Supplementary materials

Contents

1. Model description

Thembisa is a combined demographic and HIV model, that has been developed for South Africa. The model is deterministic and compartmental, with the adult population being divided into a number of compartments that are defined in terms of age, sex, sexual experience, propensity for concurrent partnerships and commercial sex, sexual preference, marital status, male circumcision status, HIV testing history and receipt of pre-exposure prophylaxis (PrEP). HIV-positive adults are further stratified according to their HIV stage (defined in terms of CD4 count) and receipt of antiretroviral treatment (ART). The model simulation begins in 1985, and the numbers of individuals in each compartment is updated at monthly time steps. The model allows for sexual activity from as early as age 10, and thus the 'adult' compartments start from age 10 (10, 11, 12, …, 89, 90+). For the purpose of this study, we include the 10-14 age group in the paediatric estimates, although some of the parameters in this age group (for example, rates of transition between CD4 compartments and ART mortality rates) are determined in the adult component of the model and are therefore outside of the scope of this study.

The version of Thembisa on which this analysis is based is Thembisa version 4.2, which is explained in detail elsewhere [1]. The model is programmed in C++, and an Excel version of the model (which produces almost identical results) is freely available from the Thembisa website (www.thembisa.org). The purpose of this appendix is to describe those aspects of the model that are directly relevant to the paediatric HIV estimation process.

1.1 Births to HIV-positive mothers

Fertility rates in HIV-positive women are specified as multiples of corresponding fertility rates in HIV-negative women of the same age. Mathematically, the fertility rate in HIV-positive women aged x in year t, in CD4 stage s, with HIV testing history v, ART status a and ART duration d, is calculated as

$$F(x, t)\,\Gamma(s, v, a, d),$$

where $F(x, t)$ is the fertility rate in HIV-negative women, and $\Gamma(s, v, a, d)$ is the HIV-positive multiplier. The indices used in defining the multiplier are specified as follows:

- CD4 stage (s) is defined as 1 if the woman is in the acute phase of HIV infection, and 2, 3, 4 or 5 if the woman has progressed out of the acute phase of infection and has a CD4 count of ≥500, 350-499, 200-349 or <200 cells/μl respectively.
- HIV testing history (v) is defined as 0 if the woman has never tested for HIV, 1 if the woman has tested for HIV but not been diagnosed positive, and 2 if the woman has been diagnosed positive.
- ART status (a) is defined as 0 if the woman is ART-naïve and 1 if the woman has started ART.
- ART duration (d) is defined based on time since *first* ART initiation. The index is 0 for women who have started ART for the first time in the current year (or who have never started ART), 1 for women who started ART in the previous year, 2 or 3 for women who started ART 2 or 3 year previously respectively, and 4 for women who started ART 4 or more years previously.

For a full listing of all possible HIV compartments for HIV-positive women, see Table 4.4 of the Thembisa 4.2 report [1]. One complication to note is that the model compartments for treated women are defined in terms of baseline CD4 count at ART initiation (s') rather than

current CD4 count (s). As described in section 4.6 of the Thembisa report, the variable $\psi_d(s|s')$ represents the fraction 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. Another complication is that ART-experienced women are assumed to interrupt ART at a constant rate (and can also resume ART after an interruption). It is assumed that CD4 counts return to those just before ART initiation in the women who interrupt ART [2, 3], and the CD4 effects that apply during ART interruptions are thus the same as the baseline CD4 effects.

The $\Gamma(s, v, a, d)$ multiplier is calculated as the product of a number of adjustment factors:

$$\Gamma(s, v, a, d) = B_0\, B_1(s)\, B_2(v)\, B_3(a).$$

The $B_1(s)$ adjustment factor represents the relative fertility rate in HIV-positive women in CD4 compartment s to that in HIV-positive women with CD4 counts of 500 cells/μl or higher (by definition, $B_1(1)$ and $B_1(2)$ are both 1). Based on a recent analysis of pregnancy incidence rates in HIV-positive women in the Western Cape province of South Africa [4], we set these ratios to 0.99 in the CD4 350-499 category, 0.90 in the CD4 200-349 category, and 0.66 in the CD4 <200 category. These rate ratios are consistent with CD4 effects observed in other African cohorts [5-7].

The $B_2(2)$ adjustment factor represents the relative fertility rate in HIV-diagnosed women compared to undiagnosed HIV-positive women (by definition, $B_2(0)$ and $B_2(1)$ are both 1). This factor is difficult to estimate with confidence, but one might expect that $B_2(2)$ should be less than 1, since HIV diagnosis is typically associated with increases in condom use [8-10]. Studies have also shown that HIV-diagnosed women report lower childbearing intentions when compared to HIV-positive undiagnosed women and HIV-negative women, with odds ratios for the relationship between HIV diagnosis and childbearing intentions typically close to 0.4 [11-13]. This odds ratio of 0.4 is probably a lower bound on the $B_2(2)$ factor, since many HIV-positive women become pregnant despite reporting no childbearing intentions [11]. We therefore assign a beta prior distribution to represent the uncertainty around the $B_2(2)$ parameter, with a mean of 0.70 and a standard deviation of 0.14. This prior distribution has 2.5 and 97.5 percentiles of 0.40 and 0.93 respectively, the former corresponding to the likely lower bound on $B_2(2)$ and the latter being close to the likely upper limit of 1.

The $B_3(1)$ adjustment factor represents the relative rate of fertility in women on ART when compared to women who are untreated (by definition, $B_3(0)$ is 1). Based on the previously-mentioned analysis of Western Cape data [4], the $B_3(1)$ parameter has been set to 1.35. (This is the result from a sensitivity analysis in which HIV-positive women were censored after their last visit or laboratory result, which is considered more reliable than the main analysis for the purpose of estimating differences between groups of HIV-positive women.) This higher rate of pregnancy incidence in women on ART, after controlling for recent CD4 count, is consistent with the findings of some studies [5, 14], although results from other studies have been inconsistent [15, 16].

The B_0 adjustment factor represents the relative rate of fertility in undiagnosed HIV-positive women in the early stages of HIV infection (CD4 ≥500 cells/μl), when compared to fertility in sexually experienced HIV-negative women of the same age. This parameter is difficult to estimate directly, as most studies do not report fertility rates in undiagnosed HIV-positive women, or do not include comparisons with HIV-negative women. However, one might expect

B_0 to be greater than 1 if women who have recently acquired HIV are more sexually active and therefore more likely to become pregnant. In a sensitivity analysis of the Western Cape data, it was found that pregnancy incidence rates in women on ART with CD4 counts above 500 cells/μl were 1.42 (95% CI: 1.38-1.45) times those in HIV-negative women [4]. Substituting this and the other previously-assumed values into the equation for $\Gamma(s, v, a, d)$ gives

$$1.42 = B_0\, B_2(2) \times 1.35.$$

Equivalently, $B_0 = (1.42/1.35)/B_2(2) \approx 1/B_2(2)$. We use this approximation to determine B_0 from $B_2(2)$.

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

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

and this equation is then used to solve for $F(x,t)$, given the $\overline{F}(x,t)$ value. Observed average fertility rates are specified for every age and year up to 2016. In the years that follow 2016, 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 [17].

Figure S1 shows the resulting model estimates of HIV prevalence in pregnant women, compared against national survey estimates of HIV prevalence in women attending public antenatal clinics. There is good overall agreement between the model estimates and the survey data, although in some age groups (e.g. 20-24) the model does not match the data closely. Because of uncertainty regarding HIV prevalence in pregnant women attending private antenatal facilities (which is thought to be substantially lower than that in women using public antenatal clinics [18]), the model estimates of HIV prevalence in pregnant women are adjusted upward using an 'antenatal bias' correction, for the purpose of calibrating the model to public antenatal survey data.

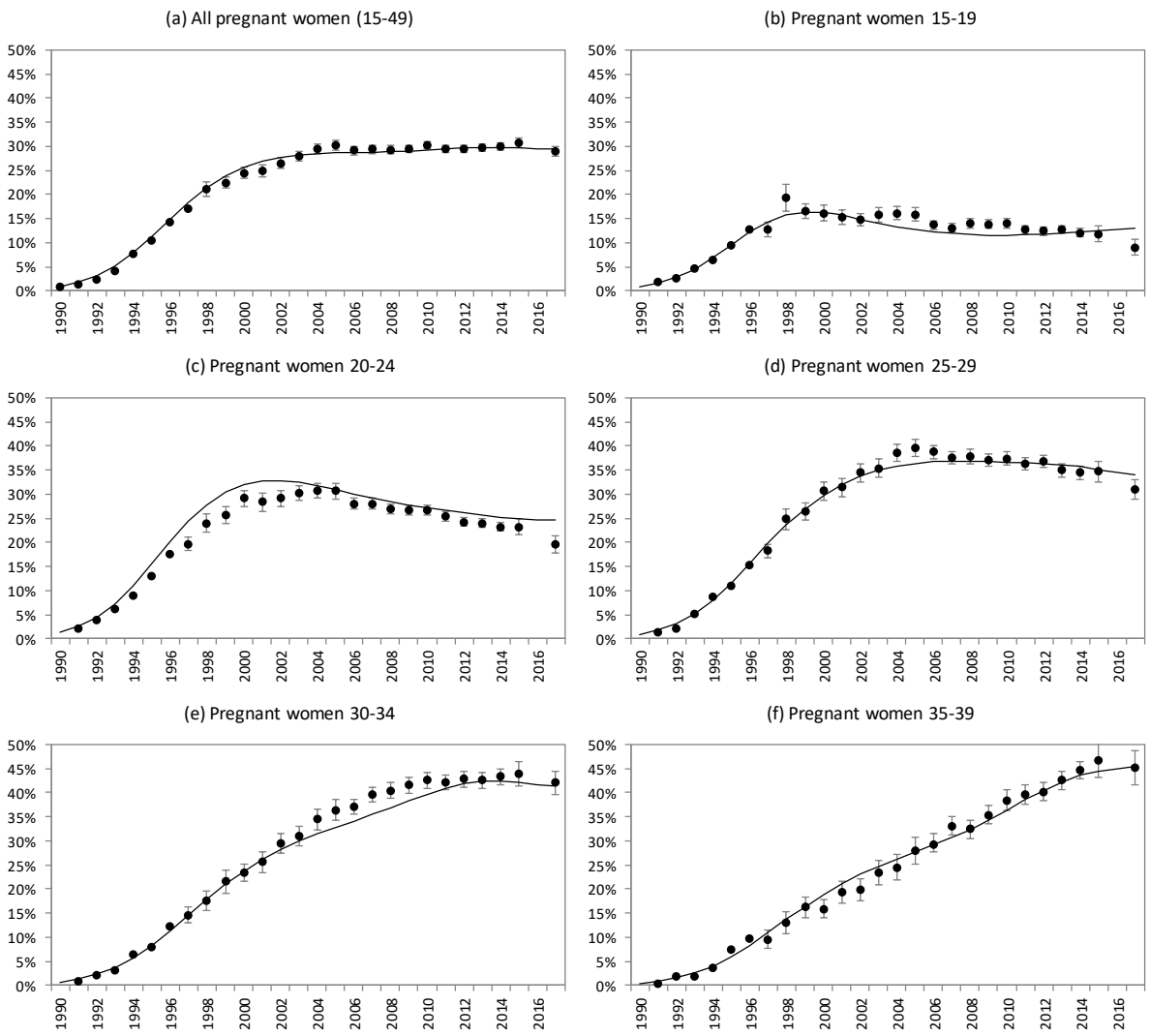

Figure S1: HIV prevalence levels in pregnant women attending public antenatal clinics
Dots represent HIV prevalence levels reported in surveys conducted from 1990-2015 and 2017 (the 1998 data were adjusted to correct an error in the provincial weights in that year). Solid lines represent the posterior mean model estimates of HIV prevalence in pregnant women, after adjusting for antenatal bias.

1.2 Modelling of intrauterine and intrapartum transmission

We define the following symbols:

$J_0(t)$ = number of births, in month t, to women who were HIV-seronegative at their first antenatal visit;

$J_1(s, t)$ = number of births, in month t, to women who were HIV-seropositive but untreated at their first antenatal visit, in CD4 stage s;

$J_2(t)$ = number of births, in month t, to women who were receiving ART at their first antenatal visit;

$V(t)$ = proportion of pregnant women presenting for their first antenatal visit in month t who receive HIV testing at their first visit;

Se = sensitivity of HIV screening algorithm used in pregnant women (excluding women in the window period from the denominator);

T_1 = average gestation (in weeks) at which women first seek antenatal care;

T_2 = average gestation (in weeks) at which women are offered rescreening;
T_3 = average gestation (in weeks) at which women deliver;
$Z(t)$ = proportion of pregnant women to whom the offer of HIV screening is repeated in late pregnancy, in month t;
v_0 = proportion of pregnant women who agree to retesting in late pregnancy if they previously tested negative;
v_1 = proportion of pregnant women who agree to testing in late pregnancy if they refused testing (or were not offered testing) at their first antenatal visit.

The assumed values of the time-varying parameters, $V(t)$ and $Z(t)$, are shown in Table S1. The value of Se has been set at 0.975, reflecting the variable performance of rapid testing algorithms in South Africa [19-22]. The values of T_1 and T_3 have been set at 23 weeks and 39 weeks respectively, and the assumed average duration at rescreening (T_2) is 34 weeks. The proportion of women testing negative who agree to retesting (v_0) has been set at 0.80 [23], and the proportion v_1 has been arbitrarily set to 0.5.

Table S1: Time-dependent PMTCT and ART parameters

Year	Antenatal testing ($V(t)$)		Retesting offer ($Z(t)$)		Linkage to ART in pregnancy ($\alpha_1(t)$)		Dual therapy ($D(t)$)		Children starting ART ($S(t)$)
	Rate	Sources	Rate	Sources	Rate	Sources	Rate	Sources	
Pre-1999	0.0%		0%		0.0%		0.0%		0
1999-00	0.9%		0%		0.0%		0.0%		0
2000-01	2.9%		0%		1.9%		0.0%		589
2001-02	7.5%	[24]	0%		2.5%		0.0%		715
2002-03	15.6%	[25, 26]	0%		2.5%		0.0%		869
2003-04	31.3%		0%		3.6%		0.8%		2 196
2004-05	42.0%	[27]	0%		12.6%		4.0%	[28]	7 035
2005-06	54.5%	[29]	0%		22.6%	[30]‡	6.4%		10 717
2006-07	72.2%	[31]	0%		29.1%		6.8%		17 456
2007-08	84.0%	[32]	5%	[33]	35.5%	[34]‡	18.7%	[35]	22 352
2008-09	89.0%	[36]	15%		44.5%	[37]‡	53.2%		29 495
2009-10	93.0%		25%	[38]	55.0%		85.4%		40 961
2010-11	97.0%	[39]	35%	[38]	64.1%	[40]	90.0%	[41]	49 582
2011-12	98.0%	[42]	45%	[38]	75.4%	[40]	90.0%		33 399
2012-13	98.0%		55%		75.9%		75.0%		30 169
2013-14	98.0%		65%		76.3%	[43]	45.0%		19 167
2014-15	98.0%		75%		91.2%	[43]	0.0%		20 131
2015-16	98.0%		85%		93.0%	[43]	0.0%		18 171
2016-17	98.0%		95%		95.0%	[44]	0.0%		16 849
2017-18	98.0%*		95%†		95.0%†		0.0%		14 062

* Rates are assumed to remain constant at 98% after 2017. † Rates are assumed to remain constant at 95% after 2017. ‡ Adjusted to take into account differences in access to ART between provinces.

To calculate the number of HIV-positive mothers in different risk categories, we define the following symbols:
$J_{1,1}(t)$ = number of births, in month t, to untreated women who tested HIV-positive at their first antenatal visit;
$J_{1,i,j}(t)$ = number of births, in month t, to untreated women who were HIV-positive at their first antenatal visit, with testing status i at their first antenatal visit and testing status j in later pregnancy (testing status 0 means untested, status 1 means tested positive, and status 2 means tested negative).

$$J_{1,1}(t) = J_1(t) \times V(t) \times Se$$

$$J_{1,0,0}(t) = J_1(t)(1-V(t))(1-Z(t)\nu_1)$$
$$J_{1,0,1}(t) = J_1(t)(1-V(t))Z(t)\nu_1 Se$$
$$J_{1,0,2}(t) = J_1(t)(1-V(t))Z(t)\nu_1(1-Se)$$
$$J_{1,2,0}(t) = J_1(t)V(t)(1-Se)(1-Z(t)\nu_0)$$
$$J_{1,2,1}(t) = J_1(t)V(t)(1-Se)Z(t)\nu_0 Se$$
$$J_{1,2,2}(t) = J_1(t)V(t)(1-Se)Z(t)\nu_0(1-Se)$$

In calculating births to women who are seronegative at their first antenatal visit, we further define the following symbols:

$J_{0,0}(t)$ = number of births, in month t, to women who were HIV-negative at their first antenatal visit and remained HIV-negative prior to delivery;

$J_{0,1,i}(t)$ = number of births, in month t, to women who were HIV-seronegative at their first antenatal visit but became infected prior to delivery, with their infection either identified in late pregnancy (i = 1) or not (i = 0);

$I(t)$ = annual HIV incidence rate in pregnant women and recently pregnant women, in month t.

$$J_{0,0}(t) = J_0(t)(1-I(t)(T_3-T_1+4)/52)$$
$$J_{0,1,1}(t) = J_0(t)(I(t)(T_2-T_1)/52)Z(t)\nu_0 Se$$
$$J_{0,1,0}(t) = J_0(t)[(I(t)(T_2-T_1)/52)(1-Z(t)\nu_0 Se)+(I(t)(T_3-T_2+4)/52)]$$

The 4 in the first and third equations is the assumed window period on standard antibody tests [45]. The period of 4 weeks is added to reflect the fact that some women who are HIV-seronegative at their first antenatal visit will in fact be in the window period.

The calculation of the HIV incidence rate in pregnant and recently-pregnant women, $I(t)$, is based on the age-specific HIV incidence rates and fertility rates by age, as well as levels of PrEP uptake in pregnancy. In the absence of PrEP, the formula for calculating $I(t)$ is

$$I(t) = 1-\exp\left(-\frac{\sum_{x=15}^{49} N_1(x,t)f(x,t)/\omega}{\sum_{x=15}^{49} N_0(x,t)f(x,t)}\right)$$

where $N_1(x, t)$ is the number of acutely infected women aged x at time t, $N_0(x, t)$ is the number of HIV-negative women, $f(x, t)$ is the fertility rate in sexually experienced HIV-negative and acutely-infected women aged x at time t, and ω is the average duration of acute HIV infection in pregnant women (in years). The implicit assumption that is made here is that HIV incidence and fertility are independent of one another, conditional upon age. Although there is some evidence to suggest that pregnant women are more susceptible to HIV acquisition per sex act [46, 47], pregnant women also differ substantially from non-pregnant women in their behaviours and relationship characteristics, and the net effect of these confounding biological and behavioural factors may be that overall HIV incidence rates are roughly similar in pregnant and non-pregnant women [48-50].

In order to calculate rates of mother-to-child transmission at birth, in the universal treatment era, we define the following symbols:

π_i = probability of mother-to-child transmission at or before birth, in the absence of ARV prophylaxis, if the mother was HIV-seropositive at her first antenatal visit and in CD4 stage i (0.134 for CD4 >500, 0.152 for CD4 350-500, 0.258 for CD4 200-349 and 0.350 for CD4 <200 [51]);

$\chi_i(t)$ = proportion of pregnant HIV-positive women in CD4 stage i, out of those who were not on ART at conception at time t (calculated from the $J_1(i, t)$ values);

π^* = probability of mother-to-child transmission at or before birth, in the absence of ARV prophylaxis, if the mother was HIV-seronegative at her first antenatal visit but was HIV-positive at delivery (0.254);

$\pi_i^H(t)$ = probability of mother-to-child transmission at or before birth, if the mother initiated highly active antiretroviral therapy (HAART) after conception in HIV stage i (this changes with respect to time t, depending on the average duration of HAART prior to delivery, as described elsewhere [52]);

π_0 = probability of mother-to-child transmission at or before birth, if the mother initiated HAART before conception (0.003);

α_0 = proportion of diagnosed HIV-positive pregnant women, not initiating long-term HAART, who receive single-dose nevirapine (0.71);

$\alpha_1(t)$ = proportion of untreated ART-eligible women, diagnosed as HIV-positive during pregnancy, who start HAART prior to delivery (Table S1);

ζ_0 = efficacy of single-dose nevirapine (sd NVP) in preventing mother-to-child transmission at birth (0.40).

We now define the following model outputs:

$Y_{0,i}(t)$ = number of uninfected children born in month t, with mothers in state i (0 = uninfected; 1 = infected and not aware of HIV status; 2 = infected and aware of HIV status but untreated; 3 = infected and receiving HAART);

$Y_{1,i}(t)$ = number of infected children born in month t, who were perinatally exposed to ARV prophylaxis (i = 1) or not exposed (i = 0).

These are calculated as follows:

$$Y_{0,0}(t) = J_{0,0}(t)$$

$$Y_{0,1}(t) = \left(J_{1,0,0}(t) + J_{1,0,2}(t) + J_{1,2,0}(t) + J_{1,2,2}(t)\right)\left(1 - \sum_{i=1}^{4} \chi_i(t)\pi_i\right) + J_{0,1,0}(t)(1-\pi^*)$$

$$\begin{aligned} Y_{0,2}(t) = {} & \left(J_{1,1}(t) + J_{1,0,1}(t) + J_{1,2,1}(t) + J_{0,1,1}(t)\right)(1-\alpha_1(t)) \\ & - \left(\left(J_{1,1}(t) + J_{1,0,1}(t) + J_{1,2,1}(t)\right)\sum_{i=1}^{4} \chi_i(t)\pi_i + J_{0,1,1}(t)\pi^*\right) \\ & \times (1-\alpha_0\zeta_0)(1-\alpha_1(t)) \end{aligned}$$

$$\begin{aligned} Y_{0,3}(t) = {} & \left(J_{1,1}(t) + J_{1,0,1}(t) + J_{1,2,1}(t)\right)\sum_{i=1}^{4} \chi_i\alpha_1(t)\left(1-\pi_i^H(t)\right) + J_2(t)(1-\pi_0) \\ & + J_{0,1,1}(t)\alpha_1(t)\left(1-\pi_1^H(0)\right) \end{aligned}$$

$$\begin{aligned} Y_{1,0}(t) = {} & \left(J_{1,0,0}(t) + J_{1,0,2}(t) + J_{1,2,0}(t) + J_{1,2,2}(t)\right)\sum_{i=1}^{4} \chi_i(t)\pi_i + J_{0,1,0}(t)\pi^*(1-\alpha_1(t)) \\ & + \left(\left(J_{1,1}(t) + J_{1,0,1}(t) + J_{1,2,1}(t)\right)\sum_{i=1}^{4} \chi_i(t)\pi_i + J_{0,1,1}(t)\pi^*\right)(1-\alpha_0)(1-\alpha_1(t)) \end{aligned}$$

$$Y_{1,1}(t) = \left(J_{1,1}(t) + J_{1,0,1}(t) + J_{1,2,1}(t)\right)\sum_{i=1}^{4} \chi_i(t)\alpha_1(t)\pi_i^H(t) + J_{0,1,1}(t)\alpha_1(t)\pi_1^H(0)$$
$$+\left(\left(J_{1,1}(t) + J_{1,0,1}(t) + J_{1,2,1}(t)\right)\sum_{i=1}^{4} \chi_i(t)\pi_i + J_{0,1,1}(t)\pi^*\right)\left(1-\alpha_1(t)\right)$$
$$\times\alpha_0\left(1-\zeta_0\right) + J_2(t)\pi_0$$

The total number of intrauterine and intrapartum infections is then calculated as $Y_{1,0}(t) + Y_{1,1}(t)$.

The above calculations, which apply in the context of universal maternal ART eligibility, are slightly different in the period prior to 2014. Firstly, in the period before 2014, there was provision of AZT to mothers who were not yet eligible for HAART. A fraction $D(t)$ of the women receiving sd NVP 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 $\alpha_0 + (1 - \alpha_0) \times D(t) \times 0.79$, where 0.79 is the assumed constant of proportionality and α_0 is the previously-defined proportion of women who receive sd NVP (Kate Kerber, personal communication, based on national survey data [41]). The $D(t)$ parameters are assumed to increase from zero in 2002/3 up to 90% in the 2010-2012 period, as shown in Table S1. 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.

The second difference, in the period before 2014, is that the proportion of ART-eligible women who start ART ($\alpha_1(t)$) is multiplied by the CD4 stratum-specific proportions of women who are eligible to start ART in pregnancy. These ART-eligible proportions are shown in Table 3.3 of the Thembisa 4.2 report [1].

Table S2 summarizes the key mother-to-child transmission parameters.

Table S2: 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 [51]
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%	-	[53-58] and previous calibration [59]
% of HIV-diagnosed women who receive single-dose nevirapine, if not starting ART	71.0%	-	Kate Kerber (pers. comm.), based on national survey data [41]
% reduction in perinatal MTCT if mother receives single-dose nevirapine only	40.0%	-	[60]
% reduction in perinatal MTCT if mother receives short-course zidovudine only	65.0%	-	[61]
% reduction in perinatal MTCT if mother receives single-dose nevirapine + short-course zidovudine	85.8%	-	[62, 63] and previous calibration [59]
Transmission rate at/before birth, from women on long-term ART pre-conception	0.3%	-	[64-69]
Probability of MTCT from chronically-infected mothers, per year of mixed feeding	14.0%	2.5%	Meta-analysis [70], 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 [71]
Ratio of postnatal transmission risk per month of EBF to postnatal transmission risk per month of mixed feeding	0.50	0.15	[72, 73]
% reduction in monthly postnatal MTCT risk if child receives extended nevirapine prophylaxis	60.0%	-	[74-76]
% 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 [70]
ART initiated during pregnancy	78%	-	[77-86]
ART initiated before conception	96%	-	[66, 69, 87]

* 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 section 2.1 for more detail). EBF = exclusive breastfeeding; MTCT = mother-to-child transmission.

1.3 Modelling of postnatal transmission

To model postnatal transmission of HIV, we define the following variables:

$N^0_{g,i,v}(a,t)$ = number of uninfected children of sex g (0 = male; 1 = female), aged exactly a months at the start of month t, whose mothers are in HIV stage i (0 = uninfected; 1 = acutely infected with HIV; 2 = chronically infected and not aware of HIV status; 3 = chronically infected and aware of HIV status but untreated; 4 = infected and receiving HAART), practising feeding of type v (0 = no breastfeeding; 1 = mixed feeding; 2 = exclusive breastfeeding);

$E_{v,i}(t)$ = proportion of women of HIV status i (0 = uninfected or unaware of HIV status; 1 = known to be HIV-positive) who choose feeding of type v after delivery in month t;

SR_g = proportion of births that are of sex g;

The proportion of births that are male (SR_0) is set to 0.5039. The proportion of HIV-negative and undiagnosed women who choose to practise mixed feeding from birth ($E_{1,0}$) is set to 0.867, and the exclusive breastfeeding (EBF) proportion is set to zero ($E_{2,0} = 0$), based on the results of the 1998 Demographic and Health Survey (DHS) [88], which was conducted prior to the

introduction of the South African PMTCT programme, and which showed minimal EBF. The remaining women are assumed to use replacement feeding from birth ($E_{0,0}$ = 0.133). The fractions of HIV-diagnosed mothers who practise mixed or exclusive breastfeeding are assumed to have changed over time, in line with changes in recommended infant feeding practices [89]. In the years up to 2010, 56% of HIV-diagnosed women are assumed to have chosen replacement feeding from birth ($E_{0,1}$ = 0.56), 13.6% are assumed to have practised mixed feeding from birth, and the remaining 30.4% are assumed to have initiated EBF. In 2013 and subsequent years, following the phasing out of the free provision of formula milk to HIV-positive mothers, 20% of HIV-diagnosed mothers are assumed to choose replacement feeding, 24.8% choose mixed feeding and the remaining 55.2% choose exclusive breastfeeding.

To calculate the initial proportion of HIV-negative births in the different states, the following equations are applied:

$$N^0_{g,0,v}(0,t) = Y_{0,0}(t-1)SR_g E_{v,0}(t)$$
$$N^0_{g,1,v}(0,t) = 0$$
$$N^0_{g,2,v}(0,t) = Y_{0,1}(t-1)SR_g E_{v,0}(t)$$
$$N^0_{g,3,v}(0,t) = Y_{0,2}(t-1)SR_g E_{v,1}(t)$$
$$N^0_{g,4,v}(0,t) = Y_{0,3}(t-1)SR_g E_{v,1}(t)$$

By setting $N^0_{g,1,v}(0,t) = 0$, we are implicitly assuming that all those women who acquired HIV during the late phase of pregnancy progress to the 'chronic' stage of infection shortly after delivery and are no longer in the highly infectious acute phase of infection. It could be argued that it is more correct to include some fraction of $J_{0,1,0}(t)$ and $J_{0,1,1}(t)$ in $N^0_{g,1,v}(0,t)$. However, since the average interval in which women can acquire HIV during late pregnancy without being seropositive at their first antenatal visit is 20 weeks ($T_3 - T_1 + 4$), these recently infected women will have been infected for an average of 10 weeks at the time of delivery. In the model it is assumed that the acute stage of high infectiousness lasts for three months on average, which is close to the average of 10 weeks duration of infectiousness at delivery. It is therefore reasonable to assume that on average the recently infected women cease to be highly infectious shortly after delivery. In reality, some women will progress from the acute phase to the chronic phase well before delivery, and will have a relatively low risk of transmitting the virus to their infants, while others will only progress to the chronic stage some weeks after delivery, and will be at a very high risk of transmitting the virus while breastfeeding. Our approach is therefore reasonable for an 'average' woman who seroconverts in late pregnancy, but might not capture the heterogeneity in transmission risks for women seroconverting at different durations of pregnancy.

The following symbols are defined to represent changes in feeding practices in relation to infant age:

$\delta_{v,i}(a)$ = proportion of women of HIV status i (0 = uninfected or unaware of HIV status; 1 = known to be HIV-positive) practising feeding of type v to child of age a, who discontinue feeding of type v in the next month;

$w(a)$ = proportion of women discontinuing EBF between child ages a and a + 1 (in months) who practise abrupt weaning;

$B_{v,i}(a)$ = proportion of women of HIV status i choosing feeding type v at birth, who are still practising feeding type v when their child is age a;

$m_{v,i}$ = median duration of feeding type v in women of HIV status i;
$\phi_{v,i}$ = Weibull shape parameter to determine rate of stopping feeding type v in women of HIV status i.

Breastfeeding durations are assumed to be Weibull-distributed. For women who are HIV-negative or HIV-positive but undiagnosed ($i = 0$), the median duration of mixed feeding ($m_{1,0}$) is assumed to be 18 months, and the Weibull shape parameter ($\phi_{1,0}$) is set to 2, based on data collected in the 1998 DHS [88]. The proportion $B_{v,i}(a)$ is calculated as

$$B_{v,i}(a) = 0.5^{\left(\left(a/m_{v,i}\right)^{\phi_{v,i}}\right)}$$

As noted previously, the 1998 DHS data show minimal EBF prior to the introduction of PMTCT programmes in South Africa, and it is therefore assumed that all breastfeeding by HIV-negative and undiagnosed HIV-positive mothers is mixed feeding. This is consistent with other studies that have shown the practice of EBF in South Africa to be uncommon when compared with feeding practices in other African countries [90], and more recent evidence confirms that HIV-negative South African women tend to practise EBF only for short durations [90-92]. There are therefore no parameters specified for $m_{2,0}$ and $\phi_{2,0}$.

In women who are diagnosed HIV-positive ($i = 1$) and choose to practise mixed feeding ($v = 1$), the time spent breastfeeding is assumed to be exponentially distributed (i.e. $\phi_{v,1} = 1$), so that the proportion $B_{v,i}(a)$ is simply calculated as

$$B_{1,1}(a) = 0.5^{a/m_{1,1}}.$$

In the case of HIV-diagnosed women who initially practise EBF ($v = 2$), the duration of EBF is assumed to be subject to a maximum of 6 months, so that

$$B_{2,1}(a) = \begin{cases} 0.5^{a/m_{2,1}} & \text{for } a < 6 \\ 0 & \text{for a} \geq 6 \end{cases}$$

The median durations of mixed feeding and EBF have been set at 7 months and 2 months respectively, based on studies of feeding practices in South African women who are diagnosed HIV-positive [93-95]. It is further assumed that 30% of women who stop EBF stop breastfeeding completely ($w(a) = 0.3$ for all a) and the remainder continue to breastfeed but introduce other liquids and solids (for the same median duration of 7 months as women who practise mixed feeding from birth).

The rate at which women discontinue feeding strategy v between infant ages a and $a + 1$ is

$$\delta_{v,i}(a) = 1 - B_{v,i}(a+1)/B_{v,i}(a).$$

Using these formulas, we calculate the number of HIV-negative children who are being breastfed by HIV-positive mothers in each of four states (acutely infected, chronically infected and not aware of HIV status, aware of HIV status but not on ART and on ART), with these calculations being performed separately for mothers who practise exclusive and mixed breastfeeding. The numbers of acutely-infected breastfeeding women are calculated by

applying the incidence rate, $I(t)$, to the number of HIV-negative breastfeeding women at each infant age, and then assuming that the acutely-infected women transition to the 'chronically infected and not aware of HIV status' state after an average of 3 months. In the period up to 2015, there is assumed to be no maternal HIV testing at immunization clinics, but in 2016 and all subsequent years, it is assumed that 90% of mothers attending 6-week immunization clinics get tested, in line with revised HIV testing policies [96, 97]. If breastfeeding mothers who were in the 'chronically infected and not aware of HIV status' state test positive at 6 weeks, it is assumed that they switch to the breastfeeding distribution that would be expected in HIV-diagnosed mothers. No other movements between the four maternal states are modelled. This might be considered conservative, as it is possible that some of the breastfeeding mothers who were not on ART at delivery might initiate ART in the postpartum period. However, it is also possible that the model may be overly optimistic, as it does not consider the possibility that breastfeeding mothers on ART may discontinue ART while breastfeeding.

The assumptions about the monthly HIV transmission probabilities through breastfeeding, and the data sources on which they are based, are summarized in Table S2. Where annual rates are specified, these are converted into monthly rates. As the model does not have separate states for treated breastfeeding mothers who initiated ART before and during pregnancy, the average reduction in the monthly postnatal transmission risk is calculated as a weighted average of the 78% and 96% specified in Table S2. For example, if the fraction of treated breastfeeding mothers who started ART before pregnancy is 60% in a given year, and the simulated probability of postnatal transmission is 0.10 per year of mixed feeding by an untreated mother, then the monthly probability that a treated HIV-positive mother transmits HIV during mixed breastfeeding is calculated as $(1 – (1 – 0.1)^{1/12}) \times (1 – 0.6 \times 0.96 – 0.4 \times 0.78) = 0.00098$.

The model also does not have separate states to represent infants who receive extended nevirapine prophylaxis while being breastfed, which was part of PMTCT policy over the 2011-2013 period (it is assumed to have been discontinued after the adoption of WHO option B in 2013). It is assumed that over the 2011-2013 period, 80% of HIV-diagnosed breastfeeding mothers who were not on ART administered extended nevirapine prophylaxis to their infants for the duration of breastfeeding (no data are available to support the 80% uptake assumption), and that this reduced the monthly postnatal transmission risk by 60% (Table S2). For example, if the assumed annual probability of transmission through mixed feeding is 0.10 (for an untreated HIV-positive mother who is not in the acute phase of HIV infection, and for an infant who is not receiving nevirapine), then in 2011 the average monthly probability of transmission from an HIV-diagnosed, untreated breastfeeding mother is $(1 – (1 – 0.1)^{1/12}) \times (1 – 0.8 \times 0.6) = 0.00455$.

1.4 Modelling of untreated paediatric HIV disease progression

The structure of the paediatric HIV survival model is illustrated in Figure S2. As explained in the main text, 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 [98]). 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 allows for different rates of disease progression in perinatally-infected children who are PMTCT-exposed and -

unexposed, the default assumption is that the rate of progression from early to late disease in perinatally-infected children is independent of their PMTCT exposure.

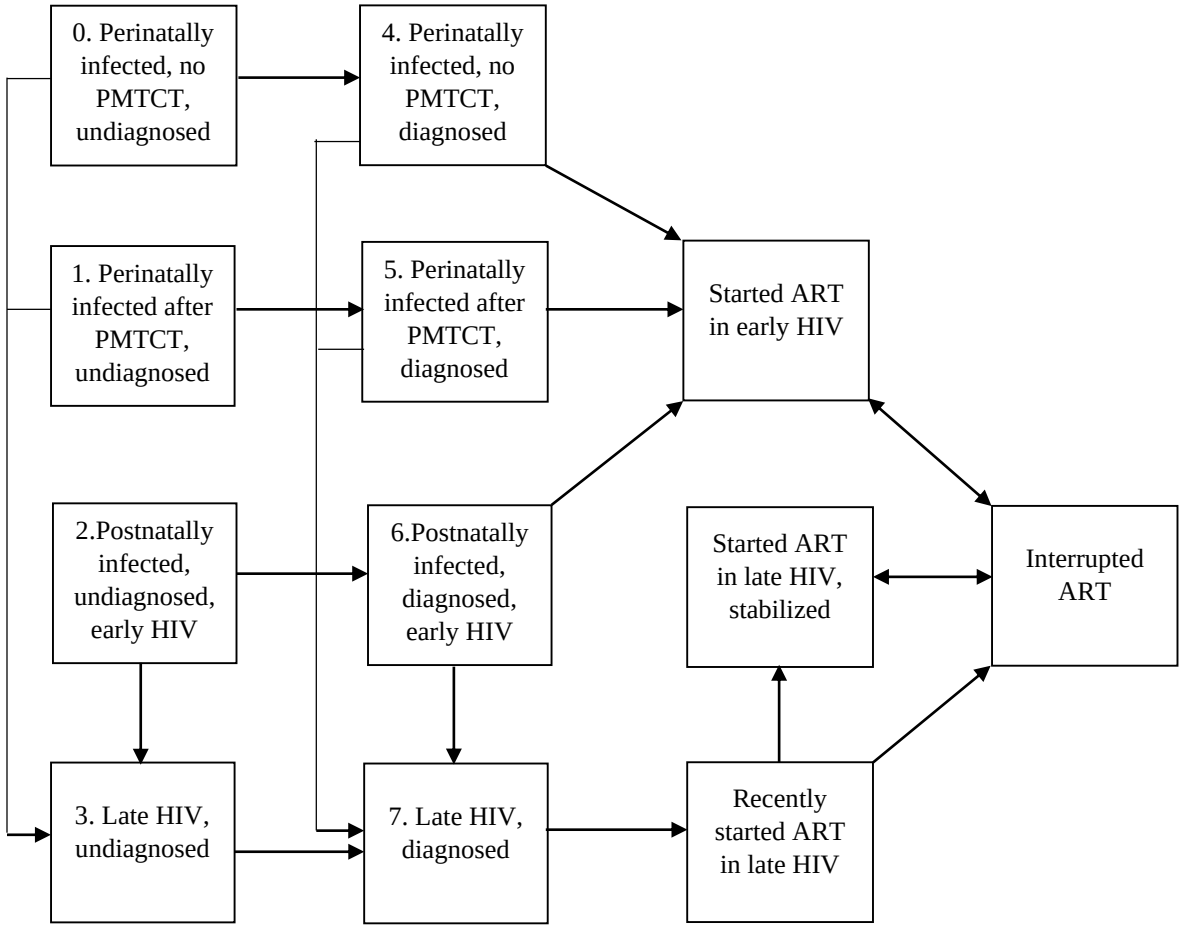

Figure S2: Model structure

All states are defined separately for males and females, for each age (in months) up to 10 years. After 10 years, children are moved into an 'adolescent and adult' staging system. Non-HIV mortality is allowed for in all states, and HIV-related mortality is allowed for in all states except the 'early HIV' untreated states (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

$$\eta(x) = G_p + H_p c^x,$$

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 $\theta G_p + H_p (\theta c)^x$, where θ is a constant scaling factor. This functional form was chosen to ensure that there is relatively less of a reduction in disease progression in postnatally infected infants soon after birth (when $x = 0$) than at older ages, in line with data showing poorer HIV survival in HIV-infected infants who acquire HIV soon after birth compared to those acquiring HIV at

older ages [99]. The assumed parameter values and the data sources on which they are based are summarized in Table S6.

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 [100, 101], 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

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

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 S6.

1.5 Modelling of HIV testing and ART initiation

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

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

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 S2, 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 S3. Rates of PCR testing at 6 weeks are based on public sector statistics [40, 102], adjusted to reflect under-count due to late immunization [103, 104] and over-count due to non-return of test results to caregivers [105-107]. After birth testing was introduced in 2015, birth screening coverage increased to 68.7% in 2015-16 [43, 108], and to around 90% thereafter [109]. 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 [108, 110]. For example, Kalk *et al* [108] 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 [111], assuming that all infants who are tested for HIV would at least have received NVP prophylaxis postnatally [112]. 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 [113], ART eligibility for infants in early disease only became official policy in 2010 [114], with some earlier provision following the 2008 WHO guideline revision [115]. The fraction of eligible, diagnosed infants who link to care and start ART (l) has been fixed at 0.80, based on a 71% rate of ART initiation in HIV-diagnosed infants in the Western Cape in 2010 [107], an 88% rate of ART initiation in a small sample of 26 HIV-diagnosed infants in Johannesburg [116] and an 86% rate in another small sample of 21 HIV-diagnosed infants in Cape Town [110].

Table S3: 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

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

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 S3); $\tau_s(x, t)$ 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 [117], 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 multiple of those in sexually experienced girls aged 15, as determined in the adult component of the model. The multiple is φ_1 in the period up to 2005, φ_2 in the period following 2010, and the multiple is linearly interpolated between the φ_1 and φ_2 values over the 2006-2009 period. This change in multiple over time is allowed for in the model as it is hypothesized that there may have been substantial differences in testing patterns following the introduction of national HIV testing campaigns in South Africa in 2010; several barriers to HIV testing in children have remained [118], despite the rapid scale-up of testing in adults. Prior distributions have been specified to represent the uncertainty around the φ_1 and φ_2 ratios (see Table S6). 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 Table S6). 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 [35], 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

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

where $k(t)$ is the rate of HIV testing in sexually-experienced non-pregnant girls aged 15, $\varphi(t)$ 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 2) or because the child receives HIV screening at the standard birth/2 month screening (equation 1).

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 the same as those assumed for newly diagnosed adults with opportunistic infections (see Appendix B of the Thembisa 4.2 report [1]). If children do not initiate ART at the time of HIV diagnosis, the model allows for later ART initiation, provided they are eligible. 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:

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

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 S2); $\rho(t)$ 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 value of 0.5 has been assigned. By rearranging the terms in the above equation, $\rho(t)$ 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 S1 for each year up to mid-2018 (monthly numbers are calculated by dividing these annual totals by 12). These annual numbers starting ART are calculated using a B-spline model, fitted to reported total numbers of children on ART in the public and private sectors (for details of the likelihood function, see section 2.2.4).

1.6 Modelling of HIV survival after ART initiation

1.6.1 Mortality after ART initiation in late HIV disease

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

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

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 described more fully in section 1.6.3.

1.6.2 Mortality after ART initiation in early HIV disease

The AIDS mortality rate in children who start ART in early disease, $\psi(x)$ at age x, 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 are estimated from South African ART programmes participating in the International epidemiology Databases to Evaluate AIDS (IeDEA) collaboration [119]. These parameters have been set to 0.06 and 0.2 respectively, based on attempts to fit the model to IeDEA data.

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), and were in the 'early' phase of HIV disease at the time of ART initiation. To be consistent with the model definition in section 1.4, children were considered to be in the early phase of HIV disease if they did not meet any of the criteria for ART eligibility in the WHO 2006 paediatric ART guidelines [98], 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 were not ART-eligible at the time they started ART, based on immunological criteria, means 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 [120]), 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 S4 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 S4: Baseline characteristics of children starting ART in early disease (n = 2828)

	%	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 S5). 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 year 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), and $\mu_0(x)$ is the non-HIV mortality rate at age x. 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 $\beta = 0.06$ and $P = 0.2$, this model produced estimates of mortality roughly consistent with the IeDEA data (Table S5). 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 S5: 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

1.6.3 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 [121]).

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

$$\mu(x) = a\left(b^{x}\right), \qquad (3)$$

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 (3) 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 [100]. The resulting model fits to the data are shown in Figure S3. 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.

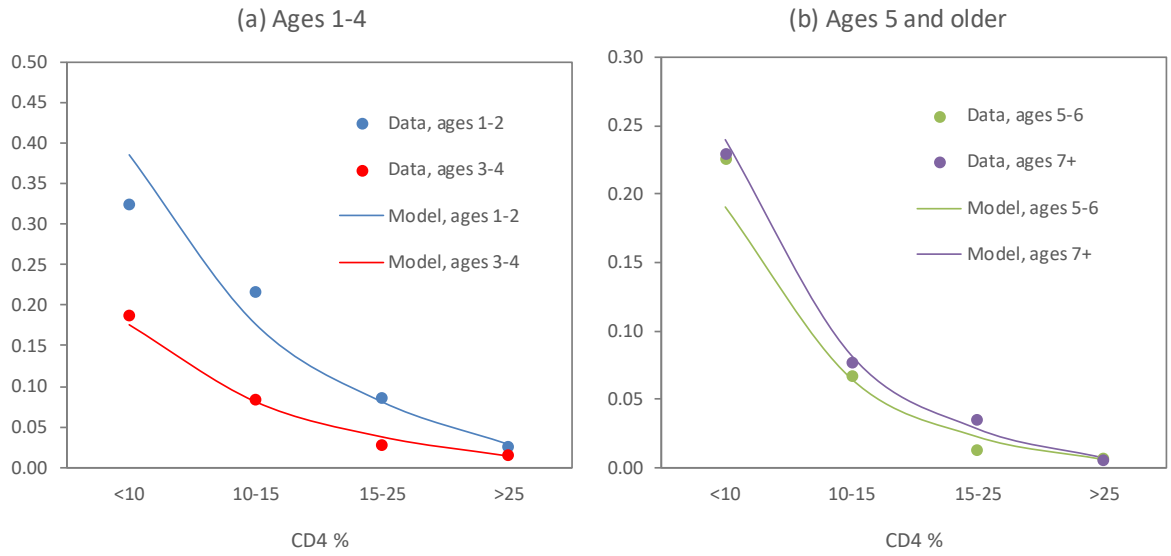

Figure S3: Effect of CD4 count on mortality in the absence of ART
For the purpose of fitting the models to the data points, the average mortality rates reported over different ranges have been taken to apply at the midpoints of the relevant ranges. Mortality data from the >15% CD4 range have been included 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

$$\int_0^{0.15} ke^{\lambda x} dx = 1,$$

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 [100], we estimate that roughly 55% of all children who have CD4 percentages <15% have a CD4 <10%. From this it follows that

$$0.55 = \frac{e^{0.1\lambda} - 1}{e^{0.15\lambda} - 1},$$

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

$$q_0 = \int_0^{0.15} f(x) a b^x dx$$
$$= \frac{\lambda a\left(\left(e^{\lambda} b\right)^{0.15} - 1\right)}{\left(\lambda + \ln(b)\right)\left(e^{0.15\lambda} - 1\right)}.$$

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 1.4, 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 $q_{\min}$:

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

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

$$A_t = \frac{q_{\min}}{q_0} + \left(1 - \frac{q_{\min}}{q_0}\right)\exp(-mr_{t-}), \qquad (4)$$

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

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

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 [121].

The m parameter in equation (4) 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 1.6.1, 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

$$B_t = \frac{v_{\min}}{v_0} + \left(1 - \frac{v_{\min}}{v_0}\right)\exp(-mr_{t-}), \qquad (5)$$

where $B_t \equiv v_t / v_0$. Note that the *m* parameter is assumed to be the same as that in equation (4), 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 (4) and (5), 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

$$v(x) = z\left(h^x\right).$$

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 [119]. 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 percentage; 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

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

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 [121].

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 1.6.1). 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 [119]. 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 percentage. 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 assumed previously:

$$w_t = w_{\min} + \left(w_0 - w_{\min}\right)\exp\left(-mr_{t-}\right),$$

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

$$C_t = \frac{w_{\min}}{w_0} + \left(1 - \frac{w_{\min}}{w_0}\right)\exp\left(-mr_{t-}\right). \quad (6)$$

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:

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

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 [121].

1.7 Modelling of ART interruption

Although the model allows for children to interrupt ART and resume ART (Figure S2), 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: an ART interruption rate of 0.25 per annum and a rate of ART resumption (after an interruption) of 0.90 per annum. (See Appendix G of the Thembisa report [1] for a full description of these parameters.) 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.

1.8 Modelling of sexually-acquired HIV in adolescents

Adolescents are divided into two broad risk groups: ‘high risk’ adolescents are defined as those with a propensity for concurrent relationships and/or commercial sex, and ‘low risk’ adolescents are defined as those with no propensity for concurrent partnerships or commercial sex. The high risk group is assumed to comprise 35% of the male adolescent population and 25% of the female adolescent population. Times to sexual debut in high-risk youth are assumed to follow a log-logistic distribution; the median age of sexual debut, for high-risk youth, is set to 17.5 and 16.5 years in males and females respectively. The age-specific rates of sexual debut among low-risk youth are assumed to be 0.58 times those in high-risk youth [122-127]. 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 [128-130], as demonstrated in Figure S4. The figure shows that there is almost no data on sexual experience below age 15, and thus the assumptions about sexual debut prior to age 15 are driven by the log-logistic extrapolation to the younger ages, rather than real data. Estimates of sexual activity in the 10-14 age group therefore need to be treated with some caution.

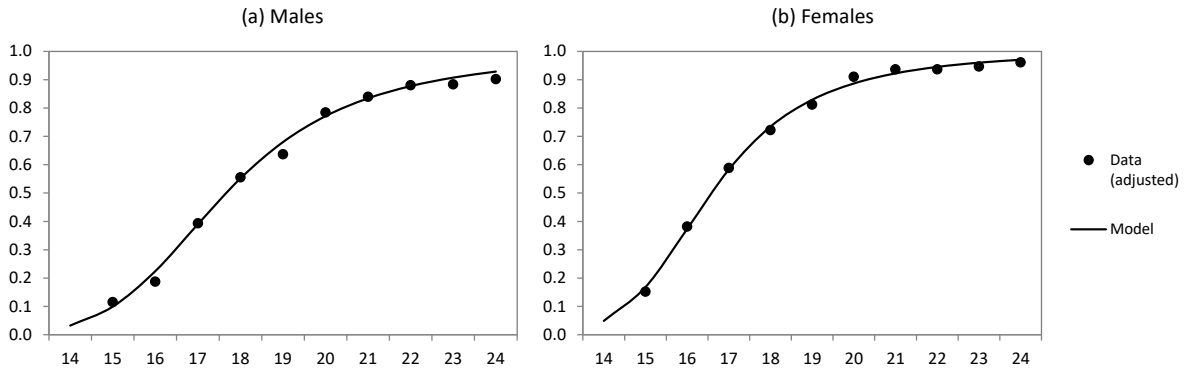

Figure S4: Proportion of youth who are sexually experienced, by age and sex
Data in panel (b) have been adjusted to reflect probable under-reporting of sexual experience by young women (assuming that the odds ratio relating true sexual experience to reported average sexual experience is 2 [131]).

Assumptions about sexual behaviour and sexual transmission of HIV are described in more detail in the Thembisa 4.2 report [1]. Briefly, sexually-experienced individuals form non-marital relationships at a rate that depends on their age, sex and risk group (the model also simulates marital/cohabiting relationships, but these are not relevant to the population below age 15). Assumptions are made about patterns of sexual mixing, by age and risk group, based on data on partner age differences and based on calibration of the model to HIV prevalence trends by age and sex. Sexual acquisition of HIV is modelled based on assumed probabilities of transmission per act of unprotected sex, as well as assumptions about numbers of sex acts per non-marital relationship and rates of condom use. Rates of condom use vary by age, sex and knowledge of HIV status, and are also assumed to have increased over time in response to HIV communication programmes and condom distribution. HIV transmission probabilities per unprotected sex act are assumed to depend on age, sex, sex of partner (higher in men who have sex with men), HIV stage of partner, risk group and male circumcision status.

2. Model calibration

2.1 Prior distributions

Prior distributions have been specified for 17 of the mother-to-child transmission and paediatric HIV survival parameters. Table S6 summarizes the prior distributions. With the exception of the final parameter (defined in section 2.2.7), all of these parameters have been explained in previous sections.

Table S6: Prior distributions for parameters considered in calibration to paediatric HIV data

Parameter	Symbol	Prior distribution	Prior mean, std. deviation	Sources and section references
Relative rate of fertility in HIV-diagnosed untreated women	$B_2(2)$	Beta (6.8000, 2.914)	0.70, 0.14	[11-13], section 1.1
Probability of MTCT from chronically-infected mothers, per year of mixed feeding	-	Beta (26.83, 164.8)	0.14, 0.025	Meta-analysis [70], adjusted to reflect effect of excluding EBF (section 1.3)
Probability of MTCT from acutely- infected mothers, per month of mixed feeding	-	Beta (23.73, 124.6)	0.16, 0.03	Derived from meta-analysis [71], section 1.3
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	[72, 73], section 1.3
Children infected at/before birth				
Annual rate of progression to late disease in older children	G_p	Gamma (16.00, 40.00)	0.40, 0.10	$\theta G_p = 0.14$ is consistent with rates of progression observed by Charlebois *et al* [132] in children aged ≥1 year (section 1.4)
Excess annual rate of progression to late disease in neonates	H_p	Gamma (16.00, 8.00)	2.00, 0.50	[133, 134], section 1.4
Excess progression reduction factor, per year of age	c	Beta (9.20, 13.80)	0.40, 0.10	[133-136], section 1.4
Relative rate of progression to late disease if infected postnatally	θ	Beta (3.189, 5.922)	0.35, 0.15	[137-140], section 1.4
Children in late disease, untreated				
Annual rate of AIDS mortality in older children	G_m	Gamma (16.00, 133.3)	0.12, 0.03	[100, 101], section 1.4
Excess annual rate of AIDS mortality in neonates	H_m	Gamma (25.0, 7.14)	3.50, 0.70	Based on fitting model to mortality data from children diagnosed with HIV-related symptoms at different ages [101], section 1.4
Excess AIDS mortality reduction factor, per year of age	d	Beta (0.188, 3.563)	0.05, 0.10	
HIV testing rates				
Relative rate of testing in virgin adolescents: 2005	φ_1	Beta (3.00, 12.00)	0.20, 0.10	Unpublished data (Franziska Meinck), section 1.5
Relative rate of testing in virgin adolescents: 2010	φ_2	Beta (3.00, 12.00)	0.20, 0.10	Unpublished data (Franziska Meinck), section 1.5
Relative rate of testing in early disease (relative to late disease)	$1/Q$	Uniform (0.00, 1.00)	0.50, 0.29	Vague prior, section 1.5
Effect of ART on mortality				
Relative rate of mortality in 'stable' ART phase compared to untreated children with late disease	Φ_1	Beta (3.50, 31.50)	0.10, 0.05	Based on fitting model to mortality data from IeDEA-SA Collaboration [119], section 1.6.1
Reduction in mortality (on log scale) per unit increase in rate of ART initiation (in late disease) over last 3 years	m	Gamma (4.59, 0.612)	7.5, 3.5	Same as for adults [121], in absence of paediatric Data, section 1.6.3
Relative rate of recording of deaths in undiagnosed and HIV-negative children, relative to HIV-diagnosed	$e^{-\gamma}$	Uniform (0.00, 1.00)	0.50, 0.29	Vague prior, section 2.2.7

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

2.2 Likelihood definition

Table S7 summarizes the data sources that are used in the calibration of the model, as well as the data sources that are used for validation purpose. The likelihood is calculated as the product of likelihood values calculated separately for each calibration data source. The sections that follow explain the approach to calculating each component of the likelihood.

Table S7: Data sets used in model calibration and validation

Data source	Data type	Years	Disaggregation	Ref.
(a) Calibration data sets				
HSRC household surveys	HIV prevalence	2005, 2008, 2012, 2017	Age, sex	[141]
Routine antibody testing in children	Total tests	2015-2017	-	-
	HIV prevalence	2015-2017	-	-
Routine ART data (TIER)	Numbers on ART	2004-2018	-	-
Routine ART data (NHLS)	Age distribution	2011-2018	Age	[142]
Vital registration	Numbers of deaths	1997-2016	Age, sex	[143]
Child Healthcare Problem Identification Programme	% of deaths with HIV+ diagnosis	2010-2017*	Age	[144]
(b) Validation data sets				
Routine PCR testing in Infants (NHLS)	Perinatal transmission	2003-2014	-	[145]
National Burden of Disease	AIDS deaths	1997-2012	-	[146]

Calibration data sets are used in the Bayesian estimation procedure, in the calculation of the likelihood function. Posterior estimates generated in the Bayesian analysis are compared against the validation data sets to assess the plausibility of the calibration procedure. * Data are also available for 2005-2009, but are not used for calibration due to concerns about the low coverage of the reporting system prior to 2010. HSRC = Human Sciences Research Council. NHLS = National Health Laboratory Service. TIER = Three Interlinked Electronic Registers.

In general, Thembisa estimates of 'stock' variables (e.g. HIV prevalence and numbers of children on ART, which are defined at a point in time) are quoted at the mid-point of each year. However, in the case of 'flow' variables (e.g. new cases of mother-to-child transmission and AIDS deaths, which are defined over a period of time), Thembisa estimates relate to the period from mid-year to mid-year. For example, the number of paediatric AIDS deaths in 2017-18, referred to in the main text, is the model estimate of paediatric AIDS deaths between 31 July 2017 and 30 June 2018.

For calibration purposes, it is necessary to adjust some of the model estimates to correspond to the period to which the data relate. For example, the vital registration system reports numbers of recorded deaths in each calendar year, so in order to calibrate the model to the number of recorded deaths in 2016, we calculate the model estimate for the 2016 calendar year as the average for the 2015-16 and 2016-17 projection years. The same applies to the data from the Child Healthcare Problem Identification Programme, the routine PCR testing data and the National Burden of Disease estimates – all data sources relate to calendar years rather than mid-year to mid-year intervals. However, routine testing data relate to the Department of Health financial year, which runs from 1 April to 31 March. As this differs from the model projection years by only 3 months, we do not make any adjustments for calibration purposes.

2.2.1 HIV prevalence data from household surveys

The method used to calculate the likelihood in respect of the paediatric HIV prevalence data has been described previously [51], but has been updated to include data from the 2012 and 2017 national household prevalence surveys [147, 148]. As with adults, we have relied on data from the 2005, 2008, 2012 and 2017 household surveys conducted by the Human Sciences Research Council (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.

2.2.2 Number of routine antibody tests in children

Total numbers of HIV antibody tests performed in children are available for only three years (2015-2017). Data were supplied by the South African Department of Health (Tshepo Molapo, personal communication), and therefore relate only to the public sector. Relatively little antibody testing in children is believed to be conducted in the private sector, as the private sector contributes a small fraction of total tests in adults [149], and most of this is testing in workplace programmes and testing for life insurance purposes (neither of which is relevant to children). We assume that the total number of paediatric antibody tests in each year is 3% greater than the corresponding public sector total, to make allowance for the limited testing that occurs in private medical schemes. (The 3% is based on the estimated fraction of adult HIV antibody tests that are conducted in medical schemes [149].) 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.

We define $T'(t)$ as the model estimate of the total number of antibody tests in children in year t (calculated from the $\tau_s(x, t)$ terms defined in section 1.5), and $G'(t)$ as the corresponding empirical estimate (based on the adjusted totals in the previous paragraph). For the purpose of defining the likelihood, 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,

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

2.2.3 HIV prevalence from routine antibody testing in children

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

$$\rho(t) = Z(t)\big(JR(t) + \big(1 - R(t)\big)\big), \qquad (7)$$

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. The HIV prevalence among children tested for HIV in the private sector is unknown, but is generally believed to be lower than that in the public sector, and thus a uniform (0, 1) distribution is assigned to represent the uncertainty in J. This means $\mathrm{E}[J]$ is 0.50 and $\mathrm{Var}[J] = 0.29^2$. It follows from equation (7) that $\mathrm{Var}[\rho(t)] = \mathrm{Var}[J]\,(R(t)Z(t))^2$.

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:

$$\theta(t) = \rho(t)\big(Se + Sp - 1\big) + 1 - Sp\,,$$

where Se and Sp are the sensitivity and specificity respectively. We have previously shown [150] that the mean and variance of this expression are

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

and

$$\begin{aligned}\mathrm{Var}\big[\theta(t)\big] = {} & \mathrm{Var}\big[Se\big]\Big(\mathrm{Var}\big[\rho(t)\big] + \mathrm{E}\big[\rho(t)\big]^2\Big) \\ & + \mathrm{Var}\big[Sp\big]\Big(\mathrm{Var}\big[\rho(t)\big] + \big(1 - \mathrm{E}\big[\rho(t)\big]\big)^2\Big) \\ & + \big(\mathrm{E}\big[Se\big] + \mathrm{E}\big[Se\big] - 1\big)^2\,\mathrm{Var}\big[\rho(t)\big]\end{aligned}$$

respectively. We set the expected specificity to 0.997 and the standard deviation around the specificity to 0.002, based on a review of African studies of the sensitivity and specificity of rapid testing (see Table B2 of the Thembisa report [1]). 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 test sensitivity is strongly associated with a high fraction of HIV infections that are in the acute stage of HIV infection [151], and therefore it might reasonably be 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.

Note that $\mathrm{E}[\rho(t)] = Z(t)(\mathrm{E}[J]R(t) + (1 - R(t)))$. 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 S8 shows the calculations of these different quantities over the 2015-2017 period.

Table S8: 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%	$0.20\%^2$

For the purpose of defining the likelihood function in respect of the HIV prevalence data, suppose that $P(t)$ represents the model-based estimate of HIV prevalence in children 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. (Although it would be more correct to compare $P(t)$ to $\rho(t)$, we compare it to $\theta(t)$ in order to be consistent with the approach adopted in the calibration of the adult model.) 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 uncertainty regarding private sector HIV prevalence and test specificity). The $\varepsilon_\theta(t)$ term is assumed to follow a N(0, $\sigma_\theta^2(t)$) distribution, with $\sigma_\theta(t)$ being estimated as $\text{Var}[\theta(t)]^{0.5}/(\text{E}[\theta(t)]\ (1 - \text{E}[\theta(t)]))$, the delta approximation to the standard deviation on the logit scale. The likelihood function in respect of the HIV prevalence data is

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

2.2.4 Total numbers of children on ART

The annual number of children starting ART is estimated separately for each province, based on fitting B-splines to reported numbers of children on ART at different time points [152]. Provincial totals are then aggregated to calculate the total annual numbers of children starting ART in each year at a national level (shown in Table S1). The purpose of including the likelihood here is not to re-estimate the annual numbers of children starting ART (since those numbers are fixed) but rather to penalize the parameter combinations that lead to implausibly low levels of paediatric HIV prevalence or implausibly low rates of paediatric HIV testing; if the modelled number of diagnosed HIV-positive children is less than the reported numbers of children on ART, it is probably an indication that the model is not generating enough mother-to-child transmission or not generating enough HIV testing.

For the purpose of calculating the likelihood, we assume that the error terms (the differences between the modelled numbers of patients on ART and the corresponding reported numbers of ART patients, on a log scale) are normally distributed with zero mean and variance σ_m^2. We define the reported total to be the sum of the totals reported for the private and public sectors:

$$\Omega(t) = R^0(t) + R^1(t).$$

The public and private sector totals are shown in Table S9. Note that estimates for the private sector are not produced at the same time intervals as those for the public sector, and we have therefore interpolated from the available private sector totals to obtain estimates at the time points for which public-sector totals are available.

Table S9: Reported numbers of children on ART in the South African public and private sectors

Month	Public*	Private	Month	Public	Private	Month	Public	Private
2001 June	0	513	2010 June	100282	12587	2016 June	165135	7519
2002 June	0	1278	2010 July	103407	12816	2016 July	165496	7515
2003 June	0	2148	2010 Aug	105224	13045	2016 Aug	167248	7510
2004 June	0	3148	2010 Sept	107042	13274	2016 Sept	168024	7506
2004 July	1618	3231	2010 Oct	109516	13502	2016 Oct	170869	7502
2004 Dec	3051	3648	2010 Nov	112179	13731	2016 Nov	169386	7498
2005 Jan	3327	3731	2010 Dec	113759	13960	2016 Dec	168274	7494
2005 June	6831	4148	2011 Jan	118167	12900	2017 Jan	162347	5995
2005 Dec	11959	5037	2011 Feb	123185	13108	2017 Feb	165135	5991
2006 Jan	12926	4911	2011 March	129512	13316	2017 March	166316	5988
2006 June	18159	5613	2011 April	131572	13524	2017 April	161425	5985
2006 Dec	23369	6398	2011 May	133383	13732	2017 May	162627	5981
2007 Jan	24538	6165	2011 June	137113	13940	2017 June	162966	5978
2007 June	30767	6782	2012 March	124619	12886	2017 July	163279	5980
2007 Dec	37694	7755	2014 April	155076	10459	2017 Aug	163822	5983
2008 Jan	38849	7450	2014 June	158073	10505	2017 Sept	163110	5985
2008 June	48039	8214	2015 June	159253	9037	2017 Oct	165514	5988
2008 Dec	59523	9826	2016 Jan	165026	7525	2017 Nov	162657	5990
2009 Jan	61819	9319	2016 Feb	165063	7524	2017 Dec	162764	5993
2009 June	73730	10559	2016 March	163634	7522	2018 Jan	159907	5995
2009 Dec	85630	12145	2016 April	165427	7521	2018 Feb	160869	5998
2010 Jan	87555	11376	2016 May	165048	7520	2018 March	164196	6000

* Public sector totals to June 2009 reflect cumulative ART enrolment, not current enrolment.

Secondly, we define $G(\boldsymbol{\Theta},t)$ to be the model estimate of the number of patients we would expect to be reported as on ART at time t, if parameter combination $\boldsymbol{\Theta}$ is entered into the model. Because the reporting of ART totals has changed over time, it is necessary to reflect this in the definition of $G(\boldsymbol{\Theta},t)$. In the period up to 2009, $G(\boldsymbol{\Theta},t)$ represents the number of children *ever* started on ART, but in later periods $G(\boldsymbol{\Theta},t)$ represents the modelled number of children *currently* on ART.

The variance of the error terms is approximated by the formula

$$\hat{\sigma}_m^2 = \frac{1}{n_0}\sum_{t\in T_0}\left(\ln\left(G(\boldsymbol{\Theta},t)\right) - \ln\left(\Omega(t)\right)\right)^2. \qquad (8)$$

where T_0 is the set of time points for which reported paediatric ART totals are available, and n_0 is the number of time points in this set. The likelihood function is then calculated as

$$L(\boldsymbol{\Omega} \mid \boldsymbol{\Theta}) = \prod_{t \in T_0} \frac{1}{\sqrt{2\pi}\hat{\sigma}_m} \exp\left(- \frac{\left(\ln(G(\boldsymbol{\Theta}, t)) - \ln(\Omega(t))\right)^2}{2\hat{\sigma}_m^2} \right),$$

where $\boldsymbol{\Omega}$ represents the vector of $\Omega(t)$ values, for all $t \in T_0$.

2.2.5 Age distributions of children on ART

The age profile of children on 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 are the reported fractions of children on ART in each age group, over the 2011-2018 period, obtained from the National Health Laboratory Service (NHLS) [142]. The data are summarized in Table S10.

Table S10: Age distributions of children on ART

	2011	2012	2013	2014	2015	2016	2017	2018*
Numbers								
1-4 years	30883	31069	30466	29437	28477	27726	25601	9860
5-9 years	42083	47493	51456	53925	55208	54206	51874	20416
10-14 years	31118	39300	46971	53864	62026	68310	73219	32397
Proportions								
1-4 years	29.7%	26.4%	23.6%	21.5%	19.5%	18.5%	17.0%	15.7%
5-9 years	40.4%	40.3%	39.9%	39.3%	37.9%	36.1%	34.4%	32.6%
10-14 years	29.9%	33.3%	36.4%	39.3%	42.6%	45.5%	48.6%	51.7%

Data supplied by Lise Jamieson, based on previous analysis [142]. * Data for 2018 are incomplete and the absolute numbers are therefore markedly lower than in previous years.

A number of limitations need to be considered when interpreting these data. The ART totals are estimated based on recorded numbers of viral load tests performed in children. This implies that children who are on ART but who do not get viral load tests done are not counted. There is also the risk of double-counting children who have multiple viral load tests in a given year – although this risk is minimized by using a probabilistic matching algorithm to identify laboratory records that relate to the same patient. In infants, however, this probabilistic matching algorithm is considered to be particularly unreliable, as tests are often entered under the mother's name [142], and consequently infants are excluded from the estimates of numbers of children on ART.

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 0-4 years, 1 for 5-9 years and 2 for 10-14 years), and $R(x, t)$ is defined as the corresponding reported fraction from the NHLS data (Table S10). The likelihood function is defined on the assumption that the difference between these proportions is normally distributed with zero mean, i.e.

$$R(x, t) = M(x, t) + \varepsilon(x, t)$$

where $\varepsilon(x, t) \sim N(0, (\sigma_a M(x, t))^2)$. 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 bias in the data rather than the random multinomial error.

The bias in the data arises due to two main factors. The first is that our model estimates ART totals at the middle of each year, whereas the NHLS totals represent the numbers of children on ART at any time over the course of the year. This means that children who started ART in the second half of the year could be included in the data but not in our model. (In South Africa, for many years, guidelines recommended baseline viral load testing in children [114, 117].) This is a significant source of bias in the early years of the paediatric ART programme, when the annual numbers of children initiating ART for the first time were large relative to the numbers of children currently on ART, and we have therefore conservatively excluded the NHLS data up to 2010 for the purpose of evaluating the model fit to the data. In the years after 2010, however, the potential bias is still substantial. In 2011, for example, the number of children entering HIV care for the first time [142], as a fraction of the totals in Table S10, are 66% in the 1-4 age group, 44% in the 5-9 age group and 48% in the 10-14 age group. If it is conservatively assumed that all of these children entering HIV care start ART, and that 50% do so in the second half of the year, then the reported numbers on ART in 2011 would over-estimate the numbers on ART at mid-2011 by 33% (50% × 66%) in the 1-4 age group, and by roughly 23% in the 5-14 year age group. This in turn would imply that the fraction of treated children who are aged 1-4 could be over-estimated by around 10% (33% - 23%). This 10% is likely to be an upper bound on the bias, as (a) many of the children entering HIV care do not start ART, and (b) in the years after 2011, the numbers of children entering HIV care for the first time comprise an increasingly small fraction of the number currently on ART.

The second source of bias, as mentioned previously, is that the data relate to the 1-4 year age group, whereas the model estimates the fraction of treated children aged 0-4 years. In a worst-case scenario, where the numbers of children on ART is roughly equal at all ages, this would imply a roughly 20% under-estimation of the numbers of children on ART. However, this estimate of the extent of the bias is too extreme because it does not take into account that children aged 0 can age into the 1-4 age group over the course of the reporting period. For example, when considering the number of children aged 0 who are on ART at mid-2011, if we conservatively assume that all children started ART immediately after birth then approximately half of these children should be aged between 6 and 12 months, and should therefore turn 1 (and be eligible for their 12-month viral load test) in the second half of 2011. This means that they should already be included in the 1-4 total for 2011, so that the bias is actually only half of 20% (i.e. 10%). 10% is likely to be a lower bound on the under-estimation of the fraction of treated children who are aged 0-4, because in reality there are relatively few children who do start ART immediately after birth, and because the numbers of children on ART is not constant with respect to age over the 0-4 age group (see Figure 2 of the main text).

We have thus argued that the reported fraction of treated children who are aged 1-4 is unlikely to differ from the modelled fraction of treated children who are aged 0-4 by more than 10%, if the model is a true representation of paediatric HIV in South Africa. By the same reasoning, the reported fractions in the 5-9 and 10-14 year age groups are unlikely to differ from the respective modelled fractions by more than 10%, since the bias in the denominator is the same. We have therefore set σ_a, the coefficient of variation that defines the 'data error' process, to 0.05. This means that under the assumption of normally-distributed error terms, the 95% confidence intervals around the proportions in Table S10 span the interval from 10% below to 10% above the point estimates.

2.2.6 Recorded numbers of deaths in children

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 [143]. 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 those assumed in the most recent Rapid Mortality Surveillance report [153], and are shown in Table S11. 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 [154, 155]: 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 [156, 157].

Table S11: 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 $\varepsilon_g(x,t) \sim N(0, \sigma^2)$. The calculation of the variance σ^2 is similar to that in equation (8), i.e. it is estimated based on the variance of the difference between the model estimates and the recorded death estimates (on a log scale).

2.2.7 Proportion of deaths with an HIV-positive diagnosis

The model is also calibrated to data from the Child Healthcare Problem Identification Programme (Child PIP), a mortality audit system focusing on child deaths in health facilities [144]. In a sample of South African health facilities, data are collected on the circumstances leading to each child death and the causes of death. For each death, information is captured on whether the child was known to be HIV-positive, which is useful in estimating (a) levels of HIV diagnosis in HIV-positive children, and (b) levels of AIDS mortality in HIV-positive children. However, there are number of potential sources of bias that need to be considered. The first is that relatively few health facilities contributed data to Child PIP before 2010, and reporting might therefore not be representative of health services generally. We have therefore only used the data from the 2010-2017 period, as the number of Child PIP deaths peaked in 2010 and thereafter started declining [158], in line with national trends in the under-5 mortality rate [153]. Although this does not preclude the possibility of a bias in the reporting in the period from 2010 onward, the fact that the numbers of recorded deaths declined in line with national totals at least suggests that any bias was reasonably stable over time in the period after 2010.

The second source of potential bias is that children who have been diagnosed HIV-positive may be more likely to be taken to health facilities when they fall sick than other children who fall sick, because caregivers are more likely to appreciate the urgency of treatment when the child has been diagnosed positive [159]. Alternatively, HIV testing may be more likely to be conducted in a child who is sick in a health facility than in children who do not get taken to health facilities when they fall sick. Because of this potential source of bias, we allow for uncertainty in the quantity e^{γ}, which we define as the relative rate of death recording in Child PIP facilities, for children who have been diagnosed HIV-positive prior to death, compared to the rate of death recording in Child PIP facilities for children who have not been diagnosed positive. We would expect this ratio to be greater than 1 – or equivalently, we would expect the ratio $e^{-\gamma}$ to be less than 1. We therefore assign a uniform (0, 1) distribution to represent the uncertainty in the ratio $e^{-\gamma}$ (Table S6).

Table S12 summarizes the Child PIP data that we use in calibrating the model. For the purpose of calibration we consider only deaths in the 1-4 year and 5-9 year age groups. In infants a high proportion of deaths occurs in the first months of life, and the fraction of deaths with an HIV-positive diagnosis is therefore sensitive to the exact timing of PCR screening and the delay in test turnaround – which we do not model with a high degree of precision. Many of the deaths in the neonatal period are recorded through the Perinatal Problem Identification Programme (rather than Child PIP), which also contributes to inconsistency between model definitions and the data definitions in the first year of life. Child PIP records relatively few deaths in older children (ages 10 years or older), and we have therefore not used these data in calibration.

Table S12: Child PIP data

Year	Children aged 1-4 years			Children aged 5-9 years		
	Total deaths	HIV-diagnosed	% diagnosed	Total deaths	HIV-diagnosed	% diagnosed
2010	1768	562	31.8%	529	263	49.7%
2011	1496	414	27.7%	413	187	45.3%
2012	1471	337	22.9%	435	168	38.6%
2013	1841	371	20.2%	479	179	37.4%
2014	1947	361	18.5%	482	154	32.0%
2015	1843	337	18.3%	462	157	34.0%
2016	1592	274	17.2%	471	143	30.4%
2017	1372	253	18.4%	414	98	23.7%

For the purpose of calculating the likelihood, we define $R(x, t)$ as the recorded fraction of deaths in health facilities with an HIV-positive diagnosis, for children in age group x in year t (the proportions in Table S12). The model estimate of the fraction of deaths in which HIV is diagnosed prior to death is represented by the symbol $M(x, t)$. The likelihood is then calculated on the assumption that the difference between $R(x, t)$ and $M(x, t)$, on a logit scale, is normally distributed with mean γ, i.e.

$$\ln\left(\frac{R(x,t)}{1-R(x,t)}\right) = \ln\left(\frac{M(x,t)}{1-M(x,t)}\right) + \gamma + \varepsilon_M + \varepsilon_{x,t}, \qquad (9)$$

where $\varepsilon_M \sim N\left(0, \sigma_M^2\right)$ and $\varepsilon_{x,t} \sim N\left(0, \sigma_{x,t}^2\right)$ represent the 'model error' and 'random error' respectively. The latter represents the binomial error associated with the limited sample size, and the standard deviation is calculated using the normal approximation to the binomial distribution, adjusting to take account of the logit transformation:

$$\sigma_{x,t} = (R(x, t)\,(1 - R(x, t))\,n(x, t))^{-0.5},$$

where $n(x, t)$ is the number of deaths recorded in Child PIP in age group x in year t (Table S12). The 'model error' term takes into account potential mis-specification due to the assumption that the bias (represented by γ) is constant with respect to age and over time. The variance of the model error term is calculated as

$$\hat{\sigma}_M^2 = \frac{1}{16}\sum_{x,t}\left(\ln\left(\frac{R(x,t)}{1-R(x,t)}\right) - \ln\left(\frac{M(x,t)}{1-M(x,t)}\right) - \gamma\right) - \sigma_{x,t}^2 .$$

The interpretation of γ as the difference between $R(x, t)$ and $M(x, t)$ on a logit scale may appear to be inconsistent with the previous definition of the ratio $e^{-\gamma}$. To see that these two definitions are in fact consistent, consider the variables defined in Figure S5. Re-arranging the terms in equation (9) and setting the error terms to zero,

$$e^{\gamma} = \left(\frac{R(x,t)}{1-R(x,t)}\right) \Big/ \left(\frac{M(x,t)}{1-M(x,t)}\right) = \left(\frac{a}{c}\right) \Big/ \left(\frac{a+b}{c+d}\right)$$
$$= \left(\frac{a}{a+b}\right) \Big/ \left(\frac{c}{c+d}\right)$$

which is exactly the same as the way in which we defined e^{γ} previously, viz. the relative rate of death recording in Child PIP facilities, for children who have been diagnosed HIV-positive prior to death, compared to the rate of death recording in Child PIP facilities for children who have not been diagnosed positive.

	Death in Child PIP facility: Yes	Death in Child PIP facility: No
Child HIV-diagnosed before death	a	b
No HIV diagnosis before death	c	d

Figure S5: Association between death recording in Child PIP facilities and HIV diagnosis prior to death

2.3 Posterior simulation

The posterior distribution was simulated numerically using Incremental Mixture Importance Sampling (IMIS) [160]. Following the recommendations of Raftery and Bao [160], an initial set of 10 000 parameter combinations was randomly drawn from the prior distributions in Table S6 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.

3. Additional results

3.1 Comparison of prior and posterior distributions

Table S13 compares the prior and posterior distributions for the 17 parameters included in the model calibration. Although most of the prior and posterior distributions appear similar, several points are worth noting:

- The posterior mean of the relative rate of fertility in HIV-diagnosed women is 0.94, substantially higher than the prior mean of 0.70. This suggests that HIV diagnosis has relatively little effect on HIV-positive women's fertility rates in South Africa.
- Although the model makes provision for differences in relative rates of HIV testing in children (compared to adults) in the periods up to 2005 and after 2010, the posterior estimates on these two parameters are roughly similar (0.098 and 0.125 respectively).

- The posterior mean of the relative rate of testing in early HIV disease, compared to late HIV disease, is 0.034, suggesting a very low rate of antibody HIV testing in children who have been free of HIV-related symptoms.
- This analysis suggests that the rate of HIV diagnosis for children who die in Child PIP facilities is substantially higher than that for children who die in other settings, i.e. the Child PIP data are likely to overstate the fraction of all deaths occurring in HIV-diagnosed children.

Table S13: Comparison of prior and posterior distributions

Parameter	Prior distribution (mean, 95% CI)	Posterior distribution (mean, 95% CI)
RR of fertility in HIV-diagnosed untreated women	0.700 (0.396-0.927)	0.939 (0.908-0.960)
Probability of MTCT from chronically- infected mothers, per year of mixed feeding	0.140 (0.095-0.192)	0.109 (0.101-0.118)
Probability of MTCT from acutely- infected mothers, per month of mixed feeding	0.160 (0.106-0.223)	0.144 (0.124-0.157)
Ratio of postnatal transmission risk per month of EBF to postnatal transmission risk per month of mixed feeding	0.500 (0.213-0.787)	0.611 (0.543-0.678)
Children infected at/before birth		
Annual rate of progression to late disease in older children	0.400 (0.229-0.619)	0.405 (0.338-0.549)
Excess annual rate of progression to late disease in neonates	2.00 (1.14-3.09)	2.50 (2.22-2.77)
Excess progression reduction factor, per year of age	0.400 (0.214-0.602)	0.421 (0.366-0.468)
RR of progression to late disease if infected postnatally	0.350 (0.096-0.666)	0.206 (0.156-0.245)
Children in late disease, untreated		
Annual rate of AIDS mortality in older children	0.120 (0.069-0.186)	0.118 (0.107-0.130)
Excess annual rate of AIDS mortality in neonates	3.50 (2.27-5.00)	3.60 (3.28-3.99)
Excess AIDS mortality reduction factor, per year of age	0.200 (0.047-0.468)	0.310 (0.280-0.352)
HIV testing rates		
RR of testing in virgin adolescents: 2005	0.200 (0.047-0.428)	0.098 (0.059-0.131)
RR of testing in virgin adolescents: 2010	0.200 (0.047-0.428)	0.125 (0.110-0.142)
RR of testing in early disease (relative to late disease)	0.500 (0.025-0.975)	0.034 (0.022-0.046)
Effect of ART on mortality		
RR of mortality in 'stable' ART phase compared to untreated children with late disease	0.100 (0.025-0.217)	0.049 (0.033-0.064)
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)	3.85 (3.14-4.73)
RR of recording of deaths in undiagnosed and HIV-negative children, relative to HIV-diagnosed	0.500 (0.025-0.975)	0.280 (0.233-0.331)

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

3.2 Calibration to recorded death data by age

Figure 1e of the main text shows that the model matches the overall trend in recorded deaths in children reasonably closely, after adjusting the recorded deaths for incomplete recording. However, the model tends to slightly over-estimate mortality in the 1998-2002 period and slightly under-estimate mortality in the 2012-15 period (and the recorded number of deaths in 2016 could be an under-estimate because of unrecorded late registration, i.e. making the model fit to the data look better than it actually is). When results are disaggregated by age (Figure S6), 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). It is worth noting that the absolute numbers of deaths in the 10-14 age group are small when compared with the younger age groups, and the lack of fit in this age group is therefore not a major concern.

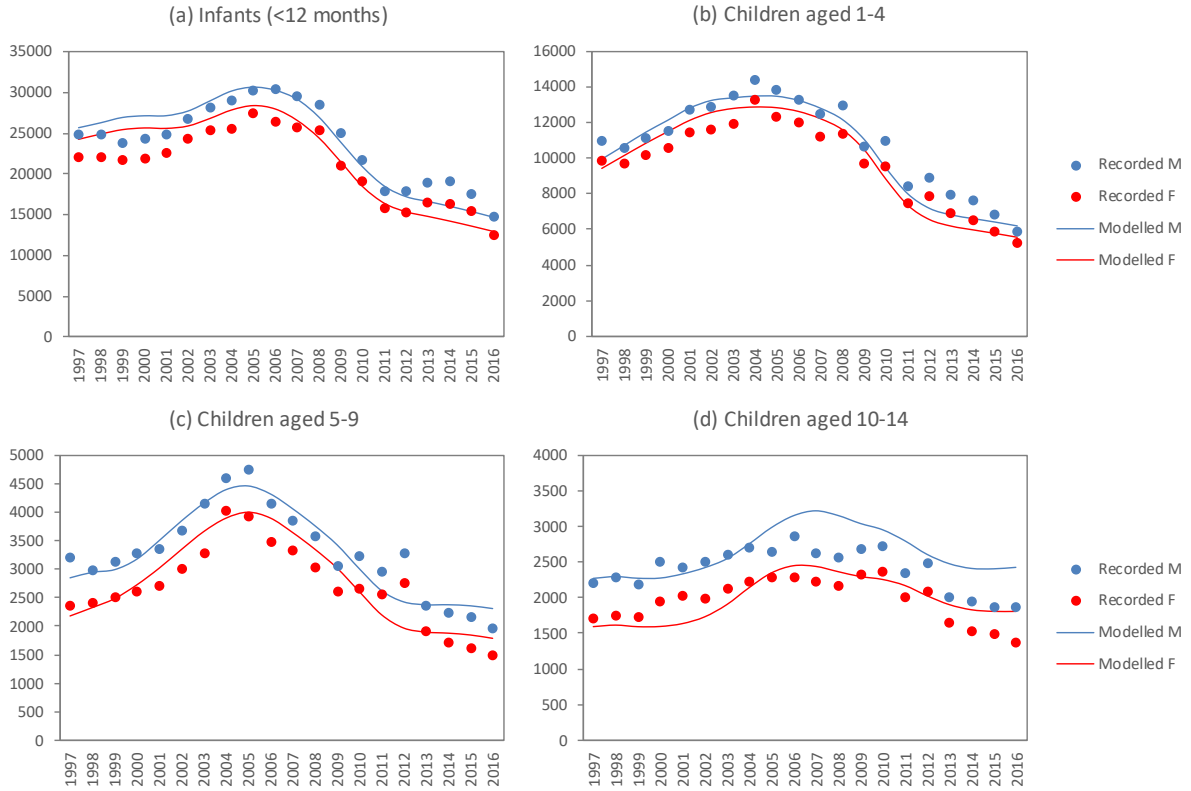

Figure S6: Comparison of modelled deaths and recorded deaths in children, by age
Recorded deaths have been adjusted upward based on the completeness assumptions in Table S11.

3.3 Posterior estimates of survival in untreated HIV-positive children

Figure S7 compares the estimated survival on HIV-positive children (in the absence of ART) with that assumed in the Spectrum model, the model used by UNAIDS for global HIV estimates. For the purpose of comparison, we assume that 50% of infections are acquired at or before birth, and the remaining 50% are acquired postnatally, at 6 months after birth (although this assumption about the timing of postnatal transmission is somewhat arbitrary and unrealistic, we use this assumption purely for comparison purposes). The parameters used in the Spectrum model of paediatric HIV survival have been published previously [161]. The survival estimates from Thembisa are calculated separately for each of the 1000 parameter combinations included in the posterior sample, and the survival rates shown in Figure S7 are calculated by averaging across the 1000 results. Both the Spectrum and Thembisa models estimate a dramatic decline in survival during the first two years of life, in the absence of ART, followed by a slower, more steady decline in survival rates in older children. Untreated survival rates are similar in the two models, although slightly higher in Thembisa at the older ages.

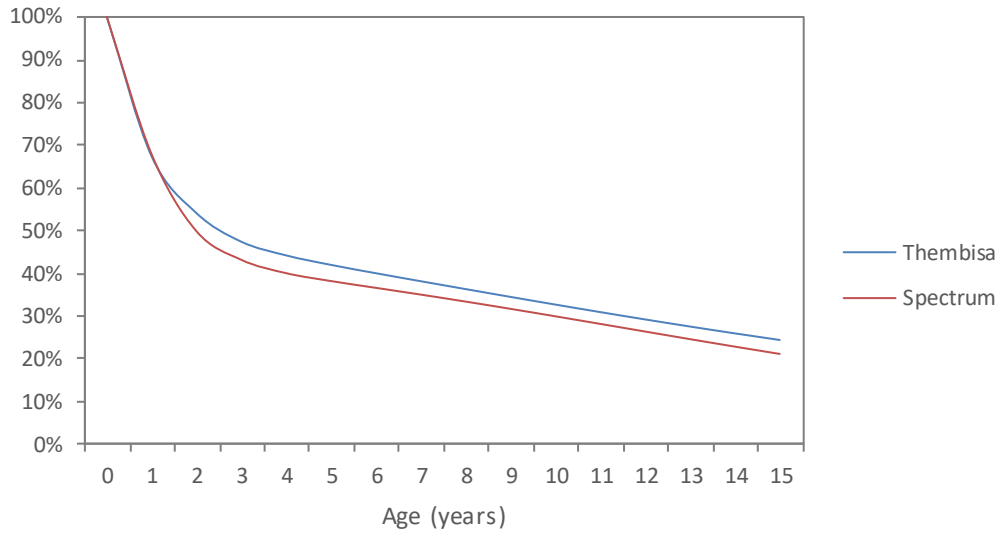

Figure S7: Comparison of HIV survival rates in vertically-infected children, in the Thembisa and Spectrum models

For comparison purposes, survival rates are calculated assuming 50% of infections are acquired at/before birth, and the remaining 50% are acquired postnatally, at age 6 months. The survival curves are calculated after excluding non-HIV mortality (i.e. the fraction surviving is the survival rate that would be expected if non-HIV mortality rates were zero).

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