the LTFU might actually have been due to mortality that was not captured by the original clinic at which women started ART. In addition, it was noted that 30% of the women were not from South Africa, and it is possible that some of these women returned to their country of origin soon after giving birth (which means that even if they resumed ART, their records would not be picked up by the NHLS).

We therefore specify parameter θ_1 to represent the fraction of women who were LTFU as a result of death, and parameter θ_2 to represent the fraction of women who left the country after giving birth. We assign a uniform prior distribution to represent the uncertainty regarding the latter, assigning equal probabilities to all values on the range [0, 0.3], the upper bound being the fraction that would be expected if all immigrants returned to their country of origin. We assign a beta prior distribution to represent the uncertainty around the parameter θ_2, with mean 0.3 and standard deviation 0.10. This prior distribution is based on a systematic review of tracing studies [418], which found that the fraction of LTFU patients who had died varied between 12% and 87% in African studies, and varied inversely in relation to the cumulative LTFU rate, being around 30% at a cumulative LTFU rate of 38% (the LTFU rate in the Clouse study). The 30% is also similar to the results of a more recent systematic review, which found that in patients who were LTFU after 2007, the fraction who were found to have died after tracing was 30% (95% CI: 21.2-38.9%) [417].

Unlike in the two previous studies, the cumulative proportion of women who had returned to care was not specified at fixed durations after the interruption occurred – the 37.6% referred to previously therefore represents the average across different follow-up durations in the study. Women started ART between the start of January 2012 and the end of July 2013, and LTFU was reported as occurring a median of 3 months after ART initiation (equivalent to a mean of 0.36 of a year). If we assume for simplicity that all women who were LTFU were LTFU after exactly 0.36 of a year, and that the distribution of ART initiation dates was uniform over the interval [2012, 2013.58], then the distribution of LTFU times must have been uniform over the interval [2012.36, 2013.92]. In September of 2015, the NHLS database was assessed for evidence of a return to care in South Africa. At this time, we would expect the cumulative fraction returned to care to be

$$\frac{(1-\theta_1)(1-\theta_2)}{2013.92-2012.36}\int_{2012.36}^{2013.94}(1-\exp(-\rho(2015.75-t-\delta)))dt,$$

where ρ is the rate of ART resumption after an interruption, and δ is the LTFU window (in this study, women were only considered LTFU if they had no clinic visit for 3 or more months, i.e. $\delta = 0.25$). The above expression simplifies to

$$(1-\theta_1)(1-\theta_2)\left(1-\frac{1}{\rho \times 1.58}\left(\exp(-1.56\rho)-\exp(-3.14\rho)\right)\right).$$

The likelihood is calculated by comparing this modelled proportion to the observed proportion (0.376), assuming that the observed proportion is normally distributed with a mean given by the above expression, and a standard deviation of 0.029 (the standard deviation is calculated from the data). As in the previous sections, we assign a vague prior to the exp(-ρ) quantity. The posterior distribution is simulated by drawing a sample of 10 000 combinations of the θ_1, θ_2 and exp(-ρ) quantities, calculating the likelihood for each, and then drawing a second sample of 1000 parameter combinations from the first sample, using the likelihood values as weights.

The resulting posterior estimates have wide confidence intervals. The estimated annual rate of ART resumption (ρ) is 0.70 (95% CI: 0.28-2.60), while the estimated proportions leaving South Africa and dying (θ_1 and θ_2) are 17% (95% CI: 1-29%) and 34% (95% CI: 15-54%) respectively.

Having obtained estimates of θ_1 and θ_2, it is possible to approximate the 'true' rate of ART interruption, $\lambda\theta^*$, where λ is the LTFU rate and $\theta^* = (1 - \theta_1)(1 - \theta_2)$. From the above information, we would expect the cumulative fraction LTFU at the end of August 2015 to be

$$\frac{1}{2013.58-2012}\int_{2012}^{2013.58}\left(1-\exp(-\lambda(2015.67-t-\delta))\right)dt$$

Setting this expression to 38.1% (the observed cumulative fraction LTFU) yields an estimate of $\lambda = 0.18$, and the corresponding estimate of $\lambda\theta^*$ is 0.10. This is likely to be an under-estimate of the true rate of ART interruption, as individuals who resumed ART at the same facility were not included in the definition of LTFU. On the other hand, it is possible that the estimate may be exaggerated, considering that some of the women who resumed ART at other clinics might have done so soon after their last visit at the original clinic (i.e. they might not have actually interrupted ART). However, Clouse *et al* reported that the median time out of care among those resuming ART was 305 days (IQR: 100-582), which suggests that the number starting ART elsewhere without any gap in ART is likely to be relatively small.

G.4 Summary

Table G3 summarizes the estimates of the rate of ART interruption and resumption from the different studies reviewed previously. None of the studies provides a truly unbiased measure of the rate of treatment interruption. The Kaplan and Clouse studies are both likely to under-estimate the true rate because they exclude individuals who interrupted ART and then resumed ART at the same clinic. The Kranzer study also is likely to under-estimate the true rate, as it excludes patients who left the study area (who may have been more likely to interrupt ART), and it followed the patients who remained in the study area intensively (i.e. follow-up may not have been typical of that in the general public health sector). For the purpose of modelling ART interruptions in Thembisa, we assume a value of 0.25 for the annual rate of ART interruption. Further work is required to consider the uncertainty around this parameter, but for now we note that this choice of parameter value leads to model estimates of the difference between cumulative and current ART enrolment (a crude measure

of the extent of ART interruptions) that are consistent with differences between reported cumulative and current enrolment (Figure 8.8).

Table G3: Summary of South African estimates

Parameter and source	Estimate (95% CI)	Comment
Rate of 'true' ART interruption ($\lambda\theta$)		
Kaplan *et al* [413]	0.16-0.19	Likely under-estimate
Kranzer *et al* [414]	0.06	Likely under-estimate
Clouse *et al* [415]	0.10	Likely under-estimate
Rate of ART resumption (ρ)		
Kaplan *et al* [413]	0.92 (0.67-1.32)	-
Kranzer *et al* [414]	0.94 (0.46-1.65)	-
Clouse *et al* [415]	0.70 (0.28-2.60)	-

Pooling the rates of ART resumption estimated in Table G3 and weighting by the inverse of the variance gives an average ART resumption rate of 0.91 (95% CI: 0.68-1.21). We therefore assign a value of 0.90 to the ρ parameter, again noting the need for further work to consider uncertainty around this parameter.

Now consider a simplified model in which mortality after ART initiation is the same regardless of whether individuals remain on ART or interrupt ART. We define $I(t)$ to be the fraction of patients who started ART t years ago who are currently interrupting ART. This fraction can be calculated using the differential equation

$$\frac{dI(t)}{dt} = \big(1 - I(t)\big)\lambda\theta - I(t)\rho$$

with the initial condition $I(0) = 0$. Substituting the previously-assumed values of 0.25 and 0.90 for $\lambda\theta$ and ρ respectively into the equation, and solving numerically, we get estimates of $I(t)$ of 0.057 for 3 months after ART initiation, 0.152 for 12 months, 0.198 for 24 months, 0.212 for 36 months and 0.216 for 48 months. These are the values assumed for the ι_d parameter in section 4.6. The values are slightly different from those estimated in a recent analysis, based on African tracing studies, which estimated that the fraction of survivors who had stopped or interrupted ART was 0.100 12 months after ART initiation and 0.265 5 years after ART initiation [419]. As this study excluded transient ART interruptions, the lower estimated fraction off ART at 12 months (0.100 compared to 0.152 in our model) is to be expected.