Supplementary material

The purpose of this supplementary material is to provide a more detailed description of the paediatric HIV model presented in the main text, and to present more detailed results and sensitivity analyses. For a full description of the model, interested readers are referred to the working paper on our website.[1] This appendix summarizes only the aspects of the model relevant to the current paper.

The model is a deterministic model of the population of children under the age of 15 in South Africa. The model projects the growth of the population at monthly intervals, starting in the middle of 1985, using as inputs the estimated annual numbers of births to HIV-negative and HIV-positive mothers from a publicly-available demographic projection model.[2] Children are grouped by age (in months), by HIV status and HIV stage (if infected), and by the type of feeding that they are receiving and their mother's HIV stage (if they are uninfected).

1. Mathematical model of vertical transmission at/before birth

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;

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

$V(t)$ = proportion of pregnant women who receive HIV testing in month t;

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 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 weren't offered testing) at their first antenatal visit.

The assumed annual numbers of births and $V(t)$ values are shown in Table 1. (In the baseline scenario, $Z(t)$ has been set to zero in all years, but values are changed in the intervention scenarios described below.) The annual numbers of births shown in the table are divided by 12 to obtain the monthly numbers of births ($J_0(t)$ and $J_1(t)$), and the specified annual rates are assumed to apply to each month in the projection year. Projection years run from mid-year to mid-year, so that the number of births specified in the 1985 row of the table, for example, is the number of births over the period from mid-1985 to mid-1986. Similarly, the proportion of women who receive HIV testing in the 2005 row of the table is the proportion that applies over the period from mid-2005 to mid-2006, and this proportion is assumed to apply uniformly over the period.

The value of Se has been set at 0.975, the average of rapid test sensitivity estimates from African populations.[3-7] As noted in the main text, 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, slightly lower than the proportion of 0.89 observed by Moodley *et al*[8] in a South African study. There is little information regarding the proportion v_1, and this has been arbitrarily set to 0.5 (see sensitivity analysis in section 4).

Table 1: Assumptions regarding mother-to-child transmission of HIV

Year	Numbers of births to mothers who are		Maternal HIV incidence[a]	% of pregnant women who receive HIV testing[c]	% of women receiving sd NVP who also receive short-course AZT[d]	% of women eligible to start ART who do so prior to delivery[e]
	HIV-negative[a,b]	HIV-positive[a,b]				
1985	1043543	0	0.0%	0.0%	0.0%	0.0%
1986	1052797	107	0.0%	0.0%	0.0%	0.0%
1987	1060887	300	0.0%	0.0%	0.0%	0.0%
1988	1067761	750	0.1%	0.0%	0.0%	0.0%
1989	1073170	1737	0.1%	0.0%	0.0%	0.0%
1990	1076522	3824	0.2%	0.0%	0.0%	0.0%
1991	1087863	8069	0.5%	0.0%	0.0%	0.0%
1992	1096031	15902	0.8%	0.0%	0.0%	0.0%
1993	1096624	28863	1.3%	0.0%	0.0%	0.0%
1994	1087908	48508	1.9%	0.0%	0.0%	0.0%
1995	1068958	75674	2.6%	0.0%	0.0%	0.0%
1996	1046191	109818	3.1%	0.0%	0.0%	0.0%
1997	1006850	145594	3.4%	0.0%	0.0%	0.0%
1998	968275	178702	3.4%	0.0%	0.0%	0.0%
1999	932835	206680	3.4%	0.9%	0.0%	0.0%
2000	901640	228193	3.3%	2.9%	0.0%	2.3%
2001	878138	245503	3.3%	7.5%	0.0%	2.7%
2002	858058	257693	3.2%	15.6%	0.0%	2.7%
2003	840860	265841	3.2%	31.3%	0.8%	4.9%
2004	826038	270953	3.1%	42.0%	4.0%	12.8%
2005	813154	274107	3.1%	54.5%	6.4%	22.9%
2006	802123	275777	3.0%	72.2%	6.8%	27.2%
2007	792657	276340	2.9%	84.0%	18.7%	37.1%
2008	784503	276072	2.8%	89.0%	53.2%	48.0%
2009	777428	275205	2.8%	91.0%	85.4%	60.0%
2010	771249	273807	2.7%	92.0%	90.0%	65.0%
2011	765776	271937	2.7%	92.0%	90.0%	75.0%
2012	761377	269745	2.6%	92.0%	90.0%	80.0%
2013	757666	267419	2.6%	92.0%	90.0%	80.0%
2014	754283	265086	2.6%	92.0%	90.0%	80.0%
2015	751017	262833	2.6%	92.0%	90.0%	80.0%

ART = antiretroviral therapy, AZT = zidovudine, sd NVP = single-dose nevirapine

[a] Source: ASSA2003 AIDS and Demographic Model[2]

[b] HIV status refers to serostatus at the time of first antenatal visit (serostatus may be different at delivery).

[c] Source: Early national surveys of primary healthcare facilities[9-11] and later reports from the District Health Information System[12-16]

[d] Source: Prior to 2008, provision of AZT together with sd NVP was limited mainly to the Western Cape province,[17] which accounted for about 8% of all HIV-positive mothers. Preliminary unpublished data from cord blood surveillance in the Western Cape in 2007-8 (Kathryn Stinson, personal communication) and surveillance data from KwaZulu-Natal in 2008-9[18] suggest that close to 90% of women who receive sd NVP also receive short-course AZT.

[e] Source: South African studies in settings where ART is available suggest that 50-75% of eligible women start ART prior to delivery.[19-21] This proportion has been adjusted downward prior to 2009, to reflect limited access to ART in previous years,[22] and is adjusted upward post-2010 to reflect anticipated improvements in antenatal services.[23] The proportion is applied to women with CD4 <200 prior to 2010, and to women with CD4 <350 from 2010 onwards, in line with new guidelines.[24]

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 women who tested HIV-positive at their first antenatal visit;

$J_{1,i,j}(t)$ = number of births, in month t, to 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.[25] 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 annual maternal HIV incidence rate, $I(t)$, is estimated from the ASSA2003 model, and is shown in Table 1. Sensitivity testing of the assumed maternal HIV incidence rate is discussed in section 6.

In order to calculate rates of mother-to-child transmission at birth, we define the following symbols (base values are specified in brackets, and the data sources and uncertainty ranges are summarized in Table 2 of the main text):

π = 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 (0.2);

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);

χ_i = proportion of pregnant HIV-positive women in CD4 stage i (0.366 for CD4 >500, 0.245 for CD4 350-500, 0.249 for CD4 200-349 and 0.140 for CD4 <200);

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 (0.35);

π^H = probability of mother-to-child transmission at or before birth, if the mother initiated highly active antiretroviral therapy (HAART) prior to delivery (0.02);

α_0 = proportion of diagnosed HIV-positive pregnant women, not initiating long-term HAART, who receive single-dose nevirapine (0.75);

$D(t)$ = proportion of diagnosed HIV-positive pregnant women delivering in month t, receiving single-dose nevirapine, who also receive short-course AZT (see Table 1);

$\upsilon D(t)$ = proportion of diagnosed HIV-positive pregnant women delivering in month t, not receiving single-dose nevirapine, who receive short-course AZT (υ = 0.4);

$U(t)$ = proportion of antenatal clinics from which HAART is readily accessible, in month t (see last column of Table 1, which is the product of $U(t)$ and $\alpha_1(t)$);

$\alpha_1(t)$ = proportion of women diagnosed as eligible to start HAART and having access to HAART, who actually start HAART prior to delivery (adjustment factor applied to $U(t)$ to allow for suboptimal referral and follow-up of pregnant women diagnosed as eligible to start HAART, starting at 0.6 prior to 2010 and increasing to 0.8 by 2012);

$\Lambda_i(t)$ = indicator variable determining whether pregnant HIV-positive women in CD4 stage i are eligible to start HAART in month t (1 = yes, 0 = no; for CD4 <200 indicator is 1 starting in 2000, and for CD4 200-349 indicator is 1 starting in 2010);

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

ζ_1 = efficacy of single-dose NVP, together with short-course AZT, in preventing mother-to-child transmission at birth (0.80);

ζ_2 = efficacy of short-course AZT in preventing mother-to-child transmission at birth (0.65).

The values of the π_i parameters have been calculated such that

$$\pi = \sum_{i=1}^{4} \chi_i \pi_i .$$

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:

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

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

$$Y_{0,2}(t) = \left(\left(J_{1,1}(t) + J_{1,0,1}(t) + J_{1,2,1}(t)\right) \sum_{i=1}^{4} \chi_i \left(1 - \Lambda_i(t) U(t) \alpha_1(t)\right) + J_{0,1,1}(t) \right)$$
$$- \left(\left(J_{1,1}(t) + J_{1,0,1}(t) + J_{1,2,1}(t)\right) \sum_{i=1}^{4} \chi_i \left(1 - \Lambda_i(t) U(t) \alpha_1(t)\right) \pi_i + J_{0,1,1}(t) \pi^* \right)$$
$$\times \left(1 - \alpha_0 \left(1 - D(t)\right) \zeta_0 - \alpha_0 D(t) \zeta_1 - \left(1 - \alpha_0\right) \upsilon D(t) \zeta_2 \right)$$
$$Y_{0,3}(t) = \left(J_{1,1}(t) + J_{1,0,1}(t) + J_{1,2,1}(t)\right) \sum_{i=1}^{4} \chi_i \Lambda_i(t) U(t) \alpha_1(t) \left(1 - \pi^H\right)$$
$$Y_{1,0}(t) = \left(J_{1,0,0}(t) + J_{1,0,2}(t) + J_{1,2,0}(t) + J_{1,2,2}(t)\right) \pi + J_{0,1,0}(t) \pi^* + \left(1 - \alpha_0\right) \left(1 - \upsilon D(t)\right)$$
$$\times \left(\left(J_{1,1}(t) + J_{1,0,1}(t) + J_{1,2,1}(t)\right) \sum_{i=1}^{4} \chi_i \left(1 - \Lambda_i(t) U(t) \alpha_1(t)\right) \pi_i + J_{0,1,1}(t) \pi^* \right)$$
$$Y_{1,1}(t) = \left(J_{1,1}(t) + J_{1,0,1}(t) + J_{1,2,1}(t)\right) \sum_{i=1}^{4} \chi_i \Lambda_i(t) U(t) \alpha_1(t) \pi^H$$
$$+ \left(\left(J_{1,1}(t) + J_{1,0,1}(t) + J_{1,2,1}(t)\right) \sum_{i=1}^{4} \chi_i \left(1 - \Lambda_i(t) U(t) \alpha_1(t)\right) \pi_i + J_{0,1,1}(t) \pi^* \right)$$
$$\times \left\{ \alpha_0 \left(1 - \left(1 - D(t)\right) \zeta_0 - D(t) \zeta_1 \right) + \left(1 - \alpha_0\right) \upsilon D(t) \left(1 - \zeta_2\right) \right\}$$

The implicit assumption being made here is that women who have recently seroconverted, having been diagnosed positive for the first time in late pregnancy, would not be eligible to initiate HAART. This is a reasonable assumption if – as under current South African guidelines – pregnant women are eligible to start HAART only when their CD4 count is below 350/μl.

2. Mathematical model of HIV transmission after birth

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);

$Q^0_{g,i,v}(a,t)$ = number of uninfected children of sex g, aged exactly a months at the start of month t, whose mothers enter the (i, v) state between time t and time $t + 1$;

$E_{v,i}(t)$ = 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, to be consistent with the ASSA2003 AIDS and Demographic model.[2] The proportions 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),[26] 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 ($E_{0,0} = 0.133$). Up to

2010, it is assumed that of women diagnosed HIV-positive and counselled on infant feeding, 50.0% used replacement feeding ($E_{0,1}$), 15.4% practised mixed feeding from birth ($E_{1,1}$) and the remaining 34.6% practised EBF from birth ($E_{2,1}$). The 50% assumption is based on limited data from a national survey of intended feeding practices in HIV-diagnosed women[27] and from a national trial conducted in 11 different South African health centres.[28] The 34.6% assumption is based on a study of women in KwaZulu-Natal,[29] which found that 69% of those HIV-diagnosed women who elected to breastfeed practised EBF (0.346 = 0.5 × 0.69).

From 2011 onwards, infant feeding practices are assumed to change, in line with a recent Department of Health decision to phase-out the free provision of formula milk to HIV-positive mothers and promote exclusive breastfeeding. The assumed changes over time in the $E_{v,i}(t)$ proportions are shown in Table 2. Of those mothers who choose to breastfeed, the proportion practising EBF from birth is assumed to remain constant at 69%.

Table 2: Changes in infant feeding practices over time

Year	% of HIV-diagnosed mothers practising			% of HIV-diagnosed breastfeeding mothers administering NVP
	Replacement feeding	Mixed feeding	Exclusive breastfeeding	
2009	50.0%	15.4%	34.6%	0.0%
2010	50.0%	15.4%	34.6%	30.0%
2011	40.0%	18.6%	41.4%	65.0%
2012	30.0%	21.7%	48.3%	75.0%
2013	20.0%	24.8%	55.2%	80.0%
2014	20.0%	24.8%	55.2%	80.0%
2015	20.0%	24.8%	55.2%	80.0%

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

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

Although it would be more correct to define $N^0_{g,i,v}(a,t)$ as the number of children aged between a months and $a + 1$ months, rather than the number of children who are aged exactly a months, working with age intervals rather than exact ages adds to the complexity of the model without changing the results materially (since we are working with age in months rather than years). In the interests of simplicity, we are therefore assuming that all births occurring in month $t - 1$ occur at the end of the month, i.e. at time t.

It is also worth noting that 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.

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 shape parameter ($\phi_{1,0}$) is set to 2, based on data collected in the 1998 DHS.[26] The model fit to the data is shown in Figure 1, after multiplying the proportion $B_{v,i}(a)$ by the proportion of mothers who elect to practise mixed feeding from birth ($E_{1,0} = 0.867$). The proportion $B_{v,i}(a)$ is calculated as

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

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.[30] There are therefore no parameters specified for $m_{2,0}$ and $\phi_{2,0}$.

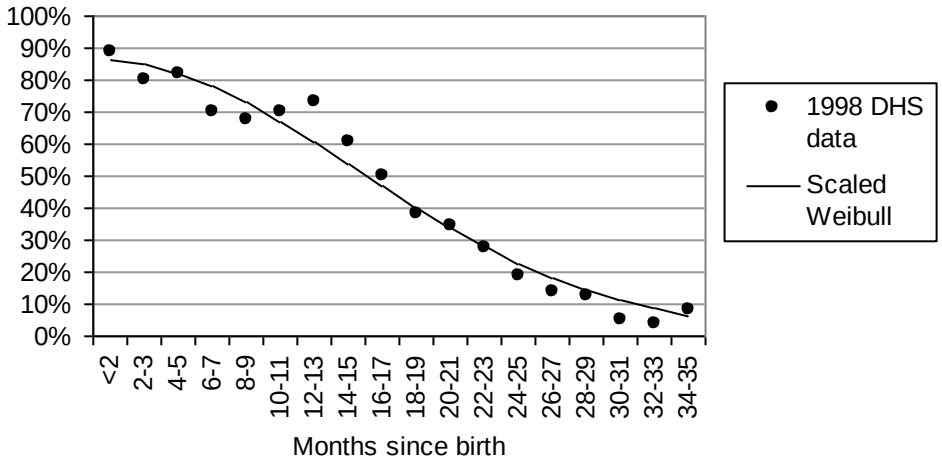

Figure 1: Proportion of children who are breastfed, prior to PMTCT

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.[29, 31, 32] 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). Figure 2 shows that the model estimates of the proportions of HIV-diagnosed women continuing breastfeeding from birth are reasonably consistent with data from two independent South African studies, although the model slightly over-estimates the proportion of breastfeeding mothers in the first 6 months of life when compared with the study of Coutsoudis *et al*,[29] and slightly under-estimates the corresponding proportions in the study of Goga *et al*.[31] The model fit is therefore a compromise between the two studies. The assumption that 34.6% of HIV-diagnosed women practise EBF, for a median duration of 2 months, leads to a modelled proportion practising EBF at 1.5 months of $0.346 \times 0.5^{(1.5/2)} = 0.206$, which is consistent with the result of a recent South African survey that found 22.9% of HIV-positive mothers to be practising EBF at the ages of 4-8 weeks.[33]

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

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

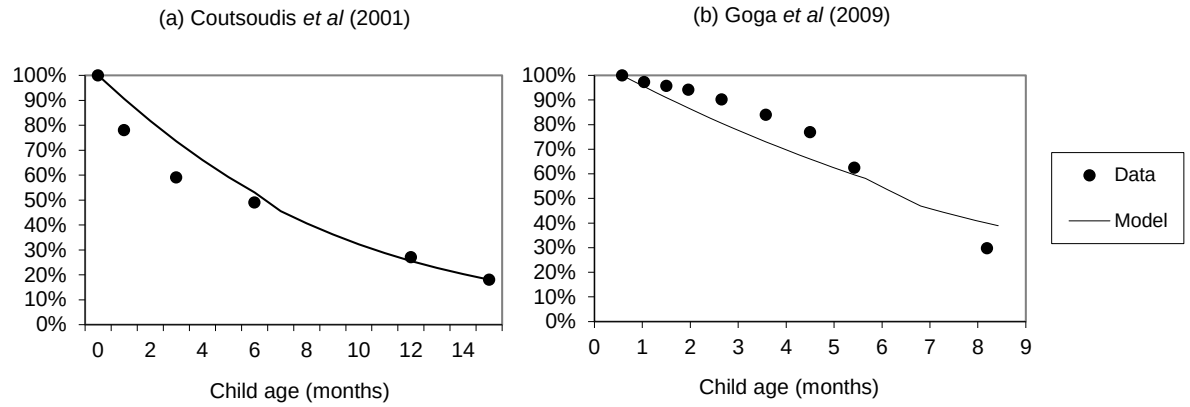

Figure 2: Proportions of HIV-diagnosed women who continue breastfeeding at different durations

In panel (a), percentages are expressed as a proportion of all women who were breastfeeding from birth. In panel (b), percentages are expressed as a proportion of all women who were practising exclusive or predominant breastfeeding at 3 weeks after birth. The model allows for differences in the proportions of women initially practising EBF versus mixed feeding in the two studies.

Non-HIV mortality is modelled by defining

$q_g(a, t)$ = probability that a child of sex g, aged exactly a months at time t, dies before reaching age $a + 1$ months due to causes other than AIDS.

These non-HIV mortality assumptions are obtained from the ASSA2003 AIDS and Demographic model.[2] Assessment of the impact of infant feeding practices on non-HIV mortality is beyond the scope of the present analysis, and we have therefore made no adjustment to these mortality rates to reflect the positive effect of breastfeeding on non-HIV mortality.[34]

To model the postnatal transmission rate, the following variables are defined:

h_i = probability of mother-to-child transmission per month of breastfeeding, if mother is in state i (0 = acutely infected; 1 = chronically infected and practising mixed feeding; 2 = chronically infected and receiving mixed feeding);

z_1 = percentage reduction in the rate of postnatal transmission if the HIV-exposed child is receiving extended nevirapine prophylaxis;

z_2 = percentage reduction in the rate of postnatal transmission if the breastfeeding mother is receiving ART;

$X(t)$ = proportion of breastfeeding women, known to be HIV-positive, whose children receive extended nevirapine prophylaxis.

The evidence on which the parameter h_0 is based is presented in Table 1 of the main text. The uncertainty ranges for parameters h_0, h_1 and h_2 (as well as the data sources on which they are based) are presented in Table 2 of the main text. Very briefly, the average values assumed for the three parameters are 0.16, 0.0125 and 0.0062 respectively, the last two probabilities being determined from a meta-analysis of postnatal HIV transmission studies[35] and from studies that have compared HIV transmission rates from mothers who practice mixed feeding and EBF.[36, 37] The monthly risk of transmission is assumed to be reduced by 60% if the mother administers extended nevirapine prophylaxis to the child,[38-40] and by 80% if the mother is

herself receiving HAART while breastfeeding.[41] The assumed proportion of HIV-diagnosed breastfeeding mothers who administer nevirapine to their infants is shown in Table 2.

Probabilities such as $\delta_{v,i}(a)$ and h_1 are defined independently of one another, i.e. they represent the probability of a movement from one state to another over a one month period if all other possible movements are ignored. Converting these independent probabilities into probabilities that depend on the other rates of decrement out of the current state is achieved using a conversion function *C*. For example, the probability that an HIV-positive mother who is practising mixed feeding (v = 1) discontinues breastfeeding in the next month, *before* transmitting HIV to her child, is calculated as

$$C\left(\delta_{1,i}(a), h_1\right) = \left(1-\left(1-\delta_{1,i}(a)\right)\left(1-h_1\right)\right)\frac{\ln\left(1-\delta_{1,i}(a)\right)}{\ln\left(\left(1-\delta_{1,i}(a)\right)\left(1-h_1\right)\right)}.$$

This calculation is performed on the assumption that the hazards for the respective decrements remain constant during the course of a particular month. More generally, if there are n possible decrements out of a particular state (with associated independent probabilities denoted $\Delta_1, \Delta_2, ..., \Delta_n$), and we wish to calculate the probability that an individual experiences the first decrement in the next month, before experiencing any of the other decrements, this would be calculated as

$$C\left(\Delta_1, \Delta_2, ..., \Delta_n\right) = \left(1-\prod_{i=1}^{n}\left(1-\Delta_i\right)\right)\frac{\ln\left(1-\Delta_1\right)}{\sum_{i=1}^{n}\ln\left(1-\Delta_i\right)}.$$

The first argument in the function relates to the decrement in which we are interested, and the remaining argument(s) relate to the other competing decrement(s). In certain of the equations that follow, we are interested in the probability that a child leaves a particular state in the same month that they enter it. Suppose that we are interested in the probability that a child entering a particular state during a given month moves to state 1 before the end of the month, and before any of the other decrements occur. This is calculated on the assumption that children enter the state at a uniform rate:

$$C^*\left(\Delta_1, \Delta_2, ..., \Delta_n\right) = \left\{1-\int_0^1\left(\prod_{i=1}^{n}\left(1-\Delta_i\right)^{1-t}\right)dt\right\}\frac{\ln\left(1-\Delta_1\right)}{\sum_{i=1}^{n}\ln\left(1-\Delta_i\right)}$$

$$= \left\{1+\frac{1-\prod_{i=1}^{n}\left(1-\Delta_i\right)}{\sum_{i=1}^{n}\ln\left(1-\Delta_i\right)}\right\}\frac{\ln\left(1-\Delta_1\right)}{\sum_{i=1}^{n}\ln\left(1-\Delta_i\right)}$$

Further suppose that we define $C^T\left(\Delta_1, \Delta_2, ..., \Delta_n\right)$ as the probability of *any* decrement from a particular state in the same month that the state is entered. This is calculated as

$$C^T(\Delta_1,\Delta_2,...,\Delta_n) = C^*(\Delta_1,\Delta_2,...,\Delta_n) + C^*(\Delta_2,\Delta_1,\Delta_3,...,\Delta_n) + ... + C^*(\Delta_n,\Delta_1,\Delta_2,...,\Delta_{n-1})$$
$$= 1 + \frac{1 - \prod_{i=1}^{n}(1-\Delta_i)}{\sum_{i=1}^{n}\ln(1-\Delta_i)}$$

The following equations determine the changes in the numbers of children whose mothers are uninfected, over each one-month period:

$$N^0_{g,0,0}(a+1,t+1) = \left[N^0_{g,0,0}(a,t) + N^0_{g,0,1}(a,t)C\left(\delta_{1,0}(a,t),1-\left[1-I(t)\right]^{1/12}\right)\right]\left(1-q_g(a,t)\right)$$
$$N^0_{g,0,1}(a+1,t+1) = N^0_{g,0,1}(a,t)\left(1-\delta_{1,0}(a,t)\right)\left(\left[1-I(t)\right]^{1/12}\right)\left(1-q_g(a,t)\right)$$
$$N^0_{g,0,2}(a+1,t+1) = 0$$

As noted previously, mothers are assumed not to practise exclusive breastfeeding if they are HIV-negative. As shown in the second equation, it is assumed that HIV-negative children who are being breastfed by HIV-negative mothers can leave this state due to either (a) their mother discontinuing breastfeeding, (b) their mother acquiring HIV, or (c) death due to non-HIV mortality. Non-HIV mortality is not treated as a competing decrement in the way that the other decrements are because the same non-HIV mortality probability is assumed to apply to all children of a given age and sex.

$$Q^0_{g,1,1}(a,t) = N^0_{g,0,1}(a,t)C\left(1-\left[1-I(t)\right]^{1/12},\delta_{1,0}(a,t)\right)$$
$$N^0_{g,1,0}(a+1,t+1) = \left[N^0_{g,1,0}(a,t) + N^0_{g,1,1}(a,t)C\left(\delta_{1,0}(a,t),h_0,1-\exp(-1/3)\right)\right.$$
$$\left. + Q^0_{g,1,1}(a,t)C^*\left(\delta_{1,0}(a,t),h_0,1-\exp(-1/3)\right)\right]\left(1-q_g(a,t)\right)$$
$$N^0_{g,1,1}(a+1,t+1) = N^0_{g,1,1}(a,t)\left(\exp(-1/3)\right)\left(1-\delta_{1,0}(a,t)\right)\left(1-h_0\right)\left(1-q_g(a,t)\right)$$
$$+ Q^0_{g,1,1}(a,t)\left[1-C^T\left(1-\exp(-1/3),\delta_{1,0}(a,t),h_0\right)\right]\left(1-q_g(a,t)\right)$$
$$N^0_{g,1,2}(a+1,t+1) = 0$$

The factor of exp(-1/3) is the probability that a woman who was in the acute phase of HIV infection at the start of the month remains in that phase for the entire duration of the month, and it is calculated on the assumption that acute infection lasts for 3 months on average. Since women in the acute phase of infection are assumed not to know their HIV status, none are assumed to practise exclusive formula feeding. Changes in maternal HIV stage (due to women progressing from acute to chronic infection or learning their HIV status) are not modelled after women discontinue breastfeeding, as there is assumed to be no postnatal transmission risk after women discontinue breastfeeding.

$$Q^0_{g,2,1}(a,t) = N^0_{g,1,1}(a,t)C\left(1-\exp(-1/3),\delta_{1,0}(a,t),h_0\right)$$
$$+ Q^0_{g,1,1}(a,t)C^*\left(1-\exp(-1/3),\delta_{1,0}(a,t),h_0\right)$$
$$N^0_{g,2,0}(a+1,t+1) = \left[N^0_{g,2,0}(a,t) + N^0_{g,2,1}(a,t)C\left(\delta_{1,0}(a,t),h_1\right)\right.$$
$$\left. + Q^0_{g,2,1}(a,t)C^*\left(\delta_{1,0}(a,t),h_1\right)\right]\left(1-q_g(a,t)\right)$$

$$N^0_{g,2,1}(a+1,t+1) = N^0_{g,2,1}(a,t)\left(1-\delta_{1,0}(a,t)\right)\left(1-h_1\right)\left(1-q_g(a,t)\right)$$
$$+ Q^0_{g,2,1}(a,t)\left[1-C^T\left(\delta_{1,0}(a,t),h_1\right)\right]\left(1-q_g(a,t)\right)$$
$$N^0_{g,2,2}(a+1,t+1) = 0$$

The third formula applies at all values of *a* other than 1. At 2 months of age, the formula is modified to take into account mothers learning their HIV status after HIV testing at the 6-week immunization visit. (Although it is not currently the practice to test women for HIV at the 6-week immunization visit, the effect of introducing this is considered in the third intervention scenario described in the main text.) The modified formula is as follows:

$$N^0_{g,2,1}(2,t+1) = \left\{N^0_{g,2,1}(1,t)\left(1-\delta_{1,0}(1,t)\right)\left(1-h_1\right)\left(1-q_g(1,t)\right)\right.$$
$$\left.+ Q^0_{g,2,1}(1,t)\left[1-C^T\left(\delta_{1,0}(a,t),h_1\right)\right]\left(1-q_g(1,t)\right)\right\}\left(1-u(t)\right)$$

In this equation, $u(t)$ is the proportion of women who receive HIV testing at 2 months after birth. As explained in the main text, this proportion is set to 0.92 × 0.66 = 0.61, from 2010 onwards, the proportion being less than 1 due to infants missing their immunization visits and due to HIV test results not being received by mothers.

The following formulas are used to calculate changes in numbers of women who are breastfeeding and who know they are HIV-positive:

$$Q^0_{g,3,1}(a,t) = N^0_{g,3,2}(a,t)C\left(\delta_{2,1}(a,t),h_2\left(1-X(t)z_1\right)\right)\left(1-w(a)\right)$$
$$N^0_{g,3,0}(a+1,t+1) = \left[N^0_{g,3,0}(a,t) + N^0_{g,3,1}(a,t)C\left(\delta_{1,1}(a,t),h_1\left(1-X(t)z_1\right)\right)\right.$$
$$+ N^0_{g,3,2}(a,t)C\left(\delta_{2,1}(a,t),h_2\left(1-X(t)z_1\right)\right)w(a)$$
$$\left.+ Q^0_{g,3,1}(a,t)C^*\left(\delta_{1,1}(a,t),h_1\left(1-X(t)z_1\right)\right)\right]\left(1-q_g(a,t)\right)$$
$$N^0_{g,3,1}(a+1,t+1) = N^0_{g,3,1}(a,t)\left(1-\delta_{1,1}(a,t)\right)\left(1-h_1\left(1-X(t)z_1\right)\right)\left(1-q_g(a,t)\right)$$
$$+ Q^0_{g,3,1}(a,t)\left[1-C^T\left(\delta_{1,1}(a,t),h_1\left(1-X(t)z_1\right)\right)\right]\left(1-q_g(a,t)\right)$$
$$N^0_{g,3,2}(a+1,t+1) = N^0_{g,3,2}(a,t)\left(1-\delta_{2,1}(a,t)\right)\left(1-h_2\left(1-X(t)z_1\right)\right)\left(1-q_g(a,t)\right)$$

The above formulas are modified in the case $a = 1$, if there is screening of mothers at 6-week immunization clinics:

$$N^0_{g,3,0}(2,t+1) = \left[N^0_{g,3,0}(1,t) + N^0_{g,3,1}(1,t)C\left(\delta_{1,1}(1,t),h_1\left(1-X(t)z_1\right)\right)\right.$$
$$+ N^0_{g,3,2}(1,t)C\left(\delta_{2,1}(1,t),h_2\left(1-X(t)z_1\right)\right)w(a)$$
$$\left.+ Q^0_{g,3,1}(1,t)C^*\left(\delta_{1,1}(1,t),h_1\left(1-X(t)z_1\right)\right)\right]\left(1-q_g(1,t)\right)$$
$$+ N^0_{g,2,0}(1,t)\left(1-q_g(1,t)\right)u(t) + \left\{N^0_{g,2,1}(1,t)\left(1-\delta_{1,0}(1,t)\right)\left(1-h_1\right)\right.$$
$$\left.+ Q^0_{g,2,1}(1,t)\left[1-C^T\left(\delta_{1,0}(1,t),h_1\right)\right]\right\}\left(1-q_g(1,t)\right)u(t)E_{0,1}(t)$$

$$
\begin{aligned}
N^0_{g,3,1}(2,t+1) = {} & N^0_{g,3,1}(1,t)\big(1-\delta_{1,1}(1,t)\big)\big(1-h_1\big(1-X(t)z_1\big)\big)\big(1-q_g(1,t)\big) \\
& + Q^0_{g,3,1}(1,t)\Big[1-C^T\big(\delta_{1,1}(1,t),h_1\big(1-X(t)z_1\big)\big)\Big]\big(1-q_g(a,t)\big) \\
& + \Big\{N^0_{g,2,1}(1,t)\big(1-\delta_{1,0}(1,t)\big)\big(1-h_1\big)\big(1-q_g(1,t)\big) \\
& + Q^0_{g,2,1}(1,t)\Big[1-C^T\big(\delta_{1,0}(1,t),h_1\big)\Big]\big(1-q_g(1,t)\big)\Big\}u(t)\big(1-E_{0,1}(t)\big)
\end{aligned}
$$

In these equations, the proportion of breastfeeding women who discontinue breastfeeding if they discover they are HIV-positive is $E_{0,1}(t)$, i.e. the same as the proportion of HIV-diagnosed mothers who choose to use replacement feeding from birth. It is assumed that women who discover that they are HIV-positive would either continue to practise mixed feeding or would discontinue breastfeeding completely (exclusive breastfeeding is unlikely to be initiated in women who are already practising mixed feeding).

To model changes in the numbers of women on ART who are breastfeeding, similar formulas are used, but postnatal transmission rates are reduced by a factor of z_2 instead of $X(t)z_1$:

$$
\begin{aligned}
Q^0_{g,4,1}(a,t) &= N^0_{g,4,2}(a,t)C\big(\delta_{2,1}(a,t),h_2\big(1-z_2\big)\big)\big(1-w(a)\big) \\
N^0_{g,4,0}(a+1,t+1) &= \big[N^0_{g,4,0}(a,t) + N^0_{g,4,1}(a,t)C\big(\delta_{1,1}(a,t),h_1\big(1-z_2\big)\big) \\
&\quad + N^0_{g,4,2}(a,t)C\big(\delta_{2,1}(a,t),h_2\big(1-z_2\big)\big)w(a) \\
&\quad + Q^0_{g,4,1}(a,t)C^*\big(\delta_{1,1}(a,t),h_1\big(1-z_2\big)\big)\big]\big(1-q_g(a,t)\big) \\
N^0_{g,4,1}(a+1,t+1) &= N^0_{g,4,1}(a,t)\big(1-\delta_{1,1}(a,t)\big)\big(1-h_1\big(1-z_2\big)\big)\big(1-q_g(a,t)\big) \\
&\quad + Q^0_{g,4,1}(a,t)\Big[1-C^T\big(\delta_{1,1}(a,t),h_1\big(1-z_2\big)\big)\Big]\big(1-q_g(a,t)\big) \\
N^0_{g,4,2}(a+1,t+1) &= N^0_{g,4,2}(a,t)\big(1-\delta_{2,1}(a,t)\big)\big(1-h_2\big(1-z_2\big)\big)\big(1-q_g(a,t)\big)
\end{aligned}
$$

Note that the South African guidelines do not recommend extended nevirapine prophylaxis in breastfed children if their mothers are already on ART, and it is therefore not appropriate to apply both the z_2 and $X(t)z_1$ factors.

Although the above formulas present the numbers of children not receiving breastfeeding according to the maternal HIV stage, the calculation in the model combines all HIV-negative children who are not receiving breastfeeding, as the maternal HIV stage is assumed not to be relevant to their HIV transmission risk after they have ceased to receive breast milk.

If $Q^1_{g,2}(a,t)$ is defined as the number of children of sex *g*, aged exactly *a* months at the start of month *t*, who become infected by breast milk between time *t* and time *t* + 1, then this is calculated as

$$
\begin{aligned}
Q^{1}_{g,2}(a,t) = \big[& N^{0}_{g,1,1}(a,t)C\big(h_0, 1-\exp(-1/3), \delta_{1,0}(a)\big) + N^{0}_{g,2,1}C\big(h_1, \delta_{1,0}(a)\big) \\
& + N^{0}_{g,3,1}C\big(h_1(1-X(t)z_1), \delta_{1,1}(a)\big) + N^{0}_{g,3,2}C\big(h_2(1-X(t)z_1), \delta_{2,1}(a)\big) \\
& + N^{0}_{g,4,1}C\big(h_1(1-z_2), \delta_{1,1}(a)\big) + N^{0}_{g,4,2}C\big(h_2(1-z_2), \delta_{2,1}(a)\big) \\
& + Q^{0}_{g,1,1}(a,t)C^{*}\big(h_0, 1-\exp(-1/3), \delta_{1,0}(a)\big) + Q^{0}_{g,2,1}C^{*}\big(h_1, \delta_{1,0}(a)\big) \\
& + Q^{0}_{g,3,1}C^{*}\big(h_1(1-X(t)z_1), \delta_{1,1}(a)\big) + Q^{0}_{g,4,1}C^{*}\big(h_1(1-z_2), \delta_{1,1}(a)\big)\big]
\end{aligned}
$$

3. Model of paediatric HIV survival

The structure of the model of paediatric HIV survival is summarized in Figure 3. Infected untreated children are assumed to progress through two stages of HIV infection before dying from AIDS, these stages distinguished by the HAART eligibility thresholds that were used in the 2006 WHO paediatric treatment guidelines.[42] Although these treatment guidelines are no longer in use in South Africa, they provide a useful means of classifying infected children according to their disease severity. Children are also classified according to whether they acquired HIV perinatally or postnatally, the latter group being assumed to have a slower rate of progression to ART eligibility.

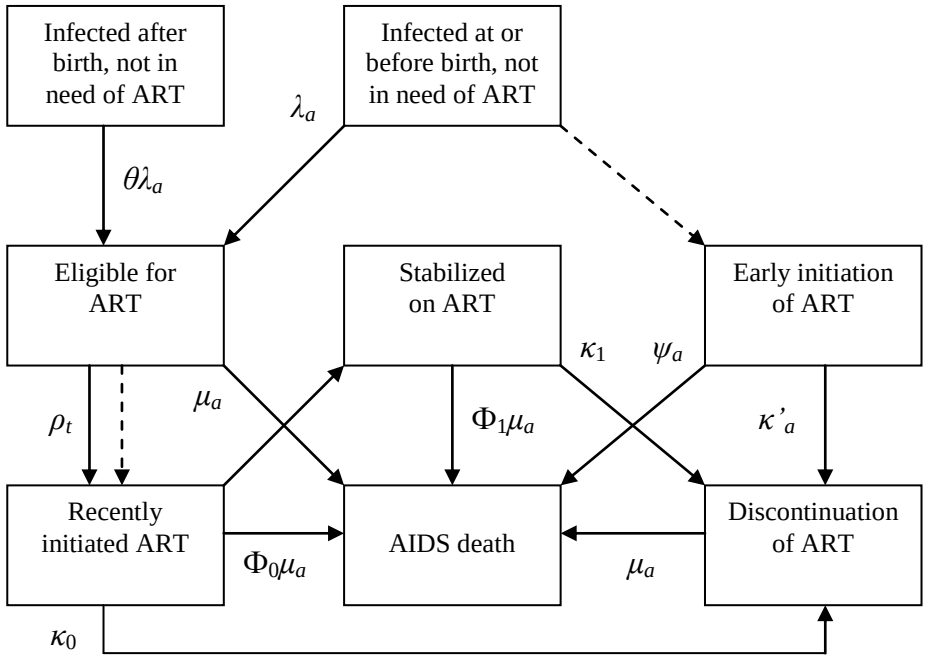

Figure 3: Multi-state model of survival in HIV-infected children
All children are assumed to experience non-AIDS mortality rates that vary by age and sex (not shown). Dashed arrows represent ART initiation at 2 months of age, following PCR screening at 6 weeks.

The time taken to reach the 2006 WHO eligibility criteria is assumed to be Makeham-distributed, so that the rate of progression to ART eligibility starts very high in the first few months of life, then drops to low levels thereafter. Mathematically, the annual rate of progression to ART eligibility at age *a*, in perinatally-infected children, is

$$\lambda_a = G_p + H_p \times c^a,$$

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. This rate is multiplied by a factor θ in postnatally-infected children. The parameters G_p, H_p and θ are allowed to vary in the uncertainty analysis, with the means of the prior distributions set at 0.4, 2.0 and 0.35 respectively. Parameter c is fixed at a value of 0.25. The values of H_p and c are based on two South African studies that have evaluated rates at which perinatally-infected infants progress to CD4 counts below the previously-used CD4 thresholds for starting ART.[43, 44] The value of θ is based on studies that have compared mortality rates in perinatally- and postnatally-infected African children.[45-48] Since almost all perinatally-infected children progress to ART eligibility in the first year of life, the children who progress to ART at older ages will be mostly postnatally-infected. A study of rates of progression in older Ugandan children[49] has therefore been used to approximate the product of G_p and θ.

After children progress to ART eligibility, untreated HIV survival times are assumed to be Makeham-distributed, with high mortality at young ages and low mortality at older ages. Mathematically, the mortality rate in untreated ART-eligible children at age a is

$$\mu_a = G_m + H_m \times d^a,$$

where G_m is the annual rate of mortality that would be expected in older ART-eligible children, 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. The parameters G_m and H_m are allowed to vary in the uncertainty analysis, with mean values of 0.12 and 3.5 respectively. Parameter d is fixed at 0.05. These parameters are derived by fitting the model to mortality data from a South African study of children diagnosed with HIV-related symptoms that render them eligible for ART,[50] conducted prior to the availability of ART in the South African public sector. Parameter G_m is also based on a collaborative study examining AIDS mortality in older children in different CD4 categories, which pools mortality data from several developing countries.[51]

Children who are in the untreated ART-eligible state are assumed to begin treatment at rate ρ_t in year t. Prior to 2008, this rate is determined from numbers of patients starting ART in the public and private health sectors in South Africa.[22] After 2008, it is assumed that the number of ART-eligible children starting therapy each month is 50% of the number progressing to the ART-eligible state in that month. In addition, it is assumed that a fraction of infected children not yet in the 'ART-eligible' state start ART at the age of 2 months, following PCR testing at 6 weeks of age. This is in line with new South African treatment guidelines,[52] which recommend PCR screening of all HIV-exposed infants at the age of 6 weeks, and immediate initiation of ART in all those infants who test positive. This fraction is set to 53% from 2010 onwards, based on current proportions of HIV-exposed infants who receive PCR testing and diagnosis soon after birth. [21, 53-57]

Children who start ART when they are in the ART-eligible state are assumed to remain at high mortality risk for an initial phase, lasting three months on average, before progressing to

a "stabilized on ART" state, in which they are assumed to experience a low mortality risk. The mortality rates in these two treatment phases are expressed as multiples of the corresponding mortality rates in untreated ART-eligible children of the same age, so that the mortality rate is $\Phi_0\mu_a$ during the high risk phase and $\Phi_1\mu_a$ during the low risk phase. The multiples Φ_0 and Φ_1 have been set at 0.95 and 0.1 respectively, these multiples being chosen to produce mortality estimates consistent with age-specific mortality rates at different treatment durations in a collaborative study of paediatric antiretroviral treatment programmes in South Africa.[58] The annual rates of treatment discontinuation are also assumed to be higher during the high risk phase than in the low risk phase ($\kappa_0 = 0.12$ and $\kappa_1 = 0.03$ respectively, based on the same study of South African ART programmes[58]).

Children who start ART before having met the 2006 WHO criteria for ART eligibility are assumed to experience a low rate of mortality, calculated as

$$\psi_a = \Phi_1\left(G_m + P \times H_m \times d^a\right),$$

where P is the factor by which the excess early mortality rate is reduced as a result of early ART initiation. This factor has been set at 0.4, to produce a mortality rate in children starting ART early that is 0.24 times the mortality rate in children in whom ART is deferred, consistent with the reduction in mortality that was observed in a randomized trial of early versus deferred paediatric ART in South Africa.[43] Rates of treatment discontinuation in children who start ART early are assumed to be similar to those in children in whom ART is deferred.

4. Comparisons of intervention impacts

Table 3 shows the expected reduction in numbers of new HIV infections in children, for each of the three scenarios described in the main text, for each year from 2010 to 2015. As noted in the main text, the most effective of the interventions is the 50% reduction in maternal HIV incidence, and the least effective is HIV screening of infants and their mothers at immunization clinics. In general, the interventions are less effective in 2010 than in subsequent years, as much of the transmission in 2010 is postnatal transmission from women who were infected in previous years. For each intervention, there is a slight reduction in effectiveness after 2012, due to assumed increases in levels of breastfeeding in those women who are diagnosed HIV-positive, as free formula milk is gradually phased out.

Table 3: Percentage reduction in MTCT due to different interventions

Intervention	% reduction in MTCT in individual years (95% CI)					Total
	2010-11	2011-12	2012-13	2013-14	2014-15	2010-15
50% reduction in maternal HIV incidence	13.2% (10.7-15.7)	16.8% (14.5-19.4)	17.3% (15.0-19.7)	17.0% (14.8-19.4)	16.8% (14.6-19.2)	16.2% (13.9-18.6)
Repeat antenatal testing at 34 weeks	8.4% (6.9-9.9)	11.3% (9.6-12.8)	12.3% (10.5-13.9)	12.2% (10.5-13.7)	11.9% (10.3-13.5)	11.2% (9.5-12.7)
Screening at 6-week immuni-zation clinics	1.2% (0.9-1.5)	3.6% (2.8-4.6)	4.5% (3.4-5.5)	4.4% (3.4-5.4)	4.2% (3.3-5.2)	3.5% (2.7-4.4)
All interventions	21.3% (18.4-24.5)	28.6% (25.6-31.5)	30.3% (27.3-32.9)	29.9% (27.0-32.5)	29.3% (26.5-31.9)	27.8% (24.8-30.5)

The effect of repeating the offer of HIV testing in late pregnancy can be split into two components: the effect of retesting women who previously tested negative and the effect of repeating the offer of HIV testing to women who previously refused testing (or who might not have been offered testing at their first antenatal visit, due to administrative oversight). It has been assumed that the rates of uptake of HIV screening in the two groups are 80% and 50% respectively. If it is instead assumed that the rates are 80% and 0% respectively, the percentage reduction in new HIV infections over the 2010-15 period is 4.9% (95% CI: 4.1-5.9%). Setting the rates to 0% and 50% results in an HIV incidence reduction of 6.2% (95% CI: 5.4-7.0%), greater than the reduction in incidence from testing only the previously tested women. Repeating the offer of HIV testing in late pregnancy therefore appears to have a greater impact on transmission from chronically-infected mothers than on transmission from mothers who seroconvert after their first antenatal visit, and the overall impact of the intervention is therefore more sensitive to the assumed proportion of previously untested women who accept testing when offered in late pregnancy.

5. Sensitivity analysis: rates of mother-to-child transmission and paediatric HIV survival

In the uncertainty analysis, ten parameters were allowed to vary: five parameters affecting the rate of mother-to-child transmission and five parameters affecting HIV survival rates in untreated HIV-positive children. The effect of each of these parameters on the proportion of MTCT from mothers who seroconverted after their first antenatal visit, in year 2008, was assessed through scatterplots and through the calculation of correlation coefficients. Figure 4 compares the sensitivity of the proportion of MTCT from recently-infected mothers to each of the transmission parameters. As might be expected, the proportion is strongly positively associated with the probability that a woman seroconverting in late pregnancy transmits HIV to her infant at/before birth, and to the monthly probability of transmission from women in the acute phase of HIV infection while breastfeeding (panels B and C respectively). The proportion is also positively associated with the uptake of nevirapine (panel A), because nevirapine reduces transmission from mothers who are diagnosed with HIV at their first antenatal visit but has minimal impact on transmission from mothers who seroconvert after their first antenatal visit. The proportion is negatively associated with the monthly probability of transmission from chronically-infected mothers who practise mixed feeding, as this parameter has more of an effect on the transmission from mothers who were seropositive at their first antenatal visit than on the transmission from mothers who seroconvert.

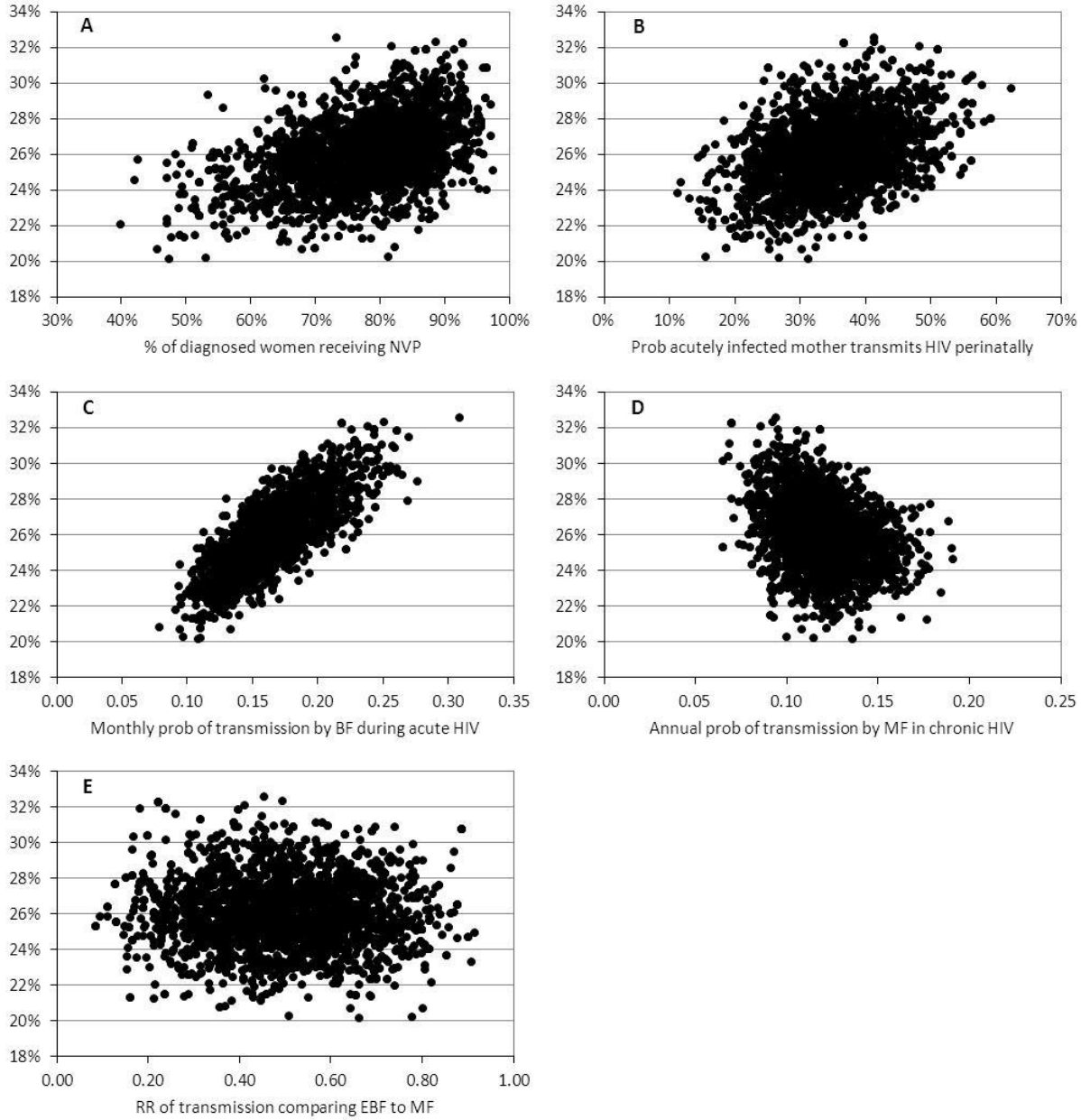

Figure 4: Correlation between HIV transmission parameters and modelled proportion of MTCT from mothers seroconverting after first antenatal visit, in 2008

The y-axis in each panel represents the fraction of MTCT from mothers seroconverting after first antenatal visit, in 2008. BF = breastfeeding; EBF = exclusive breastfeeding; MF = mixed breastfeeding; NVP = nevirapine.

Correlation coefficients for all ten parameters were calculated, and are shown in Table 4. Partial correlation coefficients were also calculated, to assess the effect of controlling for variation in parameters other than the parameter of interest.[59] The partial correlation coefficients for the HIV transmission parameters suggest much stronger correlation than the standard correlation coefficients, particularly in the case of the relative rate of transmission from mothers practising EBF when compared to that in mothers practising mixed feeding, which did not appear to be a significant factor in panel E of Figure 4. Lower transmission risk from mothers practising EBF is associated with lower rates of transmission from mothers who are seropositive at their first antenatal visit, relative to those in women who seroconvert after their first antenatal visit, as the latter group of women are less likely to be diagnosed and

hence less likely to practise EBF. Parameters determining paediatric HIV survival times have minimal effect on the proportion of MTCT that is from recently-infected mothers, either before or after controlling for other sources of variation, and scatterplots for these parameters are therefore not included in Figure 4.

Table 4: Correlation between model parameters and modelled proportion of MTCT from mothers seroconverting after first antenatal visit, in 2008

Parameter	Symbol	Correlation coefficient	Partial correlation
% of diagnosed women receiving NVP	α_0	0.44	0.98
Probability that acutely infected mother transmits HIV perinatally	π^*	0.40	0.98
Monthly probability of transmission by mixed feeding during acute infection	h_0	0.77	0.99
Annual probability of transmission by mixed feeding during chronic infection	$1-(1-h_1)^{12}$	-0.31	-0.92
Relative risk of transmission comparing EBF to mixed feeding	h_2/h_1	-0.02	-0.54
Annual rate of progression to ART eligibility in older children	G_p	0.03	0.01
Excess annual rate of progression to ART eligibility in neonates	H_p	0.01	0.01
Relative rate of progression to ART eligibility if infected after birth	θ	0.07	0.02
Annual rate of AIDS mortality in older children who are untreated and ART-eligible	G_m	-0.01	0.04
Excess annual rate of AIDS mortality in neonates who are untreated and ART-eligible	H_m	0.01	0.02

ART = antiretroviral treatment; EBF = exclusive breastfeeding; NVP = nevirapine.

6. Sensitivity analysis: maternal HIV incidence rates

As noted in the main text, it is possible that maternal HIV incidence rates may have been under-estimated, as some studies suggest that there is an elevated risk of HIV acquisition during pregnancy and lactation.[60-64] It is also possible that the model used to determine the HIV incidence rates in pregnant and breastfeeding women may have under-estimated the pace of recent HIV incidence declines, due to insufficient allowance for increases in condom use and increasing rates of HIV testing in recent years.[65] We have therefore considered two alternative scenarios to the base scenario presented in the main text: (1) a scenario in which maternal HIV incidence rates are assumed to be double those presented in Table 1; and (2) a scenario in which maternal HIV incidence rates are assumed to be the same as those in Table 1 up to 1998 (the year in which maternal HIV incidence peaks) but then decline more rapidly, reaching 1.4% by 2008 (half of the 2008 HIV incidence rate in Table 1) and remaining at 50% of the corresponding rates in the base scenario after 2008. For each of the two alternative scenarios the model is refitted, using the same Incremental Mixture Importance Sampling method as used to fit the model in the main scenario. The results for the three scenarios are compared in Table 5. The model fit to the paediatric HIV prevalence data, as represented by the natural logarithm of the integrated likelihood, is best for the scenario in which there is assumed to be a steeper decline in maternal HIV incidence after 1998 (scenario 2). However, the differences between the integrated likelihood values of the different models are not substantial enough to indicate 'strong evidence' that the model presented in scenario 2 is superior to the models in the other two scenarios, according to the significance thresholds recommended by Kass and Raftery.[66]

Table 5: Sensitivity analysis comparing estimates in different maternal HIV incidence scenarios

	Base scenario	Double maternal incidence	Halve maternal incidence post-2008
Log of integrated likelihood	-16.01	-17.27	-14.50
Probability acutely infected mother transmits HIV perinatally	34.4% (20.5-50.1)	32.4% (18.9-48.1)	34.6% (20.0-50.7)
Monthly probability of transmission by mixed feeding during acute infection	16.8% (11.1-23.2)	14.6% (9.8-20.3)	17.1% (11.8-23.0)
New HIV infections in 2008	57 000 ($51\text{-}64\times10^3$)	68 000 ($60\text{-}75\times10^3$)	42 000 ($37\text{-}49\times10^3$)
% of MTCT in 2008 from mothers who seroconvert after first antenatal visit	26.2% (22.5-30.2)	39.8% (35.2-44.8)	15.4% (13.0-17.9)
% reduction in MTCT 2010-15 if maternal HIV incidence is halved	16.2% (13.9-18.6)	23.1% (20.4-25.8)	9.9% (8.3-11.7)
% reduction in MTCT 2010-15 if rescreening occurs in late pregnancy	11.2% (9.5-12.7)	10.4% (8.7-12.0)	12.1% (10.4-13.6)
% reduction in MTCT 2010-15 if maternal HIV testing is conducted at 6-week immunization	3.5% (2.7-4.4%)	3.1% (2.3-4.1)	3.8% (3.0-4.7)
Combined effect of all three interventions	27.8% (24.8-30.5)	33.1% (30.2-35.8)	23.1% (20.4-25.5)

The posterior estimates of the probability of perinatal transmission in mothers who seroconvert during late pregnancy are similar in the three scenarios. The monthly probability of MTCT by mixed feeding during acute HIV infection is slightly higher in scenario 2 than in scenario 1, as a higher transmission rate is needed to match the observed levels of paediatric HIV prevalence when the maternal HIV incidence rate is lower. The total number of new HIV infections in 2008 is quite sensitive to the assumed maternal HIV incidence rate, ranging from 42 000 in scenario 2 to 68 000 in scenario 1. There is correspondingly wide variation in the modelled effect of halving maternal HIV incidence rates after 2010, with the reduction in MTCT ranging from 9.9% (95% CI: 8.3-11.7%) in scenario 2 to 23.1% (95% CI: 20.4-25.8%) in scenario 1, over the 2010-15 period. However, the effects of rescreening in late pregnancy and screening at immunization clinics are less sensitive to the assumed maternal HIV incidence rate and are *negatively* related to the level of maternal HIV incidence. As explained in section 4, rescreening in late pregnancy has more of an effect on transmission from chronically-infected mothers than on transmission from acutely-infected mothers, and rescreening in late pregnancy therefore has *less* overall impact when maternal HIV incidence rates are high. Testing of infants and mothers at 6-week immunization clinics is also likely to diagnose more chronically-infected mothers than recently-infected mothers. Most of the transmission from recently-infected mothers is postnatal transmission (Figure 3a of main text) and relatively few of the women who seroconvert while breastfeeding would be identified at 6-week immunization visits.

7. Sensitivity analysis: infant feeding practices post-2010

The South African Department of Health has recently announced a change in policy regarding infant feeding for HIV-positive mothers, stating that it will be gradually phasing out the free provision of formula milk at government clinics and instead encouraging all women to practise exclusive breastfeeding. In our base scenario, we have assumed that this will lead to a reduction in the proportion of HIV-diagnosed women who use replacement

feeding from birth, with this proportion declining from 50% in 2010 to 20% in 2013 (Table 2). However, there is little information on the likely extent of the changes in feeding practices by HIV-diagnosed mothers, and we therefore assess the sensitivity of our results to changes in assumed feeding practices. Figure 5 compares the results of the model in two scenarios: the base scenario in which formula milk is assumed to be withdrawn, and an alternative scenario in which there is assumed to be no change in feeding practices. Although the change in feeding policy is expected to lead to some increase in the annual number of new infections in children (Figure 5a), this effect is relatively small, due to the high proportions of HIV-diagnosed mothers who are assumed to be receiving long-term antiretroviral treatment or administering extended nevirapine prophylaxis to their children while breastfeeding. There is also relatively little change in the proportion of MTCT from mothers who seroconvert after their first antenatal visit (Figure 5b). The expected impact of the combined intervention package summarized in Table 3 (reduced maternal incidence, rescreening in late pregnancy and screening at 6-week immunization clinics) is also relatively insensitive to the assumed extent of the change in feeding practices: the reduction in new HIV infections in children over the 2010-2015 period is expected to be 27.8% (95% CI: 24.8-30.5%) in the base scenario in which free formula milk is assumed to be withdrawn, and 28.8% (95% CI: 25.8-31.6%) in the scenario in which there is assumed to be no change in feeding practices.

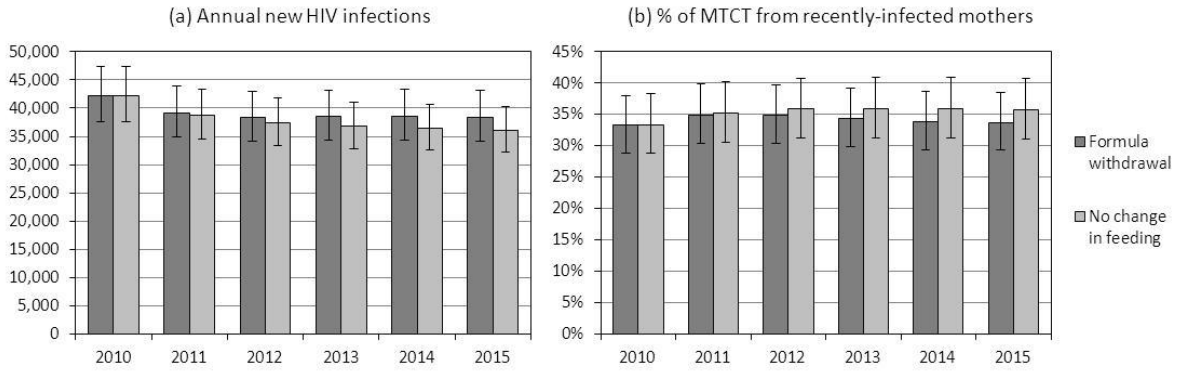

Figure 5: Effect of change in feeding practices on mother-to-child transmission

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