# A model of paediatric HIV in South Africa

Centre for Infectious Disease Epidemiology and Research working paper
December 2010

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# Synopsis

## Introduction

Several recent studies in Southern African countries have suggested a higher level of HIV prevalence in children than is estimated by mathematical models. A number of potential explanations for this high HIV prevalence in children have been suggested, including nosocomial transmission of HIV, HIV transmission as a result of sexual abuse, false positive reactions on HIV antibody tests, lower-than-expected rates of mortality in children infected with HIV, and higher rates of mother-to-child transmission than previously estimated. This study aims to characterize the paediatric HIV epidemic in South Africa using a mathematical model, and to assess which of these explanations are most likely. A further objective is to evaluate the impact of the prevention of mother-to-child transmission (PMTCT) programme and the paediatric antiretroviral treatment (ART) programme in South Africa, and to assess how the impact of these programmes may change in the future.

## Method

A mathematical model of HIV incidence in children and HIV survival has been created, using South African data sources. The model projects the size of the population under the age of 15 at monthly intervals, starting in the middle of 1985. Estimates of the 1985 population profile, non-AIDS mortality rates and annual numbers of births to mothers who are HIV-positive and HIV-negative are obtained from the ASSA2003 AIDS and Demographic model, a widely used model of the South African HIV epidemic. Estimates of HIV incidence in mothers are also obtained from the ASSA2003 model, so that the model can allow for vertical transmission from mothers who seroconvert after their antenatal HIV screening visit.

The model allows for two modes of HIV transmission in children under the age of 15: transmission from infected mothers at or before birth (intrapartum or intrauterine transmission) and transmission from infected mothers after birth, as a result of breastfeeding. In the absence of PMTCT, women who are HIV-seropositive at the time of their first antenatal screening visit are assumed to have an average probability of transmitting the virus at delivery equal to 0.2, with the probability varying according to the mother's CD4 count. A higher transmission probability applies if the mother becomes infected prior to delivery and seroconverts after her first antenatal visit. In the absence of PMTCT, women who are HIV-seropositive at delivery are assumed to have a constant HIV transmission probability per month of breastfeeding. If the woman acquires HIV while breastfeeding, a higher transmission probability is assumed to apply during the acute phase that follows HIV acquisition. Based on the 1998 South African Demographic and Health Survey (DHS), it is assumed that 86.7% of undiagnosed HIV-positive mothers breastfeed and the median duration of breastfeeding is 18 months.

Assumptions about access to PMTCT and PMTCT uptake are based on District Health Information System data collected from 2004 to 2009, and from earlier surveys. The HIV transmission probability at birth is assumed to reduce by 40% if the mother receives single-dose nevirapine during labour, by 65% if the mother receives

AZT from 28 weeks gestation, and by 80% if the mother receives both AZT from 28 weeks and single-dose nevirapine in labour. Women who initiate highly active ART (HAART) during pregnancy are assumed to have a 0.02 probability of transmitting the virus to their infant at birth. It is assumed that 50% of women who receive positive test results elect to formula feed, 34.6% initially practice exclusive breastfeeding (which is assumed to reduce the risk of transmission per month of breastfeeding), and the remaining 15.4% practise mixed feeding from birth, for a median duration of 7 months. In women who know themselves to be positive and elect to practise exclusive breastfeeding (EBF), the median duration of EBF is assumed to be 2 months, after which women either practise abrupt weaning or switch to mixed feeding. If women receive HAART while breastfeeding, the monthly postnatal transmission risk is assumed to be reduced by 80%. If the mother does not receive HAART while breastfeeding, but the infant receives extended nevirapine prophylaxis, the rate of transmission is assumed to be reduced by 60%.

Survival of HIV-infected children is modelled using a six-state model of HIV infection. Upon initial infection, children enter the first state, which represents children who are not yet eligible for ART. They then progress to a second state, which represents untreated children who are eligible to receive ART in terms of clinical or immunological criteria (this does not include all infants, although recent guidelines consider all children in their first year of life to be ART-eligible irrespective of clinical or immunological criteria). The rate at which children progress from the first state to the second is assumed to depend on their age (with faster progression at younger ages) and their mode of transmission (children infected postnatally are assumed to have slower progression). In the absence of ART, children in the second state are assumed to experience a high rate of AIDS mortality at young ages, but the AIDS mortality rate in the untreated ART-eligible state reduces after the first year.

The third HIV state represents children who have recently initiated ART and are still at a high mortality risk. The fourth state represents children who have ‘stabilized’ on ART and are at a low mortality risk. Children can discontinue ART as a result of death or defaulting therapy, and the fifth state represents the children who have discontinued ART but are still alive. The rates at which children on ART are assumed to die or discontinue ART are based on the results of a collaborative analysis of paediatric ART programmes in South Africa, which suggests that rates of retention on ART are particularly poor during the first few months of therapy. A sixth state is defined for children who start ART prior to entering the second state, as recent South African evidence shows that these children are likely to have a significantly lower rate of mortality in the first year of life than children who start ART after entering the ART-eligible state. Assumptions about the numbers of children starting ART in each year are based on public sector data collected over the period from 2004 to 2008, and data collected from disease management programmes and NGOs over the 2000 to 2008 period.

As there is substantial uncertainty regarding many of the paediatric HIV parameters, it is necessary to conduct an uncertainty analysis. A Bayesian approach is adopted, with prior distributions being specified to represent the ranges of uncertainty for ten of the model parameters that are considered most difficult to quantify. A likelihood function is specified, to represent the ‘goodness of fit’ of the model to observed levels of paediatric HIV prevalence in the 2005 and 2008 Human Sciences Research Council

(HSRC) household surveys. The posterior distribution of model outputs is approximated numerically, using the Incremental Mixture Importance Sampling algorithm. Each result presented is the average of the values in the posterior distribution, together with the 2.5 and 97.5 percentiles of the posterior distribution (95% confidence intervals).

**Results**

By the middle of 2008, an estimated 3.8% of South African children (95% CI: 3.4-4.4%) were infected with HIV, equivalent to a total of 598 000 (95% CI: 525 000-682 000) infections under the age of 15. Of these infected children, an estimated 51 000 were receiving ART, and a further 262 000 (95% CI: 157 000-385 000) were eligible for ART but ART-naïve. This implies an ART coverage of 17% (95% CI: 12-24%).

Over the period from the middle of 2007 to the middle of 2008, an estimated 68 000 (95% CI: 61 000-75 000) new HIV infections occurred in children. Of these, 58% (95% CI: 52-63%) were acquired at or before birth and the remainder were acquired after birth. 23% (95% CI: 20-27%) of all new infections occurred in children whose mothers were HIV-seronegative at the time of their first antenatal visit. The South African PMTCT programme is estimated to have reduced the number of new HIV infections in children over the 2007-2008 period by 34% (95% CI: 30-37%) relative to what would have been expected in the absence of a PMTCT programme.

Over the same period, from the middle of 2007 to the middle of 2008, an estimated 44 000 AIDS deaths (95 CI: 34 000-55 000) occurred in children, and 32% of these deaths (95% CI: 25-40%) occurred in children aged less than 12 months. The paediatric ART programme has reduced the number of AIDS deaths over the period from mid-2007 to mid-2008 by 7.2% (95% CI: 5.2-9.8%), relative to what would have been expected in the absence of ART, and the PMTCT programme has reduced the number of AIDS deaths over the same period by 16% (95% CI: 13-19%), relative to what would have been expected in the absence of PMTCT and ART. The combined effect of the PMTCT and ART programmes is a 22% reduction (95% CI: 18-26%) in the number of paediatric AIDS deaths over the 2007/2008 period.

The recent changes in PMTCT protocols introduced by the Department of Health can be expected to increase the proportion of HIV infections averted to 62% (95% CI: 59-65%) by 2015. This is mainly due to the effect of including short-course AZT in the PMTCT regimen, though some of the increase can also be attributed to the effect of greater HAART initiation in pregnant women and the introduction of extended nevirapine prophylaxis for children who are breastfed by HIV-positive mothers. Further reductions in vertical transmission could be achieved through initiation of ART in all HIV-positive pregnant women and through maternal HIV screening at immunization clinics, but the greatest reductions in HIV incidence would be achieved through better implementation of existing protocols. The recent changes to paediatric ART guidelines are expected to lead to a 29% reduction in AIDS deaths (95% CI: 26-33%) over the 2010-2025 period, relative to what would be expected in the absence of paediatric ART, if current levels of PCR testing in infants remain unchanged and if there is no change in the rate of ART initiation in older children. If it is more optimistically assumed that the proportion of perinatally-infected infants starting ART

after 6-week PCR screening increases to 80% and that the numbers of children starting ART at older ages increases to 80% of the new treatment need, the number of AIDS deaths over the 2010-2025 period would be 38% lower (95% CI: 34-43%) than the number that would be expected in the absence of paediatric ART.

Sensitivity analyses were conducted to assess the sensitivity of the model results to allowance for non-vertical transmission in children, allowance for higher non-AIDS mortality in children who are not breastfed, and allowance for higher AIDS mortality in HIV-positive children who are PMTCT-exposed than in HIV-positive children who are not PMTCT-exposed. Although the HIV prevalence data do not support the assumption that there are significant levels of nosocomial transmission of HIV in children, the significance of HIV transmission due to sexual abuse remains unclear. The model suggests shorter survival times in HIV-infected children and higher AIDS mortality when non-vertical transmission is assumed. Estimates of infant mortality and under-5 mortality are sensitive to assumptions about the effects of breastfeeding and PMTCT exposure on mortality in HIV-uninfected and infected children respectively, and estimates of the impact of PMTCT on mortality are reduced substantially when allowing for these dynamics. However, programmes to promote exclusive breastfeeding can be expected to have a significant positive impact on infant and under-5 mortality if it is assumed that breastfeeding is associated with reduced non-AIDS mortality.

The model was applied to the Western Cape (WC) and KwaZulu-Natal (KZN) provinces. These two provinces differ significantly in terms of their paediatric HIV incidence in 2007/8 (95 new infections per 1000 births in KZN versus 19 new infections per 1000 births in WC) and paediatric HIV prevalence in 2008 (5.9% in KZN versus 1.3% in WC). This is explained partly by differences in maternal HIV prevalence and partly by differences in the pace of PMTCT rollout. Over the period from mid-2007 to mid-2008, the PMTCT programme in WC is estimated to have achieved a 57% reduction (95% CI: 52-61%) in paediatric HIV incidence, compared to a 25% reduction (95% CI: 22-27%) in KZN. The rollout of ART in WC has also been much more rapid than in KZN, with paediatric ART coverage reaching 54% in WC and 16% in KZN, by the middle of 2008. The combined effect of the PMTCT and ART programmes, over the 2007-2008 period, has been a 55% reduction (95% CI: 48-64%) in AIDS deaths in WC and a 17% reduction (95% CI: 14-20%) in AIDS deaths in KZN.

The model results were compared with the results of other models. The Spectrum model used by UNAIDS estimates the number of HIV infections in South African children in 2007 (280 000, 95% CI: 230 000-320 000) to be less than half the number estimated by our model (580 000, 95% CI: 510 000-660 000). Similarly, the ASSA2003 model estimates the HIV prevalence in children in 2008 to be 2.1%, roughly half the prevalence estimated by the new model (3.9%, 95% CI: 3.4-4.4%). Another model, described by Little *et al* (2007), estimates the number of paediatric HIV infections in 2003 to be similar to our model estimates, but estimates the number of untreated ART-eligible children in 2002 to be 45 000, which is significantly lower than our new model estimates (171 000, 95% CI: 120 000-235 000). Assumptions about rates of AIDS mortality in HIV-infected children differ substantially between the models, with our new model estimating a significantly lower rate of AIDS

mortality in those children infected at or before birth, when compared with the ASSA2003 and Spectrum models.

**Discussion**

This analysis suggests that the level of HIV prevalence in children and the unmet need for ART in children is substantially greater than has been estimated in previous model-based analyses. In part, this is because most other models have assessed the rate of mother-to-child transmission using the HIV prevalence in pregnant women at their first antenatal screening visit, and have ignored the very significant vertical transmission that can occur in women who seroconvert after their first antenatal visit, either before delivery or while breastfeeding. The high HIV prevalence estimated by our model is also partly due to the lower rate of AIDS mortality estimated in our analysis, particularly in children who acquire HIV at or before birth.

Although it is possible that our model estimates of AIDS mortality rates are understated, the estimates are based on empirical data, and assuming significantly higher AIDS mortality rates would result in model estimates of paediatric HIV prevalence lower than those observed in the HSRC household surveys. It is unlikely that the HIV prevalence levels measured in the 2005 and 2008 household surveys would be exaggerated by false positive reactions, since confirmatory testing of all reactive specimens was conducted in both surveys. It is also unlikely that the high levels of paediatric HIV prevalence observed in the HSRC surveys would be due to nosocomial transmission, although the significance of sexual abuse remains unclear, and further research is required.

This analysis suggests that the PMTCT programme in South Africa has already had a significant impact on HIV incidence, and that the recent adoption of new PMTCT protocols can be expected to lead to a roughly 60% reduction in paediatric HIV incidence by 2015. Further reductions in HIV incidence could be achieved through better implementation of existing protocols. However, a significant problem is the high proportion of vertical transmission occurring from mothers who have recently seroconverted and are undiagnosed. New interventions will need to be developed to address this problem.

Although the PMTCT programme in South Africa has been moderately successful, the impact of the paediatric ART programme has been relatively small thus far. The level of ART coverage in children in 2008 (17.0%, 95% CI: 11.8-24.4%) was substantially lower than that in adults (40%), and the reduction in AIDS mortality as a result of ART over the 2007-2008 period was also significantly lower in children (7.2%, 95% CI: 5.2-9.8%) than in adults (23%). This may be a reflection of the greater challenges associated with diagnosing and treating paediatric HIV. It may also be a reflection of fundamental differences in the natural history of HIV in adults and children, as well as differences in guidelines for starting ART in adults and children. The recent recommendation that ART be initiated in all HIV-positive infants (i.e. children under 12 months of age), regardless of their CD4 or clinical status, is likely to have only a modest impact on AIDS deaths in children, as the proportion of HIV-positive infants receiving PCR testing remains low, and less than a third of current paediatric AIDS deaths occur in the first year of life. However, with expansion of PCR testing in infants and higher rates of ART initiation in infected children at older

ages, paediatric ART can be expected to have a more substantial impact on AIDS mortality in the longer term.

The model that we have developed has a number of limitations. Firstly, the model does not allow for changes over time in the CD4 distribution in HIV-positive pregnant women, nor does it consider births to women who were receiving ART at the time of conception. The integration of the paediatric HIV model with a detailed model of adult HIV would be required in order to model these dynamics more accurately. The model also does not assess the effect of maternal death on child survival, although there is evidence to suggest that children whose mothers have recently died are themselves at a higher mortality risk. Another limitation is that the model does not allow for the effect of PMTCT to vary according to both the child and the mother's adherence to antiretroviral prophylaxis; in the interests of simplicity, it is assumed that efficacy depends only on whether the mother receives prophylaxis. A further problem is that there is a lack of reliable data on PMTCT coverage, and there are particular concerns regarding the accuracy of the District Health Information System data. There is also little information regarding HIV prevalence in women attending private antenatal facilities and women who deliver 'unbooked' in public health facilities, which makes it difficult to quantify accurately levels of HIV prevalence in mothers. Lastly, it has not been possible to incorporate mortality data into this analysis. Our results suggest that the model mortality estimates are quite sensitive to unknowns such as the effect of replacement feeding on non-AIDS mortality rates, and the extent of non-vertical transmission. The model mortality estimates therefore need to be treated with caution.

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## Note on terminology

The terms “antiretroviral treatment” (ART) and “highly active antiretroviral treatment” (HAART) are used here to refer to combinations of three or more antiretroviral drugs, including either non-nucleoside reverse transcriptase inhibitors or protease inhibitors, that are used for the lifelong treatment of HIV in adults and children. The term “antiretroviral prophylaxis” is used here to refer to the use of antiretroviral drugs to prevent the mother-to-child transmission of HIV, typically through the short-term administration of antiretroviral drugs, either to the mother or to the infant.

# 1. Introduction

Several recent surveys conducted in Southern Africa have measured levels of HIV prevalence in children aged 5 to 9 of between 3 and 6% (Human Sciences Research Council 2008; Shisana *et al*, 2009). These are higher than the levels of HIV prevalence predicted by mathematical models, which generally assume that most HIV-infected children die before the age of 5 years (UNAIDS Reference Group on Estimates Modelling and Projections 2009; Dorrington *et al*, 2006). This has raised questions about the significance of paediatric HIV transmission from sources other than infected mothers, as well as questions about the specificity of the assays used in measuring paediatric HIV prevalence (Human Sciences Research Council 2008). Questions also need to be asked about the validity of the paediatric HIV survival assumptions and vertical transmission assumptions that are commonly made in models of paediatric HIV.

This study aims to characterize the paediatric HIV epidemic in South Africa using a mathematical model, and to use this model to determine the reasons for the high HIV prevalence in older children. Trends in paediatric HIV prevalence in children are significantly affected by prevention of mother-to-child transmission (PMTCT) and antiretroviral treatment (ART) programmes, and this study therefore also aims to assess the impact of the PMTCT and ART programmes that have been introduced to date in South Africa.

An additional objective of this study is to assess the potential impact of future changes to PMTCT and paediatric ART in South Africa. Recent guidelines issued by the World Health Organization (2009a) and the South African Department of Health (2010) recommend that ART should be initiated in all pregnant HIV-positive women who have CD4 counts less than 350/μl, and that children who are breastfed by HIV-positive mothers should receive nevirapine prophylaxis if their mothers are not receiving ART. In addition, the new South African ART guidelines recommend that all infants who are diagnosed HIV-positive in the first year of life should start ART immediately, regardless of the CD4 count or clinical stage. The latest guidelines issued by the WHO go even further, recommending that in settings with limited access to immunological testing, ART should also be initiated in all infected children aged 12 to 24 months (World Health Organization 2010). These changes are likely to have a significant impact on rates of mother-to-child transmission and levels of paediatric mortality, but there has been no formal estimation of the likely impact of these protocol revisions.

The first section of this paper (section 2) describes the mathematical model and reviews the evidence on which the various model parameters are based. The next section describes the statistical approach that is used in fitting the model to the HIV prevalence data and in conducting the uncertainty analysis. Section 4 summarizes the key results of the model, and the final section (section 5) discusses the explanations for the high HIV prevalence in children, and the effect of paediatric HIV prevention and treatment programmes in South Africa. Section 5 also includes discussion of the limitations of the model and scope for further model development.

# 2. Model description

This section describes the mathematical model of paediatric HIV incidence and HIV survival, and reviews the evidence on which the model parameters are based. As certain of the parameters are difficult to quantify, it is necessary to conduct uncertainty analysis. For these parameters, prior distributions are specified to represent the range of uncertainty around the parameter values. A more detailed description of the approach to uncertainty analysis is provided in section 3.

## 2.1 Demographic parameters

The projection of the child population begins in 1985, and proceeds at monthly intervals. The initial numbers of children at each age, at the start of July 1985, is obtained from the ASSA2003 AIDS and Demographic model (Dorrington *et al*, 2006), and the annual numbers of births to HIV-positive and HIV-negative mothers in subsequent years are also obtained from the ASSA2003 model. This model of the South African HIV epidemic, developed by the Actuarial Society of South Africa (ASSA), was released in 2005, based on data collected up to 2003. The ASSA2003 model produces estimates of HIV prevalence in pregnant women that are roughly consistent with observed levels of HIV prevalence in the nationally representative antenatal clinic surveys, up to 2008, and it is therefore a reasonable source of estimates of numbers of births to HIV-positive mothers.

Non-AIDS mortality rates in children are also obtained from the ASSA2003 model. The model produces estimates of $q_{at}$, the annual mortality probability for children aged $a$ (in years) in year $t$. The paediatric HIV model projects the growth of the population at monthly intervals, and it is therefore necessary to convert the annual mortality probability into a monthly mortality rate. For children aged 1 year and older, the monthly mortality rate is assumed to be one twelfth of the annual mortality rate, i.e.

$$-\frac{1}{12}\ln\left(1-q_{at}\right). \qquad (2.1)$$

However, for children under the age of 1 year, the annual mortality probability is high and much of the mortality risk is concentrated in the first month of life. We therefore follow the approach of Nagelkerke *et al* (1995) and use a Weibull distribution to calculate the monthly mortality rate from the infant mortality rate in the ASSA2003 model. Suppose that $r$ and $b$ are the rate and shape parameters respectively for the Weibull distribution describing survival up to 12 months of age, i.e. the proportion of infants surviving to age $a$ (in years) is

$$\exp\left(-ra^{b}\right). \qquad (2.2)$$

Suppose that $q_{0t}$ and $q'_{0t}$ represent the infant and neonatal mortality rates respectively in year $t$, i.e. the probabilities of death by 12 months and 1 month respectively. Then

$$q_{0t} = 1 - \exp(-r) \tag{2.3}$$

$$q'_{0t} = 1 - \exp\left(-r\left(\frac{1}{12}\right)^{b}\right), \tag{2.4}$$

from which it follows that

$$r = -\ln(1 - q_{0t}) \tag{2.5}$$

$$b = \ln\left[\frac{\ln(1 - q'_{0t})}{\ln(1 - q_{0t})}\right]\left(\ln\left(\frac{1}{12}\right)\right)^{-1}. \tag{2.6}$$

Substituting the values of $q_{0t}$ and $q'_{0t}$ estimated from the 1998 DHS (0.0454 and 0.0198 respectively, for births in the preceding five years), gives $r$ = 0.0465 and $b$ = 0.339. For convenience, we use this value of $b$ for all years, although the parameter might be expected to vary slightly over time. This makes it possible to estimate the monthly survival probabilities (ignoring AIDS mortality) in each year, given only the $q_{0t}$ values estimated by the ASSA2003 model and the assumed value of $b$ = 0.339.

## 2.2 Intrauterine and intrapartum transmission

This section begins with a review of estimates of mother-to-child transmission at birth, in the absence of any intervention, and the effects of short-course antiretroviral prophylaxis, as well as antiretroviral treatment (ART) initiated for the mother's own health. Evidence on the probability of vertical transmission from mothers who acquire HIV in late pregnancy is also reviewed. The model assumptions that are made on the basis of this evidence are explained in section 2.2.5.

### 2.2.1 The probability of transmission at or before birth, in the absence of antiretroviral prophylaxis

Although there have been several studies in Africa that have estimated the proportion of women who transmit HIV to their children before or soon after birth, it is difficult to estimate the proportion of children who are infected intrauterine/intrapartum on the basis of these studies. This is because the PCR test typically does not yield a positive result until a few weeks after HIV transmission has occurred. It is therefore necessary to wait for at least a month before one can reliably identify almost all of the infants who have been infected before or at birth (Newell 1998). However, over this time period, some infants will have acquired HIV through breastfeeding, and might also be PCR-positive at the time of testing. This makes it difficult to identify the infants who were truly infected at or before birth.

It is possible to estimate the proportion of children who become infected at or before birth, based on what is known about the rate of transmission through breast milk and the rate at which newly infected infants develop detectable virus. Suppose that $R(a)$ is the proportion of infants born to HIV-positive mothers, who test positive at age $a$ (in months) on a PCR test, and further suppose that $\pi$ is the proportion of infants who

acquire HIV at or before birth, in the absence of any antiretroviral prophylaxis. If $f$ is the proportion of HIV-positive mothers who formula-feed exclusively and $\beta(a)$ is the probability that a breastfed child acquires HIV postnatally and has PCR-detectable virus by age $a$, then

$$R(a) = \pi + (1-\pi)(1-f)\beta(a), \tag{2.7}$$

if it is assumed that all of the infants infected at or before birth have PCR-detectable virus by age $a$ (this would generally be the case for $a \geq 1.5$ (Newell 1998)). From this it follows that

$$\pi = \frac{R(a) - (1-f)\beta(a)}{1-(1-f)\beta(a)}. \tag{2.8}$$

Suppose that breast-fed infants acquire HIV at rate $h$ and newly infected infants develop PCR-detectable virus at rate $\gamma$. Then

$$\begin{aligned}\beta(a) &= \int_0^a h\exp(-ht)(1-\exp(-\gamma(a-t)))dt \\ &= 1 - \frac{\gamma\exp(-ha) - h\exp(-\gamma a)}{\gamma - h}\end{aligned} \tag{2.9}$$

The parameters $h$ and $\gamma$ have been estimated to be 0.014 × 1/12 and 2.0 per month respectively (see section 2.3). In all of the studies considered here, $a$ is 1.5 months, and hence $\beta(a)$ is 0.012. Table 2.1 summarizes the results from a number of African randomized controlled trials, conducted to assess the efficacy of various interventions in preventing mother-to-child transmission. The results shown relate only to women who were not receiving any antiretroviral prophylaxis. For all studies except the Kenyan study (Nduati *et al,* 2000), the results presented are based on a meta-analysis published by Leroy *et al* (2005) rather than the originally published results (Dabis *et al*, 1999; Wiktor *et al,* 1999; Coutsoudis *et al,* 1999b; Petra Study Team 2002). The average estimate of the proportion of infants who acquire HIV intrauterine or intrapartum is 19.7%, only fractionally lower than the proportion of infants who have detectable virus at the age of 6 weeks.

Although Table 2.1 pools the results from a number of different African studies, it is important to note that rates of mother-to-child transmission could differ between populations, even in the absence of any interventions. There is some evidence to suggest that the rate of vertical transmission may be higher from subtype C-infected women than from women infected with subtypes A and D (Blackard *et al,* 2001; Renjifo *et al,* 2004), and since subtype C is the dominant HIV-1 subtype in South Africa, this might suggest a relatively high frequency of vertical transmission in South Africa. It has also been hypothesized that differences in vertical transmission rates between populations could be due to differences in levels of vitamin A deficiency (Semba *et al,* 1994), differences in the prevalence of genital tract infections (Goldenberg *et al,* 1998) and differences in levels of caesarean section (Dabis *et al,* 2000). In addition, factors such as differences in laboratory methods and differences in viral load distributions could account for differences in vertical transmission rates

between studies. However the comparison of the South African and other African results in Table 2.1 does not suggest any significant difference between vertical transmission rates in South Africa and the rest of Africa.

Table 2.1: Probabilities of mother-to-child transmission at or before birth in children born to women who do not receive antiretroviral prophylaxis

| Study | Location | n* | % of infants breastfed ($1 - f$) | % of infants PCR-positive at 6 weeks*, $R(1.5)$ | % of infants infected at/ before birth, $\pi$ |
|---|---|---|---|---|---|
| ANRS049a, 1995-8 | Côte d'Ivoire, Burkina Faso | 189 | 97.4% | 24.3% | 23.5% |
| CDC-RETRO-CI, 1996-8 | Côte d'Ivoire | 117 | 98.3% | 23.9% | 23.0% |
| PETRA, 1996-2000 | South Africa, Tanzania, Uganda | 153 | 75.5% | 19.6% | 18.9% |
| SA Vit A Study, 1995-8 | South Africa | 602 | 66.6% | 19.4% | 18.8% |
| Nduati *et al* (2000) | Kenya | 366 | 63.5% | 14.9% | 14.2% |
| Average | | | | 20.4% | 19.7% |

* Excluding infants for whom HIV status was unknown.

### 2.2.2 The effect of short course antiretroviral prophylaxis on the probability of mother-to-child transmission at or before birth

Until 2008, the recommended prophylaxis for pregnant HIV-positive women attending public health facilities in South Africa was a single dose of nevirapine to the woman at the time of going into labour, and a single dose of nevirapine to the infant soon after birth. This relatively simple intervention was found to reduce the risk of mother-to-child transmission by age 14-16 weeks by 47% (95% CI: 20-64%) in a randomized controlled trial conducted in Uganda (Guay *et al*, 1999). In a pooled analysis of mother-to-child transmission data from African countries, which included the data from the original Ugandan trial, the efficacy of the intervention was estimated to be slightly lower, at 40% (Leroy *et al*, 2005).

Other studies conducted in Africa have confirmed the effectiveness of this intervention. Table 2.2 summarizes the results from several independent studies that have estimated the probability of mother-to-child transmission at 6-8 weeks of age in mothers who received nevirapine (in most cases, the infant also received nevirapine). The average transmission rate is 11.9%, which is 58% of the transmission rate of 20.4% estimated in Table 2.1, and thus roughly consistent with the 40% reduction in the transmission probability estimated by Leroy *et al* (2005). However, the results in Table 2.2 show considerable variation, with the average transmission rate in the four cohorts with low breastfeeding (8.7%) being considerably lower than the average transmission rate in the six cohorts with high levels of breastfeeding (14.0%). This is similar to the findings in the pooled analysis of Leroy *et al* (2005), which suggest that the rate of transmission by 6 weeks is significantly greater in breastfed infants than in non-breastfed infants (odds ratio 1.54). This difference cannot be explained in terms

of early postnatal transmission alone, since the monthly probability of transmission through breastfeeding is low relative to the intrauterine and intrapartum transmission probability.

Table 2.2: African estimates of the rate of mother-to-child transmission in nevirapine-treated mother-infant pairs

| Study | Location | Age at PCR test | % not PCR tested | % formula fed | n | % HIV+ |
|---|---|---|---|---|---|---|
| Sherman *et al* (2004) | Johannesburg | 6 weeks | 0% | 97%[b] | 300 | 8.7% |
| Geddes *et al* (2008) | Durban | 6 weeks | 19%[a] | 93%[a,c] | 61 | 8.2% |
| Coetzee *et al* (2005) | Cape Town | 6 weeks | 19%[a] | 99%[a] | 93 | 7.5% |
| Moodley *et al* (2003) | Multiple SA sites | 8 weeks | 29%[a] | 100% | 283 | 10.5% |
| | | | | 0% | 179 | 15.2% |
| Becquet *et al* (2009) | KZN | 8 weeks | - | - | - | 12.5% |
| Rollins *et al* (2007a)[d] | KZN | 6 weeks | 0% | 24%[a] | - | 15% |
| Guay *et al* (1999) | Uganda | 6-8 weeks | - | 1% | 277 | 11.9% |
| Moses *et al* (2008) | Malawi | 6 weeks | 65% | - | 1090 | 15.5% |
| Taha *et al* (2004) | Malawi | 6-8 weeks | 13% | 1% | 389 | 14.1% |
| Average | | | | | | 11.9% |

[a] Applies to all women in the study. [b] Excluding women for whom breastfeeding information was not available. [c] Intended feeding practice, not actual feeding practice. [d] Unlike the other studies, this study did not follow mother-infant pairs from birth, but recruited mother-infants pairs from immunization clinics. This may imply some selection bias.

Although the nevirapine regimen is relatively simple, it is often the case that the nevirapine dose is administered only to the child, or only to the mother, due to health system failures or due to the mother not remembering or not being able to take the nevirapine dose (Nkonki *et al,* 2007). Few studies have examined the efficacy of nevirapine when it is administered only to the mother, or only to the child. In a South African study, Gray *et al* (2005a) found that if the nevirapine dose was administered only to the infant and the infant was formula-fed, the mother-to-child transmission risk at age 6 weeks was 13.9%, 32% less than the 20.4% transmission risk estimated in the absence of any treatment (Table 2.1). Lallemant *et al* (2004) found that adding single-dose nevirapine to a regimen of AZT from 28 weeks gestation reduced the vertical transmission rate from 6.5% to 2.0% if the nevirapine dose was provided only to the mother, and to 1.3% if the nevirapine dose was provided to both the mother and the infant (both reductions were statistically significant). This suggests that the dose to the mother plays an important role. However, one study has found that in the context of AZT administration, the omission of the maternal nevirapine dose makes little difference to the transmission rate (Shapiro *et al,* 2006). Shapiro *et al* hypothesize that the effect of nevirapine may be roughly the same as long as it is received by either the mother or the child, and that there may be little additional benefit to both mother and child receiving doses.

In 2008, the Department of Health announced a change to the prevention of mother-to-child transmission protocols in South Africa (Department of Health 2008b). The new protocols recommended that – in addition to the standard single-dose nevirapine

treatment previously administered – HIV-positive pregnant women should receive AZT from 28 weeks gestation until delivery and infants born to HIV-positive mothers should receive AZT for the first week of life. This regimen has been shown to be highly effective in various settings. In Thailand, where breastfeeding is not practised by HIV-positive mothers, the HIV transmission rate dropped from 18.9% with no treatment (Shaffer *et al*, 1999) to 1.9% in women who received the combined AZT-nevirapine regimen (Lallemant *et al*, 2004). Lower levels of efficacy have been measured in Africa. For example, Dabis *et al* (2005) found that in Côte d'Ivoire, the six-week transmission probability in mother-infant pairs that were assigned to this protocol was 6.5% (95% CI: 3.9-9.1%). Similarly, in the Western Cape (South Africa), where the regimen has been used in public clinics since 2006, the estimated transmission rate around 14 weeks was 5.4% in 2006 (Hesseling *et al*, 2009), and the proportion of infants under the age of 6 months who tested PCR-positive in primary healthcare services was 4.8% in 2007 (Infectious Disease Epidemiology Unit 2008). These transmission estimates may be exaggerated slightly by early postnatal transmission, and the Western Cape transmission estimates may be exaggerated by the inclusion of HIV-exposed infants whose mothers were not fully adherent to the combined AZT-nevirapine regimen.

It is likely that some mothers will initiate AZT but fail to receive the single dose of nevirapine in labour, and it is therefore necessary to consider the efficacy of AZT when it is administered alone. Leroy *et al* (2005) estimate that if AZT is initiated at 36 weeks gestation, it has 45% efficacy in preventing HIV transmission by 6 weeks. However, greater efficacy is likely if AZT is initiated in earlier stages of pregnancy. In the PACTG076 trial, in which the median interval between AZT initiation and delivery was 13 weeks, efficacy was estimated to be 66% (Sperling *et al*, 1996). The latter is closer to the 2008 South African protocols, which recommended the initiation of AZT at 28 weeks gestation, and the more recent protocols, which recommend AZT initiation at 14 weeks.

### 2.2.3 The effect of highly active antiretroviral treatment on the probability of mother-to-child transmission at or before birth

The original South African antiretroviral treatment guidelines recommended that ART should be initiated in all HIV-positive adults who have CD4 counts below 200/μl (Department of Health 2003). In December of 2009, it was announced that the ART initiation criteria would be extended to include HIV-positive pregnant women and TB patients with CD4 counts below 350/μl, and the national guidelines were accordingly revised in April 2010. Based on a review of CD4 distributions in pregnant HIV-positive African women and estimates of relative rates of vertical transmission in different CD4 stages, it is estimated that approximately 40% of all HIV-positive pregnant women have CD4 counts below the 350 threshold, and that these women account for approximately 57% of all vertical transmission (see Appendix A). The initiation of highly active antiretroviral treatment in these women could therefore have a significant effect on overall levels of vertical transmission.

Studies suggest that pregnant women receiving highly active antiretroviral treatment (HAART) have a very low probability of transmitting HIV to their infants, either at or before birth. The evidence from African studies, summarized in Table 2.3, suggests that in women who initiate HAART during pregnancy, the average transmission rate

at or before birth is around 2%. However, women who initiate HAART prior to conception appear to have a lower average risk of transmitting HIV to their children at birth (0.6%). This is probably because a high proportion of women who initiate HAART during pregnancy do so during the late stages of pregnancy, leaving insufficient time to achieve optimal HIV suppression prior to delivery. Studies have shown that women who initiate HAART in the earlier stages of pregnancy have substantially lower vertical transmission rates than women who initiate HAART in the late stages of pregnancy (Hoffman *et al,* 2010; Black *et al,* 2008). A major operational challenge is therefore getting women to present earlier in pregnancy.

Table 2.3: Proportions of infants infected at 4-6 weeks, after birth to mothers on HAART

| Study | Location | Timing of HAART initiation | HAART initiation criteria | n | % HIV+ |
|---|---|---|---|---|---|
| Peltier *et al* (2009) | Rwanda | 28 weeks | None | 532 | 1.1% |
| Homsy *et al* (2009) | Uganda | Before conception | CD4 <250, WHO stage III/IV | 118 | 0.0% |
| Tonwe-Gold *et al* (2007) | Abidjan (Côte d'Ivoire) | During pregnancy | CD4 <200, WHO stage IV, CD4 <350 + stage III | 107 | 1.0% |
| Palombi *et al* (2007) | Mozambique, | During pregnancy | None | 809 | 0.8% |
| | Malawi, | During pregnancy | None | 341 | 1.2% |
| | Tanzania | | | | |
| Bera *et al* (2010) | East London (South Africa) | During pregnancy | CD4 <250, WHO stage IV | 495 | 2.8% |
| | | Before conception | | 172 | 1.2% |
| Hoffman *et al* (2010) | Johannesburg (South Africa) | During pregnancy | CD4 <250, WHO stage IV | 730 | 5.8% |
| | | Before conception | | 143 | 0.7% |
| Average transmission rate if HAART initiated during pregnancy | | | | | 2.1% |
| Average transmission rate if HAART initiated prior to conception | | | | | 0.6% |

### 2.2.4 The probability of intrauterine/intrapartum transmission if the mother acquires HIV in the late stages of pregnancy

The median gestational age at which women make their first antenatal visit was estimated in the 1998 DHS to be 5.2 months, or 23 weeks (Department of Health 1999). A slightly earlier median gestational age at first antenatal clinic attendance was estimated in the 2003 DHS, at 4.9 months or 21 weeks (Department of Health 2004), and in a recent survey conducted in three provinces, the median was 22 weeks (Moodley *et al,* 2009). In another recent study conducted in three public health facilities, the average gestational age at first antenatal visit was found to vary between 24 and 26 weeks, and the average gestational age at delivery was around 39 weeks (Jackson *et al,* 2007). Women should be offered an HIV test at their first visit, but there is a significant risk of women seroconverting between the time of their first antenatal visit and delivery (Kieffer *et al,* 2010; Kinuthia *et al,* 2010; Moodley *et al,* 2009). If it is assumed that the average gestational ages at first antenatal attendance and delivery are 23 weeks and 39 weeks respectively, and if it is assumed that the average window period on an ELISA test is 4 weeks (Lindbäck *et al,* 2000), there is an average interval of 20 weeks in which a woman could become infected with HIV prior to delivery, without being identified by antenatal screening.

Several studies have estimated the risk of mother-to-child transmission at or before birth if the mother acquires HIV during pregnancy, although most are based on small

numbers of women. The results of these studies are summarized in Table 2.4 (only studies in which women and their infants did not receive any form of antiretroviral prophylaxis are included). All studies were conducted in non-African populations, in which breastfeeding by HIV-positive mothers was uncommon, and most (if not all) transmission would therefore have occurred before or during birth. In one study HIV transmission was considered probable in view of the child's symptoms (Rudin *et al*, 1991), although HIV status could not be confirmed. When these probable transmission events are combined with the definite transmission events, the pooled average transmission risk is 30% (95% CI: 17-43%). This may be an under-estimate of the transmission rate that would be expected when seroconversion occurs during *late* pregnancy, as most intrauterine transmission occurs during the last few months of pregnancy, and hence women who acquire HIV during early pregnancy and reach viral set point prior to delivery may be at a lower risk of transmitting HIV intrauterine and intrapartum. The Thai study may also have under-estimated the transmission risk, as the authors acknowledged that seroconverters could have been misclassified as a result of the imperfect sensitivity of the initial HIV screening test (Roongpisuthipong *et al*, 2001).

Table 2.4: Children infected by mothers who seroconverted during pregnancy

| Study | Location | n | Transmission events | % |
|---|---|---|---|---|
| Tovo *et al* (1991) | Italy | 10 | 2 | 20% |
| Rudin *et al* (1991) | Switzerland | 4 | 2 | 50% |
| Hague *et al* (1993) | UK | 9 | 5 | 56% |
| Nielsen-Saines *et al* (2008) | Brazil | 9 | 3 | 33% |
| Roongpisuthipong *et al* (2001) | Thailand | 15 | 2 | 13% |
| Pooled | | 47 | 14 | 30% |

Larger studies that measure proxies for recent seroconversion in mothers provide similar estimates of the transmission risk. Rollins *et al* (2007a) found that among women bringing their infants to immunization clinics at age 6 weeks, there was a 30% rate of mother-to-child transmission among the women who were HIV-positive but reported themselves to be HIV-negative. These women would be comprised mainly of women who tested negative on the antenatal screening test and subsequently seroconverted, but it is possible that some might not have been tested, or might not have received their test results, which would lead to the true transmission rate in recent seroconverters being under-estimated. In a more recent study following a similar design, Rollins *et al* (2009) estimated that the rate of vertical transmission from HIV-positive mothers who said they were HIV-negative was 38% at the time of the immunization visit.

It is also important to assess whether pregnant women are at an increased risk of HIV, as this will determine the extent to which women who test HIV-negative at initial antenatal screening acquire HIV prior to birth. Few prospective studies have examined the effect of pregnancy on the risk of HIV infection. Gray *et al* (2005b) found that in Ugandan women, the rate of HIV acquisition increased significantly during pregnancy (RR 2.16, 95% CI: 1.39-3.37), after controlling for confounding behavioural factors. This result is similar to the risk ratio of 2.19 measured in a study of Malawian women (Taha and Gray 2000), which compared pregnant women to postpartum women, though this study did not adjust for confounding demographic

and behavioural factors. Since the latter study does not control for postpartum abstinence, the observed higher rate of HIV incidence in pregnancy may be due to behavioural factors rather than biological factors. A recent South African study suggested an extremely high HIV incidence in pregnancy (Moodley *et al,* 2009), but this may have been exaggerated due to the low sensitivity of the rapid HIV test that was used to determine HIV status at the first antenatal visit (Meda *et al,* 1999; Van Rensburg *et al,* 1996). The significance of pregnancy as a factor that increases women's susceptibility to HIV therefore remains unclear.

Due to concerns regarding HIV acquisition in late pregnancy, recent Department of Health protocols recommend that all women who initially test negative should be retested at 34 weeks of gestation (Department of Health 2008b). However, this recommendation is rarely implemented (Moodley *et al,* 2009).

### 2.2.5 Model assumptions

The assumed probabilities of mother-to-child transmission, at or before birth, are shown in Table 2.5 below, for various forms of antiretroviral prophylaxis. Due to the uncertainty regarding the probability of transmission from women who acquire HIV in late pregnancy, a beta prior is assigned to this parameter, with a mean of 0.35 and a standard deviation of 0.08. The probability that a seronegative pregnant woman acquires HIV or seroconverts between her first antenatal test and delivery is calculated based on the ASSA2003 estimate of HIV incidence in pregnant women, which increases from zero in 1985 to 3.4% per annum in 1998 and declines thereafter. This incidence rate is multiplied by a factor of 0.38 (20/52), on the assumption that the average interval in which a woman can acquire HIV prior to delivery, without being detected at the initial antenatal visit, is 20 weeks.

Table 2.5: Assumed probabilities of transmitting HIV, at of before birth

| Antenatal care | Transmission probability |
|---|---|
| HIV-seropositive at 1st antenatal visit, no prophylaxis | 0.20 |
| Receiving single-dose nevirapine | 0.12 |
| Receiving AZT from 28 weeks | 0.07 |
| Receiving single-dose nevirapine and AZT from 28 weeks | 0.04 |
| Receiving highly active ART, started during pregnancy | 0.02 |
| HIV-seronegative at 1st antenatal visit, acquiring HIV before delivery, not receiving antiretroviral prophylaxis | 0.35* |

* Included in the uncertainty analysis (mean of 0.35, standard deviation 0.08).

Since rates of vertical transmission of HIV are dependent on the maternal CD4 count, and since uptake of HAART relative to short-course ARV prophylaxis will also depend on the pregnant woman's CD4 count, it is necessary to estimate rates of vertical transmission that would be expected in each CD4 stage, and to re-express the effect of the short-course ARV regimens in terms of percentage reductions in transmission. Based on a review of CD4 distributions in pregnant HIV-positive African women, and relative rates of vertical transmission in different CD4 bands, we estimate that the average rate of transmission at or before birth, in the absence of PMTCT, is 35.0% if the mother has a CD4 count less than 200, 25.8% if the mother has a CD4 count of 200 to 349, 15.2% if the mother has a CD4 count of 350 to 500,

and 13.4% if the mother has a CD4 count greater than 500 (see Appendix A). The proportions of pregnant HIV-positive women in the CD4 <200, 200-349, 350-500 and >500 categories are estimated to be 14.0%, 24.9%, 24.5% and 36.6% respectively. Single-dose nevirapine is assumed to reduce the transmission probability by 40%, and when combined with AZT from 28 weeks, is assumed to reduce the probability by 80%. The efficacy of AZT alone is assumed to be 65%. It is assumed that the percentage reduction due to short-course ARV prophylaxis is the same regardless of the maternal CD4 count, as there is little consistency in the relationship between efficacy and CD4 count between different studies (Sperling *et al,* 1996; Shaffer *et al,* 1999; Lallemant *et al,* 2004).

Although recent WHO guidelines recommend that AZT prophylaxis should begin at 14 weeks gestation rather than 28 weeks gestation, the authors of the guidelines acknowledge that there is little data regarding the impact that this would have (World Health Organization 2009a). The guidelines also suggest that the single dose of nevirapine to the mother could be omitted if AZT has been administered to the mother for at least four weeks. Since this could potentially offset any benefits associated with starting AZT earlier, and since it is not yet clear how the guidelines will be implemented in practice, we assume that the earlier recommended initiation of AZT does not lead to any change in the efficacy of the combined AZT and single-dose nevirapine regimen.

## 2.3 Postpartum transmission of HIV

This section begins with a review of studies that have estimated the rate of mother-to-child transmission of HIV through breastfeeding, including the effects of different types of feeding practice and the effects of antiretroviral prophylaxis to prevent postnatal transmission. Data on infant feeding practices in South Africa are briefly reviewed, and the model assumptions about postnatal transmission of HIV are then described.

### 2.3.1 The monthly risk of HIV transmission through breastfeeding in mothers who are HIV-positive at delivery

A number of reviews have been published with the aim of determining the average postnatal transmission risk. The earliest review, which estimated that the average risk of postnatal transmission from prenatally HIV-infected mothers was 14%, did not attempt to assess how the risk varied in relation to the length of breastfeeding (Dunn *et al,* 1992). Two subsequent reviews estimated an annual probability of HIV transmission from a breastfeeding mother to a susceptible child, per year that the HIV-positive mother breast-fed. The first review estimated an annual transmission risk of 0.032 (95% CI: 0.31-0.38) (Leroy *et al,* 1998), while the second estimated a much higher annual transmission risk, 0.089 (95% CI: 0.078-0.102) (Breastfeeding and HIV International Transmission Study Group 2004). The latter estimate is much more consistent with the results of recent studies (e.g. 0.087 in Côte d'Ivoire (Becquet *et al,* 2008), 0.092 in Zimbabwe (Iliff *et al,* 2005) and 0.091 in South Africa (Rollins *et al,* 2008)) and is based on a larger pool of data. It is also based on a longer follow-up period; transmission was monitored after 4 weeks of age, while Leroy *et al* (1998) measured transmission after the age of 2.5 months.

There is some evidence to suggest that the risk of HIV transmission through breastfeeding might not be uniform with respect to the duration of breastfeeding. For example, Miotti *et al* (1999) observed a monthly transmission probability in the first year of life roughly double that in the second year of life. Piwoz and Ross (2005) also note that comparisons of vertical transmission rates in breastfeeding and non-breastfeeding women suggest a transmission risk in the first few months of life significantly higher than the 0.089 per annum estimated by the Breastfeeding and HIV International Transmission Study Group. Table 2.6 summarizes the results of African studies that have examined the difference in transmission risk between breastfeeding and non-breastfeeding women up to 3 months. However, such analyses may be misleading as they do not control for confounding factors associated with infant feeding. For example, in the study of Nduati *et al* (2000), women who breastfed had higher levels of plasma HIV-1 RNA and vaginal HIV-1 DNA than women who formula-fed, and in the study of Coutsoudis *et al* (1999a), women who breastfed had lower socio-economic status than women who did not breastfeed.

Table 2.6: Risk of postnatal transmission per month soon after birth

| Study | Infant age at time of HIV test | Proportion infected* | | Risk difference | Transmission probability per month† |
|---|---|---|---|---|---|
| | | Breast-fed | Formula-fed | | |
| Nduati *et al* (2000) | 14 weeks | 0.188 | 0.104 | 0.084 | 2.8% |
| Moodley *et al* (2003) | 8 weeks | 0.076 | 0.026 | 0.050 | 3.3% |
| Coutsoudis *et al* (1999a) | 3 months | 0.199 | 0.132 | 0.067 | 2.7% |
| Average | | | | | 2.9% |

* Of those infants who tested PCR-negative at birth. † Calculated on the assumption that the duration of exposure to breastmilk is two weeks less than the infant age at the time of the HIV test, to take into account the average 14-day delay between infection and presence of virus detectable by PCR (Rouzioux *et al*, 1995; Chouquet *et al*, 1997).

### 2.3.2 The monthly risk of HIV transmission through breastfeeding in mothers who acquire HIV after birth

Few studies have estimated the risk of HIV transmission through breast milk if a mother acquires HIV at the time that she is breastfeeding. Dunn *et al* (1992) note that this transmission risk could be substantially higher than that in women who are infected with HIV prenatally, (a) because the maternal viral load, which is a strong predictor of the vertical transmission risk, is extremely high in the first few weeks of HIV infection; and (b) because infants born to mothers infected prenatally are likely to have acquired maternal HIV antibodies transplacentally, and these antibodies may protect against HIV acquisition through breast milk. The most rigorous study to estimate breast milk transmission risk in women seroconverting after delivery was conducted in Chinese women who were infected through blood transfusion after delivery, while breastfeeding (Liang *et al,* 2009). Out of 106 children born to women who seroconverted, 38 (36%, 95% CI: 27-45%) acquired HIV, and the duration of breastfeeding was not found to be significantly associated with the HIV transmission rate.

Two other earlier studies of women infected by blood transfusion while breastfeeding have been published. Palasanthiran *et al* (1993) found that among 11 Australian women who seroconverted after delivery, who were known to be breastfeeding at the time of HIV acquisition, 3 (27%) transmitted HIV to their infants. In a much smaller sample of three breastfeeding mothers in the Democratic Republic of Congo, who were infected by blood transfusion while breastfeeding, one mother transmitted HIV to her child (Colebunders *et al,* 1988).

Three other studies have documented transmission from mothers seroconverting due to other risk factors (not necessarily transfusion). An early study in Rwanda followed mother-infants pairs at 3-monthly intervals, testing mothers serologically and testing children by PCR (Van de Perre *et al,* 1991). Out of 15 mothers who were found to seroconvert after birth, 8 transmitted HIV to their children. However, because of uncertainty regarding the timing of maternal HIV acquisition in 4 cases, it was not possible to determine the transmission probability precisely; Van de Perre *et al* estimated that the transmission probability was between 36% and 53%, depending on the assumptions made about the 4 women with uncertain timing of transmission. In all cases in which the infant acquired HIV, the infant was found to acquire HIV in the same three-month period as that in which their mother seroconverted. This suggests that the vertical transmission risk at the time of maternal HIV acquisition is extremely high, but that the transmission risk drops to relatively low levels thereafter.

Another early study in Zambia documented 3 mother-to-child transmissions from 19 mothers who seroconverted in the year after delivery, giving a transmission rate of 16% (Hira *et al,* 1990). However, no information was provided on the durations of breastfeeding in the women who seroconverted, and it is therefore not clear which infants were being breastfed at the time of the mother's seroconversion. In addition, no information on mortality was provided, and it is possible that some children could have become infected and died before they were HIV-tested. The estimated transmission rate of 3/19 could therefore be an under-estimate of the actual transmission rate.

In a more recent study in Kenya, 12 mothers were observed to seroconvert after delivery, and 5 of the children born to these mothers became infected postnatally (Embree *et al,* 2000). However, limited information was provided on the duration of breastfeeding, and it is therefore unclear to what extent the children of these 12 women were being breastfed at and after the time of maternal seroconversion.

In a review of the early literature, Dunn *et al* (1992) estimated the average risk of vertical transmission, for a mother acquiring HIV while breastfeeding, to be 29% (95% CI: 16-42%). When the pooled result from this early review is combined with the results of Liang *et al* and Embree *et al,* the revised weighted average transmission risk is 34% (95% CI: 27-42%).

### 2.3.3 Differences in HIV transmission risk associated with exclusive breastfeeding and mixed feeding

Several studies have suggested that exclusive breastfeeding (EBF) may be associated with a lower HIV transmission risk than mixed feeding (Coovadia *et al,* 2007; Coutsoudis *et al,* 1999a; Coutsoudis *et al,* 2001; Iliff *et al,* 2005; Magoni *et al,* 2005).

However, the results of these studies are difficult to interpret because in most cases, the type of infant feeding is not treated as a time-dependent covariate in the analysis of predictors of postnatal transmission. This means that observed differences in postnatal transmission between women who practise EBF and women who practise mixed feeding could be due to differences in the duration of feeding. Recent studies have addressed this statistical problem. Coovadia *et al* (2007) found that the postnatal transmission probability per 100 days of EBF (0.0290, 95% CI: 0.0195-0.0442) was lower than the transmission probability per 100 days of mixed feeding (0.0436, 95% CI: 0.0208-0.0915), though this difference was not statistically significant. Using the same data, combined with data from a West African cohort, Becquet *et al* (2009) estimated that the rates of transmission per month of breastfeeding were increased by a factor of 2.9 (95% CI: 1.1-8.0) if the infant was also fed with solids.

In another South African study, Coutsoudis *et al* (1999a) found that the postnatal transmission risk at 3 months was significantly lower in women who practised EBF for the whole 3-month period (8.3%, 95% CI: 2.8-13.9%) than it was in women who practised mixed feeding or switched from EBF to formula feeding during the 3-month period (19.9%, 95% CI: 15.0-24.9%). This may understate the true protective effect of EBF, since the former group breastfed for the whole 3-month period, while a substantial proportion of the latter group discontinued breastfeeding in the period. In an updated analysis of the same cohort (Coutsoudis *et al*, 2001), it was found that the 6-month probability of transmission in infants who were PCR-negative at birth was 0.135 in infants who were exclusively breastfed for at least 3 months, and 0.206 in other breastfed infants. Again, this is likely to understate the true benefit of EBF, since the proportion of women who were breastfeeding at 3 months and at 6 months was substantially higher in the EBF group than in the other breastfeeding group. The HIV transmission risk *per month* of EBF would therefore probably be lower than the transmission risk per month of mixed feeding by an even greater factor than the above differences suggest.

Similarly, in a Zimbabwean study, Iliff *et al* (2005) estimated the postnatal transmission risk to be 5.1 per 100 child-years if mothers practised EBF for at least 3 months, compared with 10.5 per 100 child-years if the mother practised mixed feeding. However, since postnatal transmission was assessed up to age 18 months, and since women who were practising EBF at 3 months could have switched to mixed feeding after 3 months, the true effect of EBF could potentially have been understated in this analysis.

Another study conducted in Uganda (Magoni *et al*, 2005) reported a lower 6-month HIV prevalence in children whose mothers practised EBF than in mothers who practised mixed feeding (16.0% versus 20.4%). However, no information was provided on the duration of breastfeeding in the two groups, and it is therefore unclear whether the observed difference overstates or understates the true difference in the risk of transmission per month of breastfeeding.

### 2.3.4 The effect of antiretroviral treatment and nevirapine prophylaxis on breastfeeding transmission rates

Recent WHO guidelines recommend that PMTCT programmes follow one of two strategies for reducing HIV transmission through breastfeeding (World Health

Organization 2009a). "Option A" is to provide extended nevirapine prophylaxis to infants who are being breastfed by HIV-positive mothers, until one week after the cessation of breastfeeding. "Option B" is for all women to initiate triple-drug ART during pregnancy, and to continue therapy for the duration of breastfeeding. Regardless of which option is chosen, the guidelines recommend that triple-drug ART be initiated during pregnancy in all women with CD4 counts below 350, and that this treatment be continued for life (i.e. not limited to the breastfeeding period).

Relatively few studies have examined the effect of extended nevirapine prophylaxis in infants who are breastfed. Kumwenda *et al* (2008) assessed the effect of providing nevirapine up to 14 weeks of age, and found that of children who were PCR-negative at birth, the proportion who were infected by 14 weeks was 67% lower in those children who received extended nevirapine prophylaxis than it was in controls. In a large study in Ethiopia, Uganda and India, it was found that the provision of extended nevirapine prophylaxis up to 6 weeks of age reduced the proportion infected at 6 weeks by 46% (Six Week Extended-dose Nevirapine Study Team 2008). Although both studies excluded infants who were PCR-positive at birth, they did not exclude the infants who acquired HIV intrapartum, and both studies could therefore understate the true effect of the extended nevirapine prophylaxis on the rate of transmission through breastmilk. Another study that excluded infants who were PCR-positive at two weeks of age found that extended nevirapine prophylaxis up to 28 weeks of age reduced the mother-to-child transmission risk between 2 and 29 weeks by 70% (Chasela *et al*, 2010).

Women who breastfeed while receiving HAART have a substantially lower risk of transmitting HIV to their infants. In a large study conducted in Rwanda, Peltier *et al* (2009) found that the rate of vertical transmission through breastfeeding was 0.0008 per month, among women who were receiving HAART. Another large study in Mozambique found a monthly transmission rate of 0.0016 during the first 6 months after delivery, in women who had initiated HAART during pregnancy (Palombi *et al*, 2007). In a smaller study conducted in Uganda, no transmission through breastfeeding was observed in a cohort of breastfeeding HIV-positive mothers who were receiving HAART {Homsy, 2010 #2111}, and there were also no postnatal transmission events in children born to mothers initiating HAART as part of the Mma Bana Study in Botswana (Shapiro *et al*, 2010). In a relatively small study in Côte d'Ivoire, only one transmission event was observed among 52 infants breastfed for a median of 4.7 months by HIV-positive mothers on HAART (Tonwe-Gold *et al*, 2007). Assuming that the average breastfeeding duration is equal to the median, this suggests a monthly breastfeeding transmission rate of 0.0041. The average monthly transmission rate from these five studies is 0.0013, 82% lower than the average monthly transmission rate estimated by the Breastfeeding and HIV International Transmission Study Group (2004). This is consistent with a recent study in Malawi, which found that in women who were eligible to receive HAART, the postnatal transmission rate was 82% lower in those women who initiated HAART than in those women who did not initiate treatment (Taha *et al*, 2009). In another Malawian study, however, HAART was found to reduce the postnatal transmission risk by only 49% (Chasela *et al*, 2010). In both Malawian studies, women initiated HAART after delivery, unlike the previously summarized studies, in which women initiated HAART antenatally. The Malawian studies may therefore understate the effect of HAART initiated antenatally, because of the time taken to achieve viral suppression.

### 2.3.5 Feeding practices in South Africa prior to the introduction of PMTCT

The best source of information on breastfeeding in South African women, prior to the introduction of the PMTCT programme in 2001, is the 1998 DHS (Department of Health 1999). Figure 2.1 shows the proportion of women who reported breastfeeding, according to the age of their child (in months). Of children born in the five years preceding the survey, an estimated 86.7% were ever breastfed, and among the children born in the previous three years, the median duration of breastfeeding was 16 months. If $B(a)$ is the proportion of children breastfed at age $a$, this proportion can be modelled using a scaled Weibull survivor function of the form

$$B(a) = E \times 0.5^{(a/m)^{\phi}}, \qquad (2.10)$$

where $E$ is the proportion ever breastfed (0.867), and $m$ and $\phi$ are the median and shape parameters respectively for the Weibull distribution of breastfeeding durations in those children who are ever breastfed. Setting $m$ to 18 months and $\phi$ to 2 produces a scaled Weibull distribution consistent with the observed proportions of children breastfed at each age, as Figure 2.1 shows. However, these data relate to the period prior to the introduction of PMTCT.

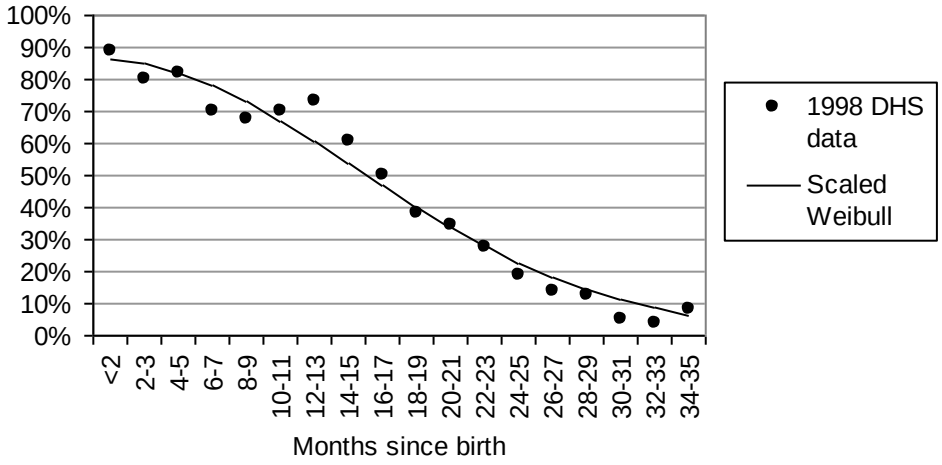


Figure 2.1: Proportion of children who are breastfed, prior to PMTCT

There is some concern that levels of breastfeeding may have declined in recent years, either due to the perception that breastfeeding is more 'modern', or due to the 'spillover effect' of the PMTCT programme on HIV-negative mothers (Doherty *et al*, 2006). However, there is little evidence of substantial changes in overall rates of breastfeeding since the 1998 DHS. The proportion of infants under the age of 6 months who were not receiving breast milk increased from 17.2% in the 1998 DHS to 26.7% in the 2003 DHS (Department of Health 2004), but then declined to 22.5% in the 2008 HSRC national household survey (Shisana *et al*, 2010). The change in the overall level of breastfeeding over the 1998-2008 period therefore appears to be modest, and could be due to HIV-positive mothers changing their feeding practices following PMTCT counselling, rather than changes in the feeding practices of HIV-negative mothers.

Exclusive breastfeeding is recommended for all women globally. However, exclusive breastfeeding was not a common practice in South Africa prior to the introduction of PMTCT, i.e. virtually all breastfeeding was mixed feeding. A small proportion of children under the age of 2 months (15.8%) were exclusively breastfed in the 1998 DHS, but this proportion dropped to very low levels at later ages. Longitudinal studies have confirmed the low rates of exclusive breastfeeding in South African settings in which women were unaware of their HIV status (Bland *et al,* 2002). However, the more recent 2008 HSRC Household Survey found that of all breastfed infants under the age of 6 months, approximately one third were receiving only exclusive breastfeeding (Shisana *et al,* 2010), and high levels of exclusive breastfeeding have also been found in recent community surveys in the Free State and Western Cape provinces (Kathryn Stinson, personal communication). This suggests that there may have been a shift towards greater exclusive breastfeeding in recent years.

### 2.3.6 Model assumptions about postnatal transmission

The scaled Weibull distribution that has been fitted to the 1998 DHS data is used to determine the proportion of women who are practising mixed feeding at each child age. This proportion is assumed to be the same for HIV-negative women and HIV-positive women who have not been counselled through the PMTCT programme. Separate assumptions about feeding practices are made for women who are diagnosed HIV-positive and counselled on infant feeding options through the PMTCT programme (see section 2.7.6).

The probability of transmission per year of mixed feeding is difficult to estimate accurately, since the published pooled analyses report only on the transmission probability per year of *any* breastfeeding, which is likely to be a lower bound on the transmission probability per year of mixed feeding if exclusive breastfeeding is indeed associated with a lower transmission risk during the first six months. However, two studies have estimated the risk of transmission per year of mixed feeding: 10.5 per 100 years in a Zimbabwean study (Iliff *et al,* 2005), and 41.2 (95% CI: 1.1-74.5) per 100 years in a pooled analysis of data from South Africa and Côte d'Ivoire (Becquet *et al,* 2009). An assumed rate of 14 per 100 years, when combined with the assumed breastfeeding durations referred to previously, would yield a probability of postnatal transmission by 24 months of 0.157, midway between the 24-month postnatal transmission rates estimated in Malawi and Kenya (10.3% and 21.0% respectively), where most women practised mixed feeding (Miotti *et al,* 1999; Nduati *et al,* 2000). Due to the uncertainty regarding the probability of vertical transmission per year of mixed feeding, we assign a gamma prior to this parameter, with a mean of 0.14 and a standard deviation of 0.025. Although the parameter is expressed as an annual probability, the transmission risk is calculated at monthly intervals, to allow for changes in feeding practices at monthly intervals.

If the mother of the child acquires HIV while she is breastfeeding, the monthly probability of HIV transmission is assumed to be 0.16 while the mother is in the acute phase of HIV infection. This acute phase is assumed to last for three months on average, based on the observed period of high infectiousness in the sexual transmission of HIV (Wawer *et al,* 2005; Lavreys *et al,* 2006). The modelled average probability of HIV transmission in the acute phase is therefore

$$\frac{-\ln(1-0.16)}{\frac{1}{3}-\ln(1-0.16)} = 0.34,^{1} \qquad (2.11)$$

which is the same as the average cumulative transmission risk from the evidence reviewed in section 2.3.2. However, as there is substantial uncertainty regarding this transmission probability, a beta prior with a mean of 0.16 and standard deviation of 0.03 is assigned to this parameter, and this parameter is further explored in the uncertainty analysis. After mothers leave the acute phase they are assumed to have the same breastfeeding transmission probability as other HIV-positive women.

In the interests of simplicity, it is assumed that no women practise EBF in the absence of PMTCT counselling of HIV-positive mothers. If HIV-positive women choose to practise EBF, it is assumed that the relative risk of transmission, per month of breastfeeding, is 0.5. To take into account the uncertainty regarding the relative risk of postnatal transmission in women practising EBF and mixed feeding, this ratio is assigned a beta prior with a mean of 0.5 and a standard deviation of 0.15. Regardless of whether women practise EBF or mixed feeding, the monthly transmission probability is assumed to be reduced by 60% if the infant is receiving extended nevirapine prophylaxis, and by 80% if the mother is receiving HAART, based on the evidence reviewed in section 2.3.4. (The 80% reduction is assumed to apply to all women receiving HAART, regardless of whether their CD4 counts were below or above 350 at the time of starting HAART.)

## 2.4 Paediatric HIV survival and progression to antiretroviral eligibility

Several studies have shown that vertically infected children have an exceedingly high mortality rate in the first year of life, but that HIV/AIDS-related mortality drops to substantially lower levels thereafter. This has been described as a 'bimodal' distribution of survival times (Downs *et al,* 1995; Spira *et al,* 1999), although the second mode (if it exists) has never been reliably estimated due to the lack of long-term data from the pre-HAART era. In developed countries, the proportion of vertically infected children dying in the first year of life varied between 6% and 26% prior to the availability of HAART (Diaz *et al,* 1998; Blanche *et al,* 1997; HIV Paediatric Prognostic Markers Collaborative Study Group 2003; European Collaborative Study 2001). In a meta-analysis of studies conducted in Africa, Marston *et al* (2005) estimated that the average proportion of vertically infected children dying from AIDS in the first year of life was around 33%, but between ages 1 and 5, the average annual probability of AIDS death reduced to approximately 0.13.

[1] The formula for the cumulative transmission risk during acute infection is derived by noting that if the length of time in the acute infection phase is exponentially distributed with mean of 3 months, and $h_0$ is the probability of transmitting HIV per month of breastfeeding during acute infection, then the probability that an acutely infected mother does not transmit HIV while breastfeeding is

$$\int_0^\infty \frac{1}{3}\exp\left(-\frac{x}{3}\right)(1-h_0)^x\,dx.$$

Several explanations have been suggested for the marked heterogeneity in HIV survival times and rates of progression to disease in vertically infected children. One significant factor is the timing of HIV transmission. Children who are infected *in utero* appear to have a higher mortality rate than those who are infected intrapartum in some studies (Zijenah *et al,* 2004), although this difference was not found to be statistically significant in a pooled analysis of data from African studies (Newell *et al*, 2004). A more substantial difference in survival has been noted between children infected postnatally (i.e. through breastfeeding) and children infected at or before the time of birth. This could be because children who are born with intact immune systems are better able to control HIV. In a recent study of Zambian children, it was found that the mortality risk in children who had acquired HIV postnatally was 0.27 (95% CI: 0.15-0.50) times that in children who had acquired HIV at or before the time of birth (Fox *et al,* 2008), and in another recent Zambian study it was found that the mortality rate in children infected after the age of 9 months was 0.3 (95% CI: 0.1-0.8) times that in children infected before 9 months (Sutcliffe *et al,* 2008). Data from a Zimbabwean cohort suggest that the relative rate of mortality in postnatally-infected children (when compared with intrauterine- and intrapartum-infected children) is 0.32 between 6 and 12 months of age, and 0.42 between 12 and 24 months of age (Marinda *et al,* 2007). In an earlier pooled analysis of African data, Newell *et al* (2004) estimated the odds ratio comparing postnatally infected children to others to be 0.52 (95% CI: 0.39-0.79), but noted that controlling for the age at which HIV was acquired substantially weakened the observed association (OR 0.74, 95% CI: 0.55-0.99), due to the removal of the confounding effect of high non-AIDS mortality in the first few months of life. The fact that there is marked heterogeneity in rates of HIV disease progression even in industrialized countries, where breastfeeding accounts for hardly any HIV transmission, suggests that differences in mode of transmission (breastfeeding versus intrauterine/intrapartum) can only partially explain the observed heterogeneity in HIV survival times.

Factors related to maternal disease stage are also very significant in predicting paediatric HIV disease progression and mortality. In a meta-analysis of studies in industrialized countries, Ioannidis *et al* (2004) estimated that each unit increase in the log of the maternal viral load at the time of delivery was associated with a 25% increase in the rate of progression to disease (HR 1.25, 95% CI: 1.04-1.52) and a 26% increase in the mortality rate (HR 1.26, 95% CI: 0.96-1.65) in vertically infected children. These associations were found to be particularly strong during the first six months of life, but ceased to be statistically significant thereafter. Even stronger associations between maternal viral load and mortality of HIV-positive infants have been observed in Uganda (Church *et al,* 2008) and in Côte d'Ivoire (Rouet *et al,* 2003). Rich *et al* (2000) also found that maternal CD4 percentage and maternal vitamin A levels were significant predictors of paediatric progression to AIDS or death at 6 months and 18 months respectively, in HIV infected children. Blanche *et al* (1994) found that infected children whose mothers had clinical AIDS at the time of delivery were significantly more likely to die before 18 months than infected children whose mother did not have AIDS (RR 4.7, 95% CI: 2.1-10.4). Differences in the severity of maternal HIV disease could affect the extent to which immunity to various pathogens is transferred from mother to child, and maternal viral load has also been shown to be highly correlated with the viral load in the infected child (Ioannidis *et al,* 2004). It is also possible that women with more advanced disease might be more likely to transfer co-infections such as cytomegalovirus to their children (Blanche *et*

*al,* 1994). All of these factors could explain the observed association between maternal disease and the rate of disease progression in their vertically infected children.

Another factor that has been found to be significantly associated with HIV disease progression is immune activation. Charlebois *et al* (2010) found that among Ugandan children, levels of CD4 and CD8 activation were positively associated with rates of progression to ART eligibility. This may explain why disease progression in African children is generally more rapid than in HIV-infected children in industrialized countries, where levels of immune activation are generally lower (Rizzardini *et al,* 1996).

Among children infected *in utero* or intrapartum, progression to antiretroviral eligibility is extremely rapid in the first year of life. Antiretroviral eligibility in the first year of life was defined in the 2005 South African Department of Health guidelines as having a CD4% <20% or being in WHO stage III or IV (Department of Health 2005), similar to the 2006 WHO guidelines, which used a CD4 cut-off of 25% instead of 20% (World Health Organization 2007). In a South African study of infants who were infected before 4 weeks of age, the median age at which infants progressed to antiretroviral eligibility (defined in terms of CD4% <25%) was 26 weeks, and by 65 weeks, 90% of the children had progressed to antiretroviral eligibility (Violari *et al,* 2008). In another South African study of 20 infants infected by 4 weeks of age, it was found that the number who had progressed to CD4% <20% was 7 by 3 months (35%), 14 by 6 months (70%) and 16 by 12 months (80%) (Mphatswe *et al,* 2007). Another South African study of 26 infected children born to mothers who formula-fed found that all children either died or developed HIV symptoms by the end of their first year of life (Jones *et al,* 2005).

After the first year of life, the rate of progression to antiretroviral eligibility drops substantially. Most guidelines recommend lower thresholds for starting antiretroviral treatment after the first year of life, since CD4 levels drop naturally as children mature. The 2005 South African Department of Health guidelines, for example, recommended starting treatment in children older than 18 months only if the CD4% is less than 15% (Department of Health 2005), and the 2006 WHO guidelines recommended that treatment should only be started in children aged 1-3 years and older than 3 years if the CD4% is less than 20% and less than 15% respectively (World Health Organization 2007). There do not appear to be studies from South Africa or other developing countries that estimate the rate of progression to antiretroviral eligibility after the first year of life. However, studies from industrialized countries, in which breastfeeding accounts for hardly any HIV transmission, can provide some information. Rates of progression estimated from these studies are summarized in Table 2.7, and are contrasted with the rates estimated from the previously-mentioned South African studies. In all cohorts, rates of progression to antiretroviral eligibility (however it may be defined) decrease as the age of the child increases. Rates of progression in South Africa appear to be substantially higher than those estimated in industrialized countries, although this may be partly due to the difference in definition of ART eligibility (immunological criteria versus clinical criteria). It is also possible that the two South African studies may exaggerate the rate of progression to ART eligibility, as they were conducted in children who became infected despite having received single-dose nevirapine, and

this may imply a selection bias towards those infants who were infected intrauterine rather than intrapartum.

Table 2.7: Annual rates of progression to ART eligibility (per 100 person years), in children who acquire HIV at or before birth

| Study | Location | Definition of ART eligibility | Rate of progression/100 PY (by age in months) | | | | |
|---|---|---|---|---|---|---|---|
| | | | 0-6 | 6-12 | 12-18 | 18-24 | >24 |
| Diaz *et al* (1998) | USA | CDC stage B* | 81 | 75 | 46 | 34 | 21 |
| Blanche *et al* (1997) | Europe | CDC stage B* | 83† | 60† | 26† | 27† | 20† |
| Violari *et al* (2008) | SA | CD4 <25% | 172 | 129 | - | - | - |
| Mphatswe *et al* (2007) | SA | CD4 <20% | 241 | 81 | - | - | - |

* Equivalent to WHO clinical stage III. † Based on survival proportions read from graph.

After progression to antiretroviral eligibility, the mortality risk is extremely high in the first year of life. Hussey *et al* (1998) estimated that in children in Cape Town developing HIV-related symptoms in the first 6 months of life (equivalent to WHO stages II, III and IV), the median survival time was 10 months from the time at which the symptoms were diagnosed. However, among children who developed their first HIV/AIDS symptoms after 12 months, 78% were still alive 2 years after their first symptom. This implies a relatively low mortality probability, of approximately 0.11 per annum. A higher 12-month mortality probability, 0.16 in children who have CD4 percentages of <15% after 12 months of age, has been estimated by the Cross Continents Collaboration for Kids (2008), based on a pooled analysis of data from 9 African cohorts and a Brazilian cohort. This is similar to the 12-month probability of 0.12, which has been estimated by the HIV Paediatric Prognostic Markers Collaborative Study Group (2003), for children aged 2 years with a CD4% of 10%, based on a pooled analysis of data from North America and Europe prior to the availability of combination antiretroviral therapy. The study showed that the 12-month probability of death increased substantially as the CD4% declined, but decreased as the age of the child increased.

To model HIV survival in children, a multi-state model is used, with the rates of transition between the various states dependent on the age of the child and the calendar year. The multi-state model is illustrated in Figure 2.2 below. It is assumed that newly infected children are initially not in need of treatment (according to the 2005 Department of Health guidelines), but that they progress to the point of treatment eligibility at rate $\lambda_a$ per annum, where $a$ is the current age. The rate of progression to treatment eligibility is assumed to be reduced by a factor of $\theta$ if the child was infected postnatally. Although it may seem more natural to parameterize the model in terms of a relative risk of death if the child is infected postnatally (since that is what most studies estimate), we parameterize the model in terms of the relative risk of progression to treatment eligibility because it is unlikely that the timing of HIV transmission would influence the mortality rate without also influencing the clinical and immunological progression of the disease. Assumptions regarding ART initiation and survival after ART initiation are explained in section 2.6.

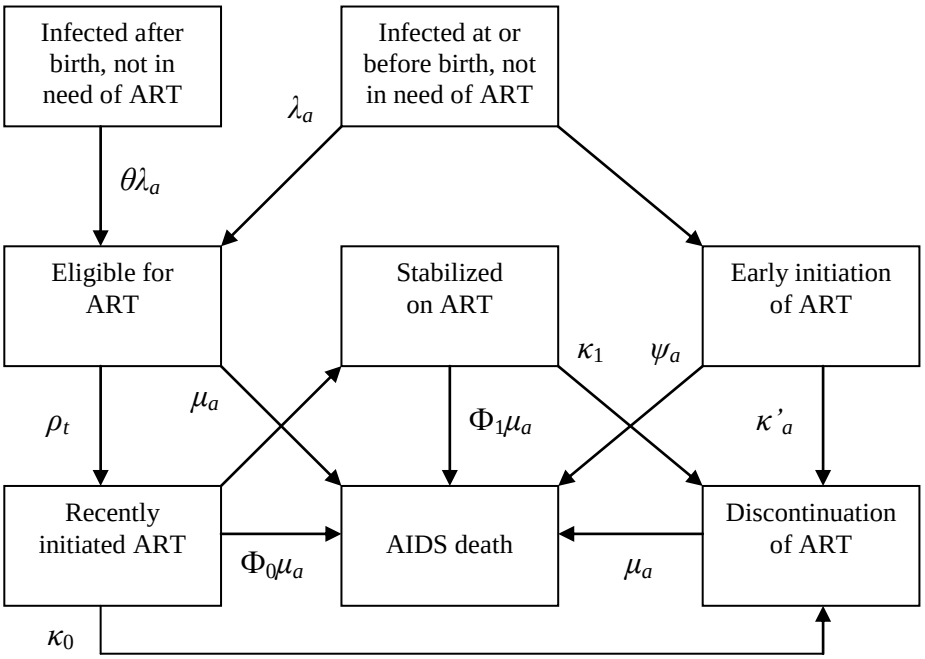


Figure 2.2: Multi-state model of paediatric survival after the acquisition of HIV infection

All children are assumed to experience non-AIDS mortality rates that vary by age and sex (not shown in the multi-state diagram).

In order to represent the declining rate of progression to ART eligibility as children age, the time to reaching ART eligibility is assumed to follow a Makeham distribution, i.e.

$$\lambda_a = G_p + H_p c^a \ , \qquad (2.12)$$

where $G_p$ is the rate of progression that would be expected 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. Based on the data presented in Table 2.6, plausible values for $G_p$ and $H_p$ appear to be 0.2 and 1.0 for industrialized countries. Since the rates of progression in South Africa appear to be roughly double those in industrialized countries, plausible values for $G_p$ and $H_p$ in the South African setting would be 0.4 and 2.0. If values of $G_p$ are assumed to be 0.4 and 0.2 for South Africa and industrialized countries respectively, then the geometric average of the factor by which the excess rate of progression reduces per year (*c*) is 0.25, calculated from the data in Table 2.7. Figure 2.3 shows that when these values are entered into equation (2.12), the resulting model estimates of rates of progression are roughly consistent with those observed in the different cohorts.

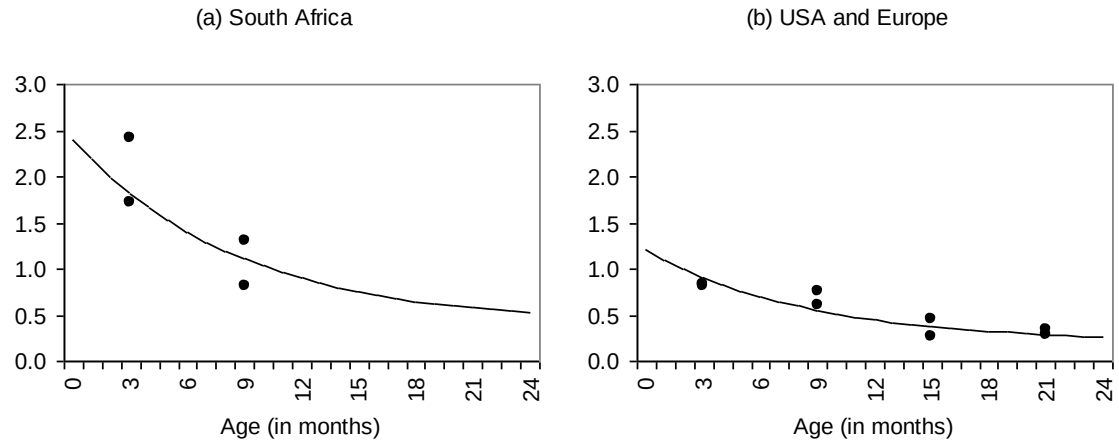


Figure 2.3: Comparison of observed and modelled annual rates of progression to ART eligibility in different settings

Observed rates, from Table 2.7, are represented by dots (centred at the midpoints of the age intervals over which they are estimated). Modelled rates, based on equation 2.12, are represented by solid lines.

Since untreated children who are ART-eligible have a rate of mortality that is decreasing with respect to age, a Makeham distribution is again used to model the time from reaching ART eligibility to death (in the absence of ART). It is therefore assumed that the AIDS-related mortality rate is of the form

$$\mu_a = G_m + H_m d^a . \qquad (2.13)$$

Based on the evidence reviewed previously, it seems reasonable to assume that the annual mortality rate in older ART-eligible children ($G_m$) is 0.12. However, the parameters $H_m$ and $d$ are difficult to determine unless one has mortality data in infants who are ART-eligible together with information on the age distribution of these infants. Fortunately, this information is provided by Hussey *et al* (1998) in their study of survival after diagnosis of HIV symptoms (mostly WHO stage III and IV) in South African children. If the assumed mortality rates in ART-eligible children are reasonable, then the observed survival rates after diagnosis should be consistent with the weighted average survival rates calculated from equation (2.13), where the weights are the proportions of children diagnosed at each age (in months). Figure 2.4 shows that this consistency is achieved when $H_m$ = 3.5 and $d$ = 0.05.

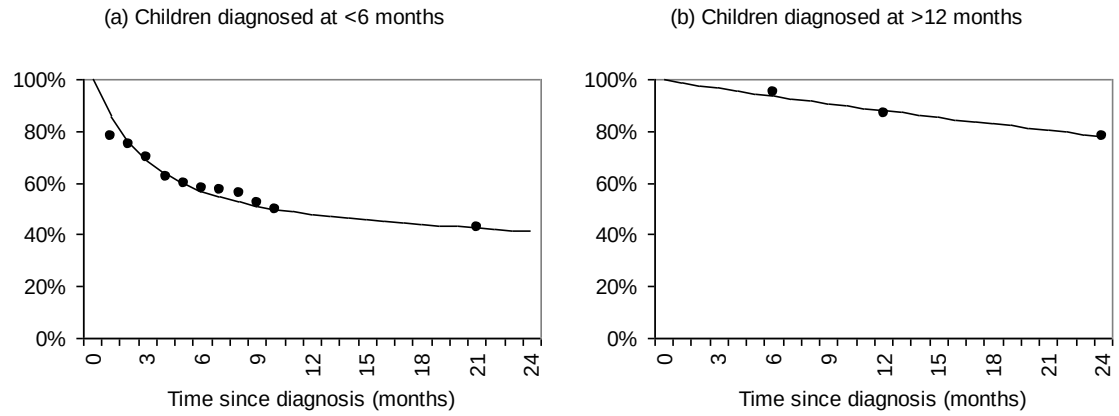


Figure 2.4: Comparison of observed and modelled survival rates after progression to ART eligibility

Observed rates are represented by dots (values read from graphs produced by Hussey *et al* (1998)). Modelled rates are represented by solid lines.

As there is substantial uncertainty regarding many of the parameters in this model, a Bayesian approach is used to quantify the uncertainty around the model outputs. Table 2.8 below specifies the prior distributions that are used to represent the ranges of uncertainty around the parameters that are considered in the uncertainty analysis. These distributions are based on the evidence previously reviewed. Parameters determining the rate of antiretroviral treatment initiation and the survival after starting antiretroviral treatment are discussed in later sections.

Table 2.8: Prior distributions for paediatric HIV survival parameters

| Parameter | Symbol | Prior distribution | | |
|---|---|---|---|---|
| | | Type | Mean | Std dev. |
| Annual rate of progression to ART need if infected at or before birth | $G_p$ | Gamma | 0.40 | 0.10 |
| | $H_p$ | Gamma | 2.00 | 0.25 |
| | $c^*$ | - | 0.25 | - |
| Relative risk of progression to ART need if infected after birth | $\theta$ | Beta | 0.35 | 0.15 |
| Annual rate of AIDS mortality if eligible for ART but not receiving treatment | $G_m$ | Gamma | 0.12 | 0.03 |
| | $H_m$ | Gamma | 3.50 | 0.35 |
| | $d^*$ | - | 0.05 | - |

* Parameter not included in uncertainty analysis.

It is possible to validate the means of the above prior distributions against other data sources. For example, if non-AIDS mortality in the first year of life is ignored, the expected probability that a child who is infected at birth dies before reaching age 1 is 0.33. This is quite consistent with the pooled analysis of African survival data conducted by Newell *et al* (2004), which estimated the mortality probability by one year to be approximately 0.37 in untreated children who acquired HIV intrapartum. (The difference between 0.37 and 0.33 can be explained by non-AIDS mortality.) Similarly, a South African study of 26 infected children born to non-breastfeeding mothers reported a 38% mortality rate by the end of the first year of life (Jones *et al*, 2005). The 0.33 mortality probability is also consistent with a South African study of survival of HIV-infected children in Durban, which found that by 12 months 14 out of

48 infected infants (29%) had died (Bobat *et al*, 1999). The implied mortality probability could be an under-estimate of the mortality probability in children infected at or before birth because children infected postnatally are included, but it could also be an over-estimate because it includes non-AIDS deaths.

The validity of the prior distributions can also be checked by comparing the observed and predicted age distribution of AIDS deaths within the first year of life. Bourne *et al* (2009) examined cause of death statistics in South African children, and noted that HIV-related deaths appeared to peak in the third and fourth months of life, with the number of HIV-related deaths after the age of three months reducing by a factor of approximately 0.85 per month. Similarly, Marinda *et al* (2007) found that among Zimbabwean infants who acquired HIV at or before birth, the mortality rate was highest between the ages of 2 months and 6 months, at 2.73 times the rate of mortality between the ages of 6 and 12 months. If the prior means in Table 2.8 are substituted into a simple model in which 60% of infected children are assumed to acquire HIV at birth and the remaining 40% acquire HIV postnatally at a uniform rate over the first year of life, then the predicted numbers of AIDS deaths are highest in the third and fourth months of life, and the predicted numbers of AIDS deaths reduce by a factor of approximately 0.89 per month thereafter. The model also predicts that in children who acquire HIV at or before birth, the ratio of the AIDS mortality rate between 2 and 6 months to that between 6 and 12 months is 1.81. These results are roughly consistent with the empirical estimates of Bourne *et al* and Marinda *et al*, although the empirical estimates suggest a sharper reduction in AIDS mortality rates after the peak at 3-4 months.

It is also possible to validate the assumed rates of progression to ART eligibility at older ages by comparing the model estimates with data from a recent study of HIV-positive children in Uganda, who were older than 12 months and not yet clinically or immunologically eligible for ART at baseline (Charlebois *et al*, 2010). In this study, 22% of children were found to have progressed to ART eligibility by 24 months after baseline. Using the baseline age distribution of children in the study, and the prior mean progression rates in Table 2.8, our model predicts that 25% of all children would have progressed to ART eligibility by 24 months after baseline, if it is assumed that all children were infected postnatally (this assumption is reasonable because most of the perinatally infected children progress to clinical or immunological eligibility in the first year of life, and would therefore not be included in those who are not yet ART-eligible after 12 months).

A potential limitation of the method used to set the assumed rates of progression to ART eligibility is that it depends largely on data from infants who have failed PMTCT (Violari *et al*, 2008; Mphatswe *et al*, 2007). It is possible that disease progression may be slower, on average, in children who become infected in the absence of any ARV prophylaxis. This is because short-course ARV prophylaxis is more likely to prevent intrapartum transmission of HIV than intrauterine transmission, and intrauterine transmission may be associated with more rapid disease progression and higher mortality (Marinda *et al*, 2007). Children who are HIV-infected in spite of having received ARV prophylaxis are therefore more likely have been infected intrauterine than children who became infected in the absence of any ARV prophylaxis, and may thus have higher mortality. Although there is little data to demonstrate this, we consider the sensitivity of the model results to changes in the

assumed relative rates of HIV disease progression in ARV-exposed and –unexposed infants in section 4.8. Elsewhere it is assumed that rates of disease progression are the same in ARV-exposed and –unexposed children.

## 2.5 The effect of infant feeding on AIDS and non-AIDS mortality rates

It has long been argued that there are significant benefits to breastfeeding, since breastfeeding is associated with the passive transfer of maternal antibodies to the infant. In developing countries, replacement feeding may be associated with significant health risks, since the clean preparation of formula milk is difficult in settings with poor access to clean running water, and there may be challenges in maintaining a continuous supply of formula milk (Doherty *et al,* 2006). In a meta-analysis of studies conducted in developing countries, it was found that children under the age of 2 who were breastfed had a significantly lower risk of mortality due to infectious diseases than children who were not breastfed, and this difference was greatest in the first 5 months of life (WHO Collaborative Study Team on the Role of Breastfeeding on the Prevention of Infant Mortality 2000). However, in a subsequent analysis of DHS data from 14 developing countries, Brahmbhatt and Gray (2003) noted that preceding maternal or infant morbidity was the reason for not breastfeeding in about two thirds of women who never breastfed, and that the mortality rate in infants who were not breastfed due to preceding morbidity was approximately ten times that in infants who were not breastfed for other reasons. This suggests that it is incorrect to infer a protective effect of breastfeeding on infant mortality if one is not controlling for the reason for avoiding/ceasing breastfeeding.

Studies of mortality rates in children born to HIV-positive mothers also yield conflicting findings regarding the benefits of breastfeeding. In a study of Zambian children who were infected with HIV, it was found that the children who were breastfed had a significantly lower mortality rate than those who were not breastfed (Fox *et al,* 2008). Another study of infants born to HIV-positive mothers in Malawi obtained similar findings (Taha *et al,* 2006). However, both studies treated breastfeeding as a time-dependent covariate in the regression model and assumed that the cessation of breastfeeding was not influenced by the health of the child, which is likely to lead to exaggeration of the benefits of breastfeeding. In a pooled analysis of African studies of children born to HIV-positive mothers (Newell *et al,* 2004), children were classified as either ever breastfed or never breastfed, and it was found that mortality rates did not differ significantly between the two groups, either in uninfected children (OR 0.94, 95% CI: 0.50-1.75) or in HIV-infected children (OR 1.08, 95% CI: 0.70-1.67). This study is probably less influenced by 'reverse causality', since decisions made by HIV-positive mothers immediately after birth about whether or not to breastfeed are more likely to be influenced by consideration of the risk of transmission through breastfeeding than by the health of the infant. Some more recent studies have also not noted any significant differences in morbidity and mortality when comparing breastfed and formula-fed children (Becquet *et al,* 2007; Rollins *et al,* 2008), but others have (Kagaayi *et al,* 2008; Kuhn *et al,* 2009).

In view of the difficulties associated with establishing causality, the best way to determine the appropriateness of different feeding strategies is through a randomized

controlled trial. However, there have been relatively few such trials. Mbori-Ngacha *et al* (2001) randomized HIV-positive Kenyan women to either breast-feed or formula-feed, and found that the rate of mortality by two years after birth was similar in the two groups of children, even after controlling for HIV status (HR 1.1, 95% CI: 0.7-1.7). In another trial, Kuhn *et al* (2008) randomized HIV-positive Zambian women to practise either exclusive breastfeeding for four months, followed by abrupt weaning, or to practise exclusive breastfeeding for four months, followed by mixed feeding for as long as the woman chose. It was found that mortality rates in uninfected children did not differ significantly between the two groups ($p = 0.71$), but the mortality rate in children who were infected by 4 months was significantly greater in the abrupt weaning arm ($p = 0.007$). However, it was also found that there was a difference between the two arms in terms of the proportion of infected children who had detectable viral loads by 3 days ($p = 0.08$), and since earlier HIV acquisition is associated with higher mortality, the observed difference in HIV mortality between the two arms could be partly due to the differences in the timing of HIV transmission rather than the effect of breastfeeding on HIV survival. In a third trial conducted in Botswana, Thior *et al* (2006) found that the cumulative mortality rate by 7 months was significantly higher in formula-fed infants than in breast-fed infants, but by 18 months, the cumulative difference in mortality was not significant. Both the Kenyan and Zambian trials suffered from high levels of cross-over into the breastfeeding/mixed feeding arm; in the Kenyan trial, 30% of the women who were assigned to exclusive formula feeding breastfed, and in the Zambian trial, 31% of women assigned to abrupt weaning at 4 months were still breastfeeding at 5 months. This would be expected to weaken any true association between infant feeding and mortality.

There is thus a lack of consistency in the evidence regarding the benefits of breastfeeding. One randomized controlled trial has suggested that longer durations of breastfeeding are significantly protective in HIV-infected children, but because the analysis did not control for differences between the two arms in the timing of HIV transmission, it is not clear how valid this finding is. Another trial has shown that formula-feeding is associated with an increased mortality risk in the first few months of life, but the study did not control for the HIV status of the child. Observational studies of mortality in HIV-infected children have provided inconclusive results. While it is biologically plausible that breastfeeding should be protective, the lack of evidence regarding the magnitude of this protective effect makes it difficult to quantify the effects of different feeding strategies on infant and child mortality. Our model allows for differences in non-AIDS mortality between uninfected children who are breastfed and formula-fed. In the results presented in section 4, this difference is assumed to be zero, but in section 4.8 a sensitivity analysis is conducted to assess the effect of assuming a difference consistent with the estimates of the WHO Collaborative Study Team on the Role of Breastfeeding on the Prevention of Infant Mortality (2000).

## 2.6 Survival on antiretroviral treatment

Studies suggest that the rate at which children are retained on antiretroviral treatment (ART) is highly dependent on the age of the child and the length of time since ART was initiated. In a pooled analysis of paediatric HIV survival data from a number of

African countries, it was found that the probability of dying during the first six months on ART was roughly 0.14 for children starting therapy in the first year of life, but among older children who had been on treatment for at least 6 months the annual probability of death was roughly 0.03 (KIDS-ART-LINC Collaboration 2008). Similar mortality rates were estimated in a pooled analysis of data from a number of South African paediatric ART programmes (Davies *et al,* 2009). This analysis of South African ART programme data also suggested that the probability of loss to follow-up during the first 3 months after starting ART was approximately 0.03, equivalent to an monthly rate of 0.01. In children who had been on ART for more than 3 months, however, the rate of loss to follow-up was substantially lower, at approximately 0.03 per annum, or 0.0025 per month. The relatively high rate of loss to follow-up in the first few months after starting ART probably reflects unrecorded mortality, as has been shown in South African adults (Fox *et al,* 2010).

In order to allow for the significant duration dependency in the rates of mortality and loss to follow-up after ART initiation, we divide the survival time on ART into two phases: a 'high risk' phase, to represent children who have recently initiated ART and who are still subject to a high rate of mortality and treatment discontinuation; and a 'low risk' phase, to represent children who have 'stabilized' on ART, with a low rate of mortality and treatment discontinuation (see Figure 2.2). The high risk phase is assumed to last for an average of 3 months. In line with the South African cohort data, the annual rates of treatment discontinuation during the high risk and low risk phases are assumed to be 0.115 and 0.03 respectively. It is also assumed that ART reduces the age-specific AIDS mortality rate by only 5% during the high risk phase and by 90% during the low risk phase. These parameters were chosen so that when the modelled cumulative mortality rates after ART initiation were weighted by the proportions of South African children starting ART at each age (in months), the resulting model estimates would be consistent with the cumulative mortality rates observed in the South African ART programmes (Figure 2.5).

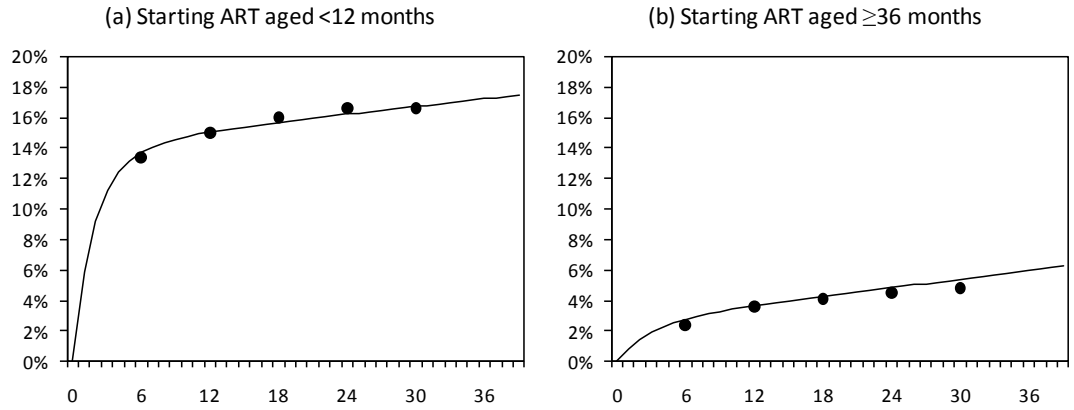


Figure 2.5: Cumulative mortality rates in children after starting ART

Dots represent observed proportions of children who have died, in a pooled analysis of South African paediatric ART programmes (Davies *et al,* 2009). Solid lines represent the weighted average of the modelled cumulative mortality rates, where the weights are the actual proportions of infants initiating ART at each age (data supplied by IeDEA Southern Africa). The 5% and 90% reduction factors have been applied to the age-specific mortality rates that would be expected in the absence of ART (see section 2.4). Both the modelled and observed mortality rates exclude the deaths that occur after loss to follow-up.

The assumptions specified thus far relate to children who initiate ART according to clinical and immunological criteria specified prior to 2008 (Department of Health 2005). In 2008, the World Health Organization modified their guidelines, recommending that all infants who test HIV-positive in the first year of life should be started on ART, regardless of their CD4 or clinical status (World Health Organization 2008). This decision was made based on the results of a South African study, which showed that infants experienced an unacceptably high level of mortality if ART was delayed until the previous clinical and immunological criteria were met (Violari *et al*, 2008). Children who start ART in the first year of life, before the previous clinical and immunological criteria are met, can be expected to have a lower mortality rate than those who start treatment only after the criteria are met. For example, in a pooled analysis of African paediatric cohorts (KIDS-ART-LINC Collaboration 2008), it was found that children on ART who met the immunological criteria had a mortality rate 2.6 times that in children who did not, and children on treatment who met the clinical criteria had a mortality rate 3.1 times that in children not meeting the criteria. It is assumed that in children aged $a$, who have started ART prior to meeting the 2005 Department of Health clinical and immunological criteria, the annual mortality rate is

$$\psi_a = \Phi_1\left(G_m + 0.4 \times H_m d^a\right), \qquad (2.14)$$

where $G_m$, $H_m$ and $d$ are the untreated AIDS mortality parameters defined in section 2.4 and $\Phi_1$ is the relative rate of mortality in low risk patients who have stabilized on ART (0.1). The factor of 0.4 has been chosen so that the modelled probability of death over a 10-month period, for a child initiating ART at the age of 2 months, is 0.24 times that which would be expected if ART were deferred until clinical or immunological criteria are met. This is consistent with the observed relative risk of death (0.24, 95% CI: 0.11-0.51) over a median follow-up of 40 weeks in the South African study mentioned previously (Violari *et al*, 2008). At older ages, the term involving the 0.4 factor is very small, so that the mortality rate in children who initiated ART prior to meeting immunological and clinical criteria is almost the same as the mortality rate of children of the same age who have stabilized on ART after deferred ART initiation. This means that the benefit of early ART initiation is assumed to be much greater at young ages than at older ages.

Infants who initiate ART prior to meeting clinical or immunological criteria are assumed to discontinue ART at the same rate as children in whom ART is deferred, i.e. at a higher rate during the first 3 months on ART than subsequently. The multi-state model used to represent survival after initiation of antiretroviral treatment is included in Figure 2.2. The values assigned to the paediatric antiretroviral parameters are summarized in Table 2.9.

A limitation of this analysis is that it relies heavily on the data from the IeDEA Southern Africa Collaboration (Davies *et al*, 2009). This is a collaboration of relatively well-resourced antiretroviral treatment programmes in South Africa, and participating programmes may therefore be experiencing relatively low mortality and loss to follow-up rates when compared with other paediatric ART programmes in South Africa. On the other hand, the IeDEA Southern Africa Collaboration includes a number of large paediatric cohorts from tertiary centres, where children with severe disease are initiated on ART, and these tertiary centres typically experience higher

mortality rates than programmes at the primary care level (Bock *et al*, 2008). It is therefore also possible that the IeDEA Southern Africa data could be biased towards overestimating the rates of mortality after ART initiation.

Table 2.9: Paediatric antiretroviral treatment parameters

| Symbol | Definition | Parameter value |
|---|---|---|
| $\rho_t$ | Rate at which ART is initiated in children who are clinically or immunologically eligible, in year *t* | Varies – see section 2.8 |
| $\Phi_0$ | Relative risk of death in 'high risk' children who recently initiated ART (compared to untreated children) | 0.95 |
| $\Phi_1$ | Relative risk of death in 'low risk' children who have 'stabilized' on ART (compared to untreated children) | 0.10 |
| $\psi_a$ | Rate of mortality on ART at age *a*, among children who started ART prior to clinical/immunological eligibility | See equation 2.14 |
| $\kappa_0$ | Rate of loss to follow-up (discontinuation excluding deaths) in 'high risk' children on ART | 0.12 |
| $\kappa_1$ | Rate of loss to follow-up (discontinuation excluding deaths) in 'low risk' children on ART | 0.03 |
| $\kappa'_a$ | Rate at which children on ART are lost to follow-up (excluding deaths) at age *a*, if children started ART prior to clinical/immunological eligibility | 0.12 if $a < 5$ mos, 0.03 if $a \geq 5$ mos* |

All rates are annual rates.

* The cutoff is set at age 5 months because it is assumed that infants starting ART prior to clinical or immunological criteria being met would do so at 2 months, soon after the 6-week visit at which the PCR test is conducted. After 3 months on ART, the rate of ART discontinuation drops significantly.

## 2.7 Rollout of prevention of mother-to-child transmission (PMTCT)

This section begins with a review of the progress that has been made to date in the provision of services for the prevention of mother-to-child transmission (PMTCT) of HIV in South Africa. The model assumptions about access to PMTCT and PMTCT uptake are described in section 2.7.6.

### 2.7.1 Proportion of pregnant women tested for HIV

Although several surveys have been conducted to estimate access to HIV testing and counselling in pregnant women, these surveys have followed different methodologies and are therefore difficult to compare (Johnson 2009).

The first survey (McCoy *et al*, 2002) was conducted in 2001 among the 18 pilot sites that had been set up to explore the feasibility of a PMTCT programme. The authors estimated that at the time of the release of the report (early 2002), 12-15% of pregnant South African women had access to PMTCT services (this included PMTCT services outside of the 18 pilot sites). However, only 51% of the women in the pilot sites agreed to be HIV-tested. Assuming that 13.5% of women had access to PMTCT services and 51% of all women offered HIV testing accepted, this would imply that only 6.9% of pregnant women received HIV testing when attending antenatal clinics at the beginning of 2002.

The second survey was based on a sample of public health facilities, and was conducted in July 2002 (Ramkissoon *et al*, 2004). In this survey, the national proportion of health facilities offering PMTCT services was estimated to be 29%, with substantial interprovincial variation. Soon thereafter, in March-May 2003, another survey in public health facilities estimated that of women attending antenatal services, the proportion who were offered testing and accepted was 66% (Reagon *et al*, 2004). A crude estimate of the proportion of women receiving HIV testing over the period from mid-2002 to mid-2003 can be obtained by multiplying the proportion of antenatal services offering PMTCT by the proportion of women attending PMTCT services who received HIV testing. When these calculations are performed separately for each province and then weighted by the ASSA2003 estimates of numbers of births to women in the public health sector, the proportion of women who receive HIV testing over the 2002-2003 period is 15.6%.

Subsequent to this, the District Health Barometer reports have provided regular information on access to HIV testing in pregnant women[2]. However, when examining the District Health Barometer data, it is clear that certain health districts have problems with data completeness and accuracy; this is evident in proportions that exceed 100% and in cells that have been left blank. The 2004 District Health Barometer data for KwaZulu-Natal also suggest implausibly high levels of PMTCT rollout, and it appears that this is due to these data being obtained from a different source from that used in other provinces. Recent publications have also noted problems with the District Health Information System data in KwaZulu-Natal (Mate *et al*, 2009; Garrib *et al*, 2008). Estimates from provinces that experienced data problems have been adjusted in an attempt to correct these problems, for the purpose of estimating the national averages. Table 2.10 shows the estimated proportions of women who receive HIV testing in each District Health Barometer study, after adjusting the provincial estimates and reweighting according to the ASSA2003 provincial estimates of the numbers of births in the public health sector.

Table 2.10: District Health Barometer surveys

| Reference | Period | Published estimate | Adjusted estimate* |
|---|---|---|---|
| - | Jan-Dec 2003 | 26.1% | 25.3% |
| Barron *et al* (2005) | Jan-Dec 2004 | 42.6% | 37.3% |
| Barron *et al* (2006) | April 2005-March 2006 | - | 49.1% |
| Barron *et al* (2008) | April 2006-March 2007 | 67.9% | 69.2% |
| Day *et al* (2009) | April 2007-March 2008 | 79.6% | - |
| Day *et al* (2010) | April 2008-March 2009 | 86.7% | - |

* Adjusted by removing anomalies for individual health districts or provinces and projecting trends observed in other health districts/provinces.

It is important to note that in all of these calculations, the denominator is the number of pregnant women who make booking visits at public antenatal clinics. A small proportion of women who deliver at public health facilities do not make prior booking visits, and would thus not receive HIV testing and counselling prior to delivery. Nationally, this proportion has been estimated to be 3% in the 2008 HSRC household

[2] The District Health Barometer data for all 53 health districts can be freely accessed from http://www.hst.org.za/generic/77.

survey (Shisana *et al,* 2010), 8% in the 2003 DHS and 6% in the 1998 DHS (Department of Health 1999); in some settings proportions as high as 13% (Qolohle *et al,* 1995) and 11.5% (Gayle Sherman, personal communication) have been observed. Although these 'unbooked' women are likely to have a substantially higher HIV prevalence than women who deliver after making booking visits (Qolohle *et al,* 1995), the relatively small size of this group means that it is unlikely to inflate significantly the proportion of delivering women who are HIV-positive. There is also a substantial proportion of pregnant women (about 18%) who attend private antenatal services (Department of Health 1999). Although it appears that these women have reasonably good access to PMTCT services (Stein *et al,* 2002), little research has been published. The prevalence of HIV in women attending private antenatal services is much lower than that in public antenatal services (Wilkinson 1999), and the vast majority of pregnant HIV-positive women therefore seek antenatal care in the public health sector.

### 2.7.2 Proportion of women testing positive who receive nevirapine

Although several studies have estimated the proportion of women testing positive who receive nevirapine, there appear to be a number of data quality problems. For example, the District Health Barometer reports on the proportion of women testing HIV-positive who receive nevirapine, which was estimated to be 61% in the 2006/2007 financial year (Barron *et al,* 2008). This could be an under-estimate if women do not disclose that they have received nevirapine to labour ward staff, but it could also be an over-estimate if there is double counting of self-administered nevirapine and nevirapine administered in the labour ward. The District Health Barometer data suggest highly erratic trends in the provision of nevirapine to pregnant women and their babies, which is probably a reflection of changes in record keeping practices rather than real changes in quality of service. Indeed, data quality concerns have led to this indicator being excluded from the most recent District Health Barometer report (Day *et al,* 2010).

In more well-resourced settings and research settings, the proportion of women testing positive who receive nevirapine is generally estimated to be between 65% and 85% (Urban and Chersich 2004; Sherman *et al,* 2004; Nkonki *et al,* 2007; Jackson *et al,* 2007). Although many women fail to receive nevirapine because they forget to take the tablet that is dispensed to them or lose the tablet (Delva *et al,* 2006), many women also fail to receive nevirapine either because they are not informed of their HIV test results or the drug is not dispensed to them (Nkonki *et al,* 2007). In a large study conducted in six antenatal clinics in the Free State and Western Cape provinces in 2007 and 2008, an estimated 73% of HIV-positive women who were tested for HIV received nevirapine; of those who did not receive nevirapine, 26% were not informed of their test results and 15% did not have the drug dispensed to them (Stringer *et al,* 2010). As there is substantial uncertainty regarding the true proportion of women testing positive who receive nevirapine, a beta prior is assigned to this parameter in the model, with the prior distribution having a mean of 75% and a standard deviation of 10%.

There is little reliable information regarding the proportion of infants who receive nevirapine if their mothers test HIV-positive. Although the District Health Barometer data suggest that the number of infants receiving single-dose nevirapine is less than

the number of mothers receiving single-dose nevirapine (Day *et al*, 2009), other studies have found the proportion of infants receiving nevirapine to be substantially higher than the proportion of mothers receiving nevirapine (Jackson *et al*, 2007; Shapiro *et al*, 2006). This may be due to mothers arriving too late in labour to receive the nevirapine dose, or delivering at home.

### 2.7.3 Proportion of women testing positive who receive zidovudine

In the Western Cape province, a dual regimen of AZT and nevirapine has been provided to pregnant women with HIV since May 2004 (Draper and Abdullah 2008). Initially, AZT was provided to the mother from 34 weeks gestation, but in 2006 the Western Cape switched to providing AZT from 28 weeks gestation (Hesseling *et al*, 2009). In a cord blood study conducted in a sample of antenatal clinics in the Western Cape in 2007 and 2008, an estimated 85% of pregnant women who received single-dose nevirapine also received AZT (Kathryn Stinson, personal communication). Public health facilities in other provinces provided only the single dose nevirapine regimen until the Department of Health announced a revision to PMTCT protocols in early 2008, which recommended the addition of AZT (from 28 weeks gestation) to the standard single-dose nevirapine regimen (Department of Health 2008b). Data collected from KwaZulu-Natal over the 2008-9 period suggest that approximately 89% of women who received single-dose nevirapine also received the short-course AZT (World Health Organization 2009b), similar to the proportion of 85% in the Western Cape in 2007/8. Although there are no nationally representative data showing the extent to which this new protocol has been introduced, unpublished data from the National Health Laboratory Service (NHLS) show that the proportion of HIV-exposed infants receiving PCR testing in the first 3 months of life, who tested positive, was 8.8% in 2008/9 and 6.5% in 2009/10 (Gayle Sherman, NHLS, personal communication). These proportions are consistent with what would be expected if dual therapy was rapidly rolled out to almost all pregnant women receiving single-dose nevirapine, and the unpublished data therefore appear to be roughly consistent with the data from KwaZulu-Natal.

There is little information regarding the proportion of women who receive AZT but do not receive nevirapine. In the previously mentioned cord blood study in the Western Cape, 47% of women who were informed of their HIV test results but did not receive nevirapine had AZT detectable in their cord blood (Kathryn Stinson, personal communication). As noted previously, 85% of the women who received nevirapine received AZT too, and data from the Western Cape and Free State provinces suggest that 26% of women who are tested for HIV but fail to take nevirapine are not informed of their test results. The proportion of women not receiving nevirapine who do receive AZT after being tested for HIV can therefore be crudely estimated as $0.47 \times (1 - 0.26) = 0.35$. Expressed relative to the proportion of women receiving nevirapine who also receive AZT, this is $0.35 / 0.85 = 0.41$.

### 2.7.4 Proportion of women testing positive and eligible for HAART who initiate HAART prior to delivery

Little information exists on the proportion of pregnant women testing HIV-positive who initiate HAART if they are eligible to do so. A study conducted in Cape Town in 2005 estimated that 51% of pregnant HIV-positive women with CD4 counts of less

than 200 cells/µl initiated HAART prior to delivery (Stinson *et al,* 2010), while 27% received some other form of PMTCT prophylaxis and 22% had no record of receiving any intervention. The authors noted that the two-tier approach to PMTCT was relatively new to the clinics that were studied, and that the proportion might be expected to increase as clinics gained experience. A more recent study in an integrated service in Cape Town estimated that in 2007, 61% of women who tested HIV-positive with CD4 counts below 200 initiated HAART during pregnancy (Médecins Sans Frontières 2010). Another study in Johannesburg, conducted in 2005, found that after the introduction of several measures to integrate antenatal and HAART services, the proportion of women eligible to initiate HAART who did so prior to delivery rose to 75% (van der Merwe *et al,* 2006). However, studies in other African countries estimate much lower proportions. A study conducted in Lusaka estimated that only 14.4% of ART-eligible women initiated ART prior to delivery, though this proportion increased to 32.9% when antenatal care and HAART provision were integrated in the same clinic (Killam *et al,* 2010). Another study in Gaborone estimated that only 37% of ART-eligible women initiated HAART prior to delivery (Chen *et al,* 2010).

These differences in ART coverage can be explained by a number of factors, both patient-related and service-related. In settings where most women present for antenatal care late in pregnancy, there is likely to be insufficient time to deal with the psycho-social issues associated with HIV diagnosis, and to prepare women for initiation of life-long HAART. The degree of integration between maternal and child health services and HIV care services is also a major factor affecting the initiation of ART in pregnancy. Related to this, the lack of healthcare providers in many settings is likely to jeopardize the continuity of care between antenatal and HIV services. The new South African PMTCT guidelines recommend that ART initiation in pregnant women be driven by antenatal services, and that these women continue to receive ART through antenatal services until six weeks after birth (Department of Health 2010). New guidelines also recommend that pregnant women should make their first antenatal clinic visit earlier, at around 11-12 weeks gestation. Both of these recommendations would be expected to lead to an increase in the proportion of ART-eligible women who initiate ART during pregnancy.

### 2.7.5 Feeding practices in women who test positive

The uptake of formula feeding by HIV-positive mothers differs considerably between provinces, from levels of less than 20% in some studies in KwaZulu-Natal (Bobat *et al,* 1997; Jackson *et al,* 2007) to levels of over 95% in some settings in the Western Cape (Coetzee *et al,* 2005; Hilderbrand *et al,* 2003). Unfortunately, there are no nationally representative surveys of the proportion of women testing positive who choose to formula-feed. However, in a survey of women testing positive at the 18 PMTCT pilot sites in 2003, Doherty *et al* (2003) found that the proportion of women who said they intended to formula-feed was 58%. This is similar to the 53% of HIV-positive women who never breastfed in a South African trial that was conducted in 11 different public hospitals across the country (Moodley *et al,* 2003).

Little information is available on the feeding practices of women who choose to breastfeed after having been counselled on their HIV-positive status. Coutsoudis *et al*

(2001) found that 69% of women who initiated breastfeeding after HIV counselling practised exclusive breastfeeding. Of these, 60% practised exclusive breastfeeding (EBF) for less than 3 months, and the remaining 40% practised EBF for between 3 and 6 months. Of those who discontinued EBF in the first 3 months, 57% switched to mixed feeding and the remainder practised abrupt weaning. However, among those who discontinued EBF between 3 and 6 months, the proportion who switched to mixed feeding was much higher, at more than 90%. In a study of three South African PMTCT pilot sites, Doherty *et al* (2007) found that of those women who intended to breastfeed exclusively, the proportion who were doing so 12 weeks after delivery was 24%, and a further 42% were practising mixed feeding. In the same cohort, Goga *et al* (2009) found that the proportions of women breastfeeding exclusively at 3 weeks, who had ceased breastfeeding completely, increased from 9.8% at 12 weeks to 37.6% at 24 weeks.

A recent study suggests that it is possible to achieve much longer durations of EBF if women are regularly counselled after birth (Bland *et al*, 2008), but such support is currently not provided in South Africa. The 2008 Department of Health recommendation was that all HIV-positive women who choose to breastfeed should practise EBF for 6 months, followed by abrupt weaning if the child is still HIV-negative (Department of Health 2008b). The more recent guidelines recommend EBF for 6 months, followed by mixed feeding until 12 months if the child is HIV-negative, or until 24 months if the child is HIV-positive (Department of Health, 2010).

### 2.7.6 Model assumptions

To assess the effect of PMTCT interventions, we consider a number of different scenarios:

1. No PMTCT scenario: No PMTCT or maternal HAART interventions are introduced.
2. Early PMTCT scenario: We consider the effect of the PMTCT interventions that were introduced prior to 2008 (including the provision of HAART to HIV-positive women who have CD4 counts less than 200), but ignore the introduction of the new protocols in 2008 and 2010. This represents the situation we would have expected if there had been no change to the Department of Health PMTCT protocols in 2008 and 2010.
3. Dual therapy scenario: This is the same as the 'Early PMTCT' scenario, except that we assume dual therapy (AZT plus single-dose nevirapine) is phased in between 2008 and 2010.
4. Intensified HAART initiation scenario: This is the same as the 'Dual therapy' scenario, but in line with new protocols, it is assumed that HAART is provided to pregnant women with CD4 counts below 350, and the proportion of ART-eligible women testing positive who initiate HAART increases to 80%, between 2010 and 2012.
5. WHO protocols, Option A: This is the same as the 'Intensified HAART initiation' scenario, except that it is assumed that extended nevirapine prophylaxis is provided to 80% of infants who are breastfed by HIV-positive mothers aware of their HIV status but not on HAART, with the change being phased in between 2010 and 2013. This scenario represents our most realistic assessment of what has happened and what is likely to happen in future, under the current guidelines.

6. WHO protocols, Option B: This is the same as the 'Dual therapy' scenario, but triple-drug ART is assumed to be initiated in 80% of all pregnant women who are diagnosed HIV-positive (with no short-course ART), and continued for the duration of breastfeeding, from mid-2010 onwards. Although it is not realistic to assume this would happen in 2010, it is useful to consider this scenario for the purpose of comparing the likely benefits of WHO options A and B.
7. Repeat antenatal testing scenario: This is the same as the 'WHO protocols, Option A' scenario, but it is assumed that antenatal testing is repeated at 34 weeks gestation, for those women who initially test negative, from mid-2010 onwards.
8. Repeat postnatal testing scenario: This is the same as the 'WHO protocols, Option A' scenario, but it is assumed that mother and infant are both tested for HIV at the 6-week immunization visit, from mid-2010 onwards.
9. Optimistic implementation of current protocols scenario: This is the same as the 'Repeat antenatal testing' scenario (since repeat testing is part of the current protocol), except that the proportions of women receiving HIV testing, the proportions of those testing positive who receive AZT and nevirapine (or HAART if they are eligible) and the proportions of those breastfeeding HIV-positive mothers who administer nevirapine to their infants all increase to 100% after the middle of 2010.
10. Intensified support for breastfeeding scenario: This is the same as the 'WHO protocols, Option A' scenario, but it is assumed that breastfeeding HIV-positive women practise exclusive breastfeeding (EBF) to a greater extent, and after introducing solids, they continue practising breastfeeding for longer durations. This change in feeding practices is assumed to occur from mid-2010 onwards, and the scenario therefore represents the effects of introducing programmes to promote greater adherence to the current infant feeding guidelines. Further details are provided below.

In order to model these different scenarios, it is necessary to define a number of different states to represent children at different risks of acquiring HIV. Figure 2.6 summarizes the model structure. The inputs of the model are the annual numbers of children born to women who are HIV-negative at the antenatal screening visit and the annual numbers born to women who are HIV-positive at the antenatal screening visit (these inputs are obtained from the ASSA2003 AIDS and Demographic model). There are seven states to represent children who are HIV-negative but at risk of acquiring HIV postnatally, and three states to represent the ultimate HIV state into which the child is categorized. Further states are defined to represent the survival of the HIV-infected children, as described in section 2.4.

The inputs from the ASSA2003 model are the estimates of the numbers of births to women from the middle of one calendar year to the middle of the next, according to the HIV status of the mother at the middle of the first calendar year. If women give birth on average at the end of the first calendar year, and their first antenatal visit is (on average) 16 weeks previously, then taking into account the 4-week window period, the HIV status of the women at the middle of the first calendar year is a reasonable approximation to the observed HIV status at the first antenatal visit (which is $(26 – (16 + 4)) = 6$ weeks after the middle of the first calendar year, on average).

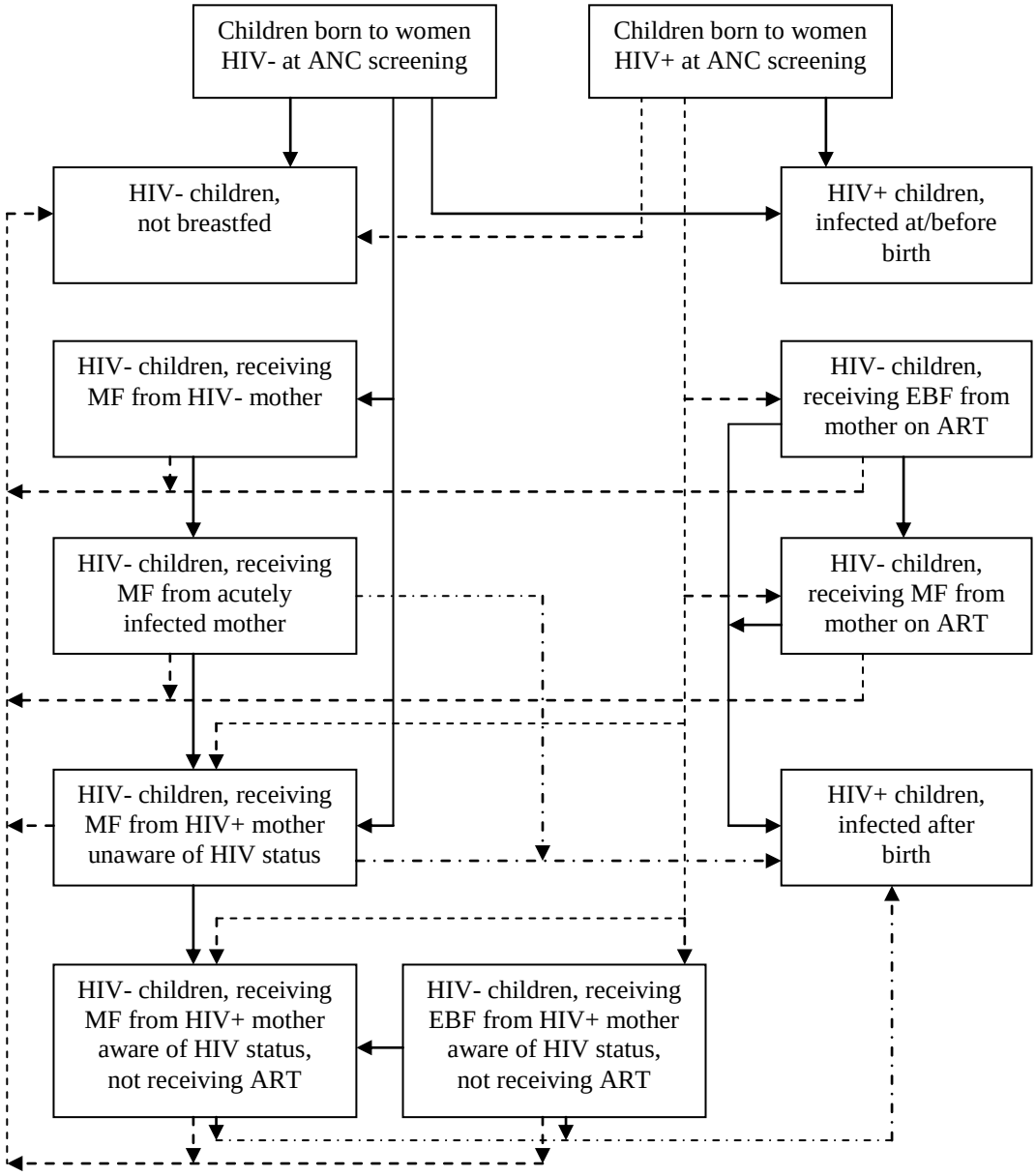


Figure 2.6: Multi-state model for mother-to-child transmission
ANC = antenatal clinic; EBF = exclusive breastfeeding; MF = mixed feeding

In all scenarios, it is assumed that 97.5% of HIV-positive women who receive testing test HIV-positive, based on an average of rapid test sensitivity estimates from African populations (Moodley *et al*, 2008; Urassa *et al*, 2002; Meda *et al*, 1999; Andersson *et al*, 1997; Van Rensburg *et al*, 1996). In scenario 7, where rescreening is offered at 34 weeks gestation, a proportion of the women who were HIV-seronegative at the first screening visit are identified as positive at rescreening, and in addition a proportion of the women who initially refused screening agree to screening when it is offered in late pregnancy. The proportion of women initially testing negative who are retested is assumed to be 80%, slightly lower than the proportion of 89% achieved in a recent South African study (Moodley *et al*, 2009). There is little information regarding the proportion of women refusing testing who subsequently accept testing in late

pregnancy, and this proportion has arbitrarily been set at 50% in scenario 7. The modelling of rescreening in scenario 7 leads to a proportion of recently seroconverted women receiving PMTCT, and also leads to an increase in the proportion of chronically infected women who are diagnosed HIV-positive. Full details of the calculations are provided in Appendix B.

A specified proportion of women, $E_v$, are assumed to adopt feeding practice $v$. In women who are HIV-negative or unaware of their HIV status, it is assumed that 86.7% practise mixed feeding and none practice exclusive breastfeeding (see discussion in section 2.3.5). Among women who know they are HIV positive, it is assumed that 50% formula-feed exclusively, 34.6% initially practise exclusive breastfeeding, and the remaining 15.4% mix breast- and bottle-feeding, based on the findings of Coutsoudis *et al* (2001).

The rates at which women change breastfeeding practice are assumed to differ according to whether they are breastfeeding exclusively or not, and according to whether or not they know their HIV status. The rate at which women discontinue feeding strategy $v$ between infant age $a$ and $a + 1$ is

$$\delta_v(a) = 1 - B_v(a+1)/B_v(a), \qquad (2.15)$$

where $B_v(a)$ is the proportion of infants who are fed according to strategy $v$ at age $a$ (in months). A Weibull hazard function is used to determine the rate at which women discontinue feeding strategy $v$. This means that

$$B_v(a) = 0.5^{\left((a/m_v)^{\phi_v}\right)}, \qquad (2.16)$$

where $m_v$ and $\phi_v$ are the median and shape parameters respectively for the Weibull hazard. The assumed median and shape parameters for the different feeding strategies are summarized in Table 2.11. The justification for the median and shape parameters for the normal mixed feeding practice is given in section 2.3.5. The assumed median durations of exclusive breastfeeding and mixed feeding in women who know they are HIV-positive, and who have received counselling on feeding options, are based on the feeding practices in a cohort of HIV-positive mothers studied by Coutsoudis *et al* (2001), and have been validated using data from other South African studies (Doherty *et al* 2007; Goga *et al* 2009).

Table 2.11: Parameters determining rate at which women change feeding practice

| Feeding practice ($v$) | Description | Median $m_v$ | Shape $\phi_v$ | Percent adoption $E_v$ |
|---|---|---|---|---|
| 1 | Normal mixed breast- and bottle-feeding by mothers uninfected/unaware of infection | 18 | 2 | 86.7 |
| 2 | Mixed breast- and bottle-feeding by mothers who know they are HIV-positive | 6 | 1 | 15.4 |
| 3 | Exclusive breastfeeding by mothers who know they are HIV-positive | 2 | 1 | 34.6 |

Women who discontinue exclusive breastfeeding are assumed to switch either to mixed feeding or to complete cessation of breastfeeding (abrupt weaning). The proportion of women discontinuing EBF at age $a$ who practise abrupt weaning, $w(a)$, appears to differ between settings. As shown in Figure 2.7, the model results are relatively consistent with the estimates of Coutsoudis *et al* (2001) when $w(a) = 0.5$ for $a < 3$ months and 0.1 for $a \geq 3$ months. However, the same assumptions produce a relatively poor fit when the model is compared with the proportions reported by Goga *et al* (2009). A better fit to the latter data set is obtained when setting $w(a) = 0.1$ for $a < 3$ months and 0.5 for $a \geq 3$ months. As the two studies appear to imply quite different rates of abrupt weaning, the assumption made in the model is that $w(a) = 0.3$ for all $a$, a compromise between the two data sources.

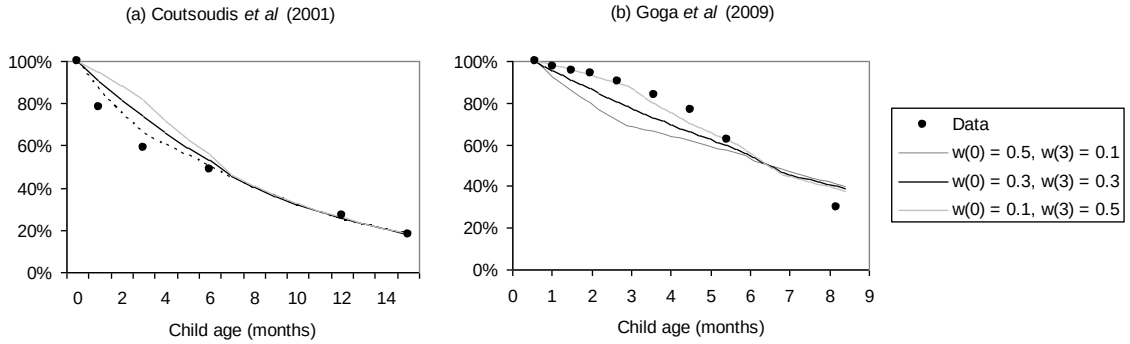


Figure 2.7: Proportions of women initially breastfeeding who are still breastfeeding
In panel (a), percentages are expressed as a proportion of all women who were breastfeeding from birth. In panel (b), percentages are expressed as a proportion of all women who were practising exclusive or predominant 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. Model results are represented by solid and broken lines.

These assumptions regarding infant feeding practices represent the reported feeding practices under the current guidelines, but they do not represent what would happen if all women were to follow the guidelines. In a study conducted in KwaZulu-Natal, intensified support for women choosing to practise breastfeeding was provided by lay counsellors who visited women in their homes at regular intervals (Bland *et al,* 2008). It was found that almost all women who chose to breastfeed, and who received the intensified support, practised exclusive breastfeeding, with the median duration of exclusive breastfeeding being 6 months. We therefore consider an additional scenario (scenario 10), in which intensified support for breastfeeding is provided from 2010 onwards. It is assumed that as a result of this support, (a) the proportion of women who elect to practise EBF at birth increases from 34.6% to 45%; and (b) the median duration of EBF in those women who start practising EBF increases from 2 months to 6 months.

In scenario 8, it is assumed that both mother and child are tested for HIV at the 6-week immunization visit, as recommended by Rollins *et al* (2007a). In the 1998 DHS (Department of Health 1999), it was estimated that 93% of South African infants received their first DPT vaccine dose and 91% received their second polio vaccine dose (the first being administered at birth). It is therefore assumed that the proportion of mother-infant pairs that receive HIV testing at the 6-week immunization visit is 92%. If the mother is HIV-positive, it is assumed that the HIV test results will be

delivered to the mother in 66% of cases, based on a study conducted in KwaZulu-Natal in women whose infants were PCR-tested at fixed primary healthcare facilities (Rollins *et al,* 2009)[3]. The proportion of HIV-infected children who are diagnosed with HIV at 8 weeks is therefore assumed to be 61% (66% × 92%). If a woman who was previously assumed to be HIV-negative tests positive and is currently practising mixed feeding, it is assumed that the probability that she will switch to replacement feeding is 0.5, the same as the proportion of women who elect to formula-feed if informed of their HIV status prior to delivery.

In all scenarios except scenario 1, the proportion of pregnant women who receive HIV testing and counselling in year *t,* $V(t)$, follows the proportions specified in Table 2.12, based on the District Health Barometer and other data sources previously discussed in section 2.7.1. Although data on PMTCT coverage are not available post-2009, it is assumed that the proportion of women receiving HIV testing will continue to rise, levelling off at 92%. It is further assumed that the proportion of women who test positive is the same as the proportion of all pregnant women who are HIV-positive, since the District Health Barometer data (Barron *et al,* 2006) suggest a similar level of HIV prevalence in women participating in the PMTCT programme to that observed in the national antenatal clinic survey (Department of Health 2006b). In all scenarios other than scenario 1, it is also necessary to specify the proportion of women receiving single-dose nevirapine who also receive AZT in year *t,* $D(t)$. Prior to May 2004, when the AZT together with nevirapine was started in the Western Cape, $D(t) = 0$, and for years 2004 to 2006, $D(t)$ does not exceed 0.08, the proportion of tested HIV-positive mothers in the Western Cape (over this period the Western Cape was the only province providing dual therapy). The assumed values of $V(t)$ and $D(t)$ are summarized in Table 2.12. The values specified for 2011 are assumed to apply in all years following 2011.

The proportion of women testing positive but failing to receive nevirapine, who receive AZT, is assumed to be 40% of $D(t)$, based on the data reviewed in section 2.7.3.

Based on the data reviewed in section 2.7.4, the proportion of ART-eligible pregnant women testing positive, who actually initiate ART, is assumed to be 60% of $U(t)$, the proportion of antenatal clinics from which ART is readily accessible in year *t*. This implies that when ART is highly accessible in a particular area, 60% of eligible women would initiate ART prior to delivery. The values of $U(t)$ are approximated by dividing the annual numbers of women starting ART in South Africa (based on data reported by Adam and Johnson (2009)) by the ASSA2003 model estimates of the numbers of new AIDS cases in women in each year, prior to 2008. After 2008, $U(t)$ is assumed to increase to 100%, on the assumption that all pregnant women would be able to access ART in public clinics. In scenarios 4-8 and scenario 10, the 60% proportion is assumed to increase to 80%, with the increase being phased in between 2010 and 2012.

[3] All mothers brought their infants to these clinics for the purpose of immunization. Because mobile clinics were excluded from the sampling frame, and because mobile clinics are generally more accessible to women in remote rural areas, it is possible that the study may underestimate the actual proportion of women who receive the results of their infants' PCR tests.

Table 2.12: Assumed trends in provision of PMTCT and ART

| Year $t$ | Percent tested $V(t)$ * | Percent of mothers receiving sd NVP who also get AZT, $D(t)$ † | Percent of ANCs from which ART is accessible, $U(t)$ |
|---|---|---|---|
| 1999/2000 | 0.9% | 0.0% | 0.0% |
| 2000/2001 | 2.9% | 0.0% | 3.8% |
| 2001/2002 | 7.5% | 0.0% | 4.6% |
| 2002/2003 | 15.6% | 0.0% | 4.5% |
| 2003/2004 | 31.3% | 0.8% | 8.2% |
| 2004/2005 | 42.0% | 4.0% | 21.3% |
| 2005/2006 | 54.5% | 6.4% | 38.2% |
| 2006/2007 | 72.2% | 6.8% | 45.4% |
| 2007/2008 | 84.0% | 18.7% | 61.8% |
| 2008/2009 | 89.3% | 53.2% | 80.0% |
| 2009/2010 | 91.0% | 85.4% | 100.0% |
| 2010/2011 | 92.0% | 90.0% | 100.0% |
| 2011/2012 | 92.0% | 90.0% | 100.0% |

Note that the proportions apply from the middle of the first specified calendar year to the middle of the next calendar year. * $V(t) = 0$ for scenario 1 in all years, and for other scenarios, $V(t) = 0$ prior to 1999. † D(t) = 8% after 2007 for scenario 2.

## 2.8 Rollout of paediatric antiretroviral treatment

The estimated annual numbers of children starting antiretroviral treatment in South Africa, from mid-2000 to mid-2008, are summarized in Table 2.13. These estimates were obtained by combining unpublished figures on numbers of children cumulatively enrolled on antiretroviral treatment in the public health sector (Department of Health 2008a; Department of Health 2006a) with estimates from the private sector (disease management programmes) and NGO-administered antiretroviral treatment programmes (Adam and Johnson 2009; Johnson and McLeod 2007). The data for the private and NGO sectors are not split between adults and children. However, data from selected NGO programmes and unpublished data from the Risk Equalisation Fund (which has monitored numbers of patients on antiretroviral treatment in medical schemes) both suggest that roughly 6% of all antiretroviral patients are children (under the age of 15). It is therefore assumed that 6% of the estimated numbers starting treatment in the private and NGO sectors are children, which is lower than the roughly 10% observed in the public health sector.

Table 2.13: Estimated numbers of children starting antiretroviral treatment in each year

| 2000/1 | 2001/2 | 2002/3 | 2003/4 | 2004/5 | 2005/6 | 2006/7 | 2007/8 |
|---|---|---|---|---|---|---|---|
| 416 | 647 | 1 108 | 2 335 | 6 189 | 13 129 | 15 386 | 19 947 |

Numbers relate to the period from the middle of the first specified calendar year to the middle of the next calendar year.

The above numbers are divided by 12 in order to obtain the number initiating antiretroviral treatment in month $t$, $S_t$. The rate at which eligible children initiate

treatment in month *t*, $\rho_t$, is calculated by noting that the probability that a child of gender *g*, aged *a* at time *t*, starts treatment in the next month is

$$\begin{aligned}
&\int_0^1 \rho_t \exp\left(-\left(\mu_a + \eta_{agt} + \rho_t\right)s\right)ds \\
&= \frac{\rho_t}{\rho_t + \mu_a + \eta_{agt}}\left[1 - \exp\left(-\rho_t - \mu_a - \eta_{agt}\right)\right] \\
&\approx \rho_t\left(1 - 0.5\left(\rho_t + \mu_a + \eta_{agt}\right)\right) \qquad (2.17)
\end{aligned}$$

where $\mu_a$ and $\eta_{agt}$ are the monthly rates of AIDS mortality and non-AIDS mortality respectively. Using the approximation in equation (2.17), we get

$$S_t = \sum_{a=0}^{179}\sum_{g} N_{g,s}^1(a,t)\rho_t\left(1 - 0.5\left(\rho_t + \mu_a + \eta_{agt}\right)\right), \qquad (2.18)$$

where $N_{g,s}^1(a,t)$ is the number of infected children of gender *g* and age *a*, who are in HIV state *s* at time *t* (state *s* = 3 corresponds to eligible for ART but not yet receiving therapy). The model does not allow for ART initiation among new entrants to state 3 in the month of entry to state 3, since the time taken to determine eligibility for ART and prepare the patient for ART would result in very few patients actually starting ART in the same month that they become eligible. Equation (2.18) can be expressed as a quadratic in $\rho_t$, and this quadratic is then solved in order to determine $\rho_t$.

Prior to mid-2000, it is assumed that no children receive antiretroviral treatment. After mid-2008, three possible antiretroviral rollout scenarios are considered. In the first (scenario 1), it is assumed that after 2009 the number of children starting ART in each period is only 50% of children becoming eligible for ART in the same period (based on the 2005 Department of Health criteria). This is equivalent to

$$\frac{\sum_{a=0}^{179}\sum_{g} N_{g,3}^1(a,t)\rho_t\left(1 - 0.5\left(\rho_t + \mu_a + \eta_{agt}\right)\right)}{\sum_{a=0}^{179}\sum_{g} Q_{g,3}^1(a,t)} = 0.5, \qquad (2.19)$$

where $Q_{g,3}^1(a,t)$ is the number of HIV-infected children of gender *g*, aged *a* at time *t*, who become eligible to receive ART between time *t* and time *t* + 1. This is again a quadratic in $\rho_t$, which is solved in order to determine $\rho_t$. The 50% coverage level is assumed to be maintained from the middle of 2009 onwards. This scenario represents what would have been expected if the new ART initiation criteria had not been introduced in 2010.

Scenario 2 is the same as scenario 1, except that the new recommendations by the South African Department of Health are implemented, i.e. all infants who test HIV-positive in the first year of life are started on antiretroviral treatment immediately. These guidelines recommend that all infants born to mothers who test positive should

be tested for HIV by PCR at 6 weeks. If the new treatment guidelines are implemented correctly, those infants testing positive at 6 weeks should be started on treatment soon after their parents have been given their positive test results. However, South African PMTCT studies have generally found the proportion of HIV-exposed infants receiving PCR testing at 6 weeks to be low, at around 80% (Coetzee *et al*, 2005; Gray *et al*, 2005a; Médecins Sans Frontières 2010; Bera *et al*, 2010; van der Merwe *et al*, 2006), and one study has reported the proportion to be as low as 62% (Peltzer and Mlambo 2010). In addition, many HIV-positive mothers who get their children tested do not receive the PCR test results. In one study in KZN it was estimated that only 66% of HIV-positive mothers whose infants were PCR-tested received the test results, although the study did not include infants tested in mobile clinics, and it may therefore have understated the true rate of receipt of PCR results (Rollins *et al*, 2009). It is assumed that the proportion of infected infants starting ART soon after birth is 53% (80% × 66%), which is consistent with the recent finding that only 50% of women in Mpumalanga who had tested positive during pregnancy knew the HIV status of their infants (Peltzer and Mlambo 2010). It is assumed that only children infected at or before birth would be started on antiretroviral treatment at 6 weeks, since relatively little postnatal transmission would have occurred before 6 weeks and much of this would not be detectable by PCR. In this second scenario, the 6-week initiation of antiretroviral treatment is assumed to be introduced from the middle of 2010. This second scenario is closest to the actual ART policy in South Africa.

Due to the uncertainty regarding the future rates of ART coverage and PCR uptake, we also consider a more optimistic scenario (scenario 3). In this third scenario, it is assumed that the proportion of infected infants starting ART as a result of PCR diagnosis at the 6-week immunization visit increases from 53% to 80%. It is further assumed that the number of children starting ART at other ages increases from 50% to 80% of the number of newly eligible children in each period (where eligibility is again defined according to the 2005 Department of Health criteria, not the new criteria). This therefore represents a scenario in which South Africa is successful both in increasing PCR coverage and in meeting the 'backlog' of unmet need in older HIV-infected children. Both the increase from 53% to 80% and the increase from 50% to 80% are assumed to be phased in linearly over the period from mid-2010 to mid-2013.

## 2.9 Application of the model to KwaZulu-Natal and Western Cape

In order to determine the variability in the impact of HIV on children in South Africa, we apply the model to two South African provinces with very different HIV profiles: KwaZulu-Natal and the Western Cape. KwaZulu-Natal is the province with the highest antenatal HIV prevalence (39% in 2008), while the Western Cape has the lowest antenatal HIV prevalence (16% in 2008) (Department of Health 2009). PMTCT programmes in the Western Cape began much earlier than in the other provinces, and the Western Cape also adopted the combined AZT and nevirapine PMTCT regimen well before other provinces did. In addition, most HIV-positive women in the Western Cape who are diagnosed HIV-positive choose to formula-feed their infants, while in KwaZulu-Natal, women who are diagnosed HIV-positive are more likely to practice exclusive breastfeeding. The Western Cape is also believed to

have scaled up provision of ART to HIV-infected children to a greater extent than KwaZulu-Natal.

In applying the model to the KwaZulu-Natal and Western Cape provinces, most of the parameters and model assumptions remain the same as described in previous sections, but certain parameters are changed. The numbers of children at each age in 1985 are estimated using the ASSA2003 lite provincial models. The annual numbers of births to HIV-positive women and HIV-negative women are also taken from the ASSA2003 lite estimates for the two provinces, as are the maternal HIV incidence rates and paediatric non-AIDS mortality rates. The proportion of pregnant women who receive HIV testing, the proportion of mothers receiving nevirapine who also receive AZT, and the proportion of antenatal clinics from which ART is readily accessible are estimated using the same data sources as described in section 2.7, and the values for the two provinces are compared in Table 2.14 below.

Table 2.14: Assumed trends in provision of PMTCT and ART

| Year $t$ | Percent tested $V(t)$ | | Percent of treated mothers receiving dual therapy, $D(t)$ | | Percent of ANCs from which ART is accessible, $U(t)$ | |
|---|---|---|---|---|---|---|
| | KZN | WC | KZN | WC | KZN | WC |
| 1999/2000 | 0.0% | 11.0% | 0.0% | 0.0% | 0.0% | 0.0% |
| 2000/2001 | 0.0% | 21.9% | 0.0% | 0.0% | 3.7% | 6.8% |
| 2001/2002 | 7.2% | 32.9% | 0.0% | 0.0% | 4.6% | 7.0% |
| 2002/2003 | 13.6% | 52.7% | 0.0% | 0.0% | 4.6% | 10.8% |
| 2003/2004 | 25.1% | 72.5% | 0.0% | 10.0% | 5.4% | 39.1% |
| 2004/2005 | 35.4% | 80.3% | 0.0% | 50.0% | 19.6% | 52.5% |
| 2005/2006 | 47.6% | 87.1% | 0.0% | 80.0% | 37.7% | 72.1% |
| 2006/2007 | 61.5% | 94.2% | 0.0% | 85.0% | 45.9% | 68.6% |
| 2007/2008 | 73.7% | 96.2% | 20.0% | 90.0% | 67.0% | 90.0% |

Note that the proportions apply from the middle of the first specified calendar year to the middle of the next calendar year.

The proportion of HIV-positive women who are counselled on infant feeding and elect to practise formula feeding is 21% in KwaZulu-Natal and 86% in the Western Cape. These assumptions are based on the average of three studies conducted in KwaZulu-Natal (Bobat *et al,* 1997; Coutsoudis *et al,* 2001; Jackson *et al,* 2007) and three studies conducted in the Western Cape (Coetzee *et al,* 2005; Hilderbrand *et al,* 2003; Jackson *et al,* 2007). In line with the evidence reviewed in section 2.7.5, it is assumed that of those women who elect to breastfeed, 69% practise exclusive breastfeeding and the remainder practise mixed feeding. As noted in section 2.2.2, the efficacy of nevirapine appears to differ in settings with high and low levels of breastfeeding, and based on this evidence it is assumed that the reduction in vertical transmission achieved with the single-dose nevirapine protocol is 31% in KwaZulu-Natal and 57% in the Western Cape.

The annual numbers of children starting ART in each province are estimated based on the same data sources described in section 2.8, and are specified in Table 2.15. As we will only be considering the model results up to 2007/8, based on actual numbers of children starting ART, we do not make any assumptions regarding the future rollout of ART to children.

Table 2.15: Estimated numbers of children starting antiretroviral treatment in each year

| Province | 2000/1 | 2001/2 | 2002/3 | 2003/4 | 2004/5 | 2005/6 | 2006/7 | 2007/8 |
|---|---|---|---|---|---|---|---|---|
| KZN | 155 | 242 | 284 | 377 | 1 594 | 4 417 | 5 288 | 5 709 |
| WC | 25 | 36 | 408 | 692 | 828 | 897 | 1 229 | 1 357 |

Numbers relate to the period from the middle of the first specified calendar year to the middle of the next calendar year.

The model does not consider migration of children between provinces. This is a limitation, since children migrating into the province may have a different HIV prevalence from children who were born in the province. It also means that the total number of children with HIV may be over-estimated or under-estimated due to the population size being over- or under-estimated. The level of ART uptake, relative to the ART need, could therefore be inaccurate. However, the ASSA2003 model estimates that over the 1985-2010 period, the number of children in the KwaZulu-Natal province is between 3.7% lower and 0.1% higher than the level that would have been expected in the absence of migration, and in the Western Cape province the child population is between 1.3% lower and 2.4% higher than the level that would have been expected in the absence of migration. The absence of any allowance for migration is therefore unlikely to introduce major bias.

## 2.10 Non-vertical transmission of HIV

It has been suggested that non-vertical transmission of HIV could be a significant factor contributing to the high prevalence of HIV in children in Southern African countries (Human Sciences Research Council 2008). This is supported by evidence from a national study of HIV incidence patterns by age, conducted in 2005, which estimated an annual HIV incidence rate of 0.5% (95% CI: 0.0-1.2%) in children aged 2 to 14 (Rehle *et al*, 2007). This is an age group in which mother-to-child transmission is likely to account for very little transmission, and the high incidence in this age group therefore suggests significant non-vertical transmission. However, the test used to measure HIV incidence in this study was the BED assay, an assay which can produce false positive reactions (Guy *et al*, 2009). Although methods exist to correct the results for these false positive reactions, the rate of false positivity appears to vary significantly between settings, making it difficult to establish the accuracy of the correction factors (Guy *et al*, 2009; Bärnighausen *et al*, 2008). There is thus significant uncertainty regarding the level of non-vertical transmission in South African children.

To assess the significance of non-vertical transmission, we consider two alternative models to the main model described in previous sections. In both models, we allow for uncertainty regarding the extent of non-vertical transmission by specifying a prior distribution on the incidence of non-vertically acquired HIV transmission in 2004, in children aged 2 to 14. This prior is a beta distribution with a mean of 0.5% and a standard deviation of 0.4%, which gives a range of uncertainty similar to that estimated by Rehle *et al* (2007). In both models, multiples are specified to ensure that this HIV incidence rate varies with respect to age and varies with respect to time.

In the first model, it is assumed that all non-vertical transmission is due to nosocomial transmission occurring in health facilities, as has been argued by Gisselquist *et al* (2002). It is assumed that all non-vertical transmission in the 0-14 age group would be from other children in the 0-14 age group, and the adjustment factor applied in year *t* is therefore the ratio of HIV prevalence in children aged 0-14 in year *t* to HIV prevalence in children aged 0-14 in 2004. To take into account that younger children attend health facilities much more frequently than older children, an age adjustment factor is also applied. This age adjustment factor is calculated by fitting an exponential curve to reported rates of healthcare utilization at different ages (Shisana *et al*, 2005a; Shisana *et al*, 2010), so that the age adjustment factor represents the ratio of the rate of healthcare utilization at age *x* to the average rate of healthcare utilization in the 2-14 age group. These age adjustment factors are shown in Figure 2.8.

In the second model, it is assumed that all non-vertical transmission is due to sexual abuse, with the non-vertical HIV transmission rate in year *t* being proportional to the HIV prevalence in adult men in year *t*. The adjustment factor applied in year *t* is therefore calculated as the ratio of HIV prevalence in men aged 15-49 in year *t* (as estimated by the ASSA2003 AIDS and Demographic model) to the HIV prevalence in men aged 15-49 in 2004. Age adjustment factors are also applied, to take into account the greater frequency of sexual abuse in older children than in younger children, based on reported cases of sexual abuse in 2008/9 (South African Police Service 2009). The age adjustment factor at age *x* is calculated as the ratio of numbers of sexual abuse cases reported at age *x* to the average number of sexual abuse cases reported in the 2-14 age group, and the age adjustment factors are shown in Figure 2.8. Although it may be argued that a gender adjustment factor should also be applied, on the grounds that roughly 70% of child rape cases occur in girls (Lammers *et al*, 2010), almost all male rape cases involve anal intercourse, which is known to be associated with a much greater HIV transmission risk than vaginal intercourse (Baggaley *et al*, 2010). It is therefore unclear whether boys would indeed be at a lower HIV risk than girls, and we have not attempted to apply different adjustment factors to boys and girls.

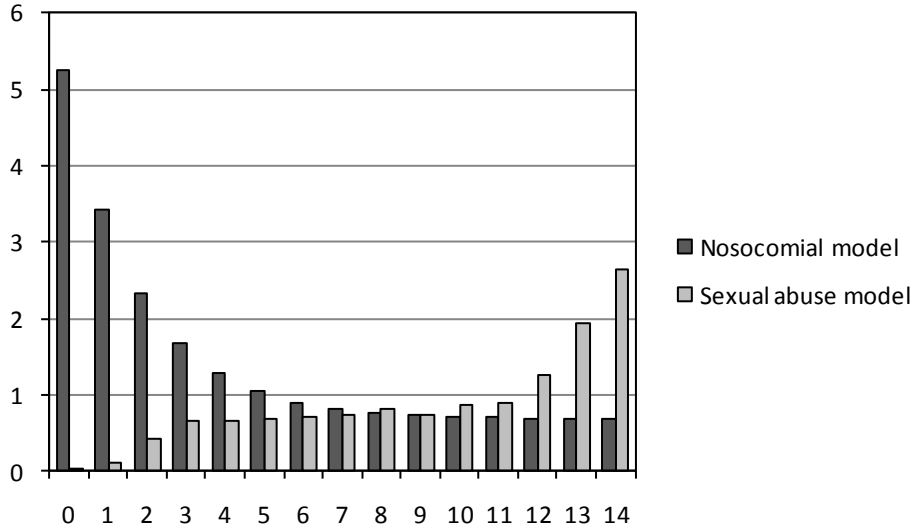


Figure 2.8: Age adjustment factors applied to the average rate of HIV incidence in children aged 2-14

# 3. Uncertainty analysis

As many of the parameters in the model are difficult to quantify precisely, it is important to conduct uncertainty analysis to assess the range of uncertainty around the outputs of the model. We adopt a Bayesian approach to uncertainty analysis, which involves three steps. Firstly, prior distributions are specified to represent the uncertainty regarding the key parameters in the model. Secondly, a likelihood function is defined, to represent the probability that a particular combination of parameter values is consistent with HIV prevalence data in children. Thirdly, a posterior distribution of model estimates is generated, by randomly sampling parameter combinations from the prior distributions and weighting different parameter combinations by the likelihood functions. Each of these three steps is described in detail in the sections that follow.

## 3.1 Prior distributions

Prior distributions are specified for ten of the model parameters that we consider to be particularly difficult to quantify. The definitions of these parameters and the discussion of the data sources on which the prior distributions are based are included in section 2. The prior distributions are summarized in Table 3.1. Beta priors are specified for those parameters that are defined on the interval [0, 1]. Gamma distributions are specified for those parameters that are defined on the range $[0, \infty)$.

Table 3.1: Prior distributions

| Parameter | Symbol | Prior type | Prior mean | Std dev. | Section |
|---|---|---|---|---|---|
| Probability of MTCT at birth if mother seroconverts after 1st antenatal visit | $\pi^*$ | Beta | 0.35 | 0.08 | 2.2 |
| Probability of MTCT per month of breastfeeding during acute HIV | $h_0$ | Beta | 0.16 | 0.03 | 2.3 |
| Probability of MTCT per year of mixed breastfeeding, if mother is chronically infected | $1-(1-h_1)^{12}$ | Beta | 0.14 | 0.025 | 2.3 |
| Relative risk of MTCT after birth if mother breastfeeds exclusively | $\xi$ | Beta | 0.5 | 0.15 | 2.3 |
| Annual rate of progression to ART eligibility in older children | $G_p$ | Gamma | 0.4 | 0.1 | 2.4 |
| Excess annual rate of progression to ART eligibility in neonates | $H_p$ | Gamma | 2.0 | 0.25 | 2.4 |
| Relative rate of progression to ART eligibility if infected after birth | $\theta_2$ | Beta | 0.35 | 0.15 | 2.4 |
| Annual rate of AIDS mortality in older children who are untreated and ART-eligible | $G_m$ | Gamma | 0.12 | 0.03 | 2.4 |
| Excess annual rate of AIDS mortality in neonates who are untreated and ART-eligible | $H_m$ | Gamma | 3.5 | 0.35 | 2.4 |
| Proportion of women testing positive who receive single-dose nevirapine | $\alpha_0$ | Beta | 0.75 | 0.1 | 2.7 |

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

In the scenarios described in section 2.10, we specify an additional prior distribution for the average HIV incidence rate due to non-vertical transmission in children aged

2-14, in the year 2004. This distribution is a beta distribution with a mean of 0.005 and a standard deviation of 0.004.

## 3.2 Likelihood function

The likelihood function calculation is based on HIV prevalence data from the 2005 and 2008 Human Sciences Research Council (HSRC) national household surveys (Shisana *et al*, 2005b; Shisana *et al*, 2009). Both surveys sampled a nationally representative selection of households and conducted HIV testing among a selection of household members who agreed to participate in the survey. HIV prevalence in children aged 2 and older was determined using dried blood spot (DBS) testing; children who tested positive on an initial enzyme immunoassay (EIA) were then retested using a different EIA, to confirm HIV infection, and if results of the second test were negative, a third test was conducted to decide the true HIV status of the child. This testing algorithm ensured that false positive reactions were kept to a minimum. Although HIV prevalence data from another household prevalence data in 2002 are available (Human Sciences Research Council 2002), it was decided not to use these data because in the 2002 survey, HIV testing was based on a single saliva test and there was no confirmatory testing of those specimens that were positive. Antibody testing in children under the age of 2 was not conducted in any of the surveys, as children under the age of 2 may have their mother's HIV antibodies without necessarily being infected with HIV. However, in the 2008 survey, PCR testing was conducted in children under the age of 2, and the proportion of children in this age group who were PCR-positive was 2.1% (95% CI: 1.2-3.6%) (Shisana *et al*, 2010).

For both the 2005 and 2008 surveys, HIV seroprevalence levels in children are reported by sex in three age groups: 2-4, 5-9 and 10-14. Suppose $x_{g,a,t}$ represents the HIV seroprevalence measured in children of gender *g*, in age group *a*, in year *t*. Also suppose that $\boldsymbol{\varphi}$ represents a vector of ten parameter values that we have sampled from the prior distributions specified in Table 3.1 (one value for each parameter), and that $H_{g,a,t}(\boldsymbol{\varphi})$ represents the model estimate of HIV prevalence in children of gender *g*, in age group *a*, in year *t*, when the $\boldsymbol{\varphi}$ parameter values are entered into the model. A logit transformation is applied to both the observed HIV seroprevalence and the model estimate of HIV prevalence, to ensure that differences between model estimates and survey estimates are approximately normally distributed. The statistical model that forms the basis for the likelihood function is then

$$\ln\left(\frac{x_{g,a,t}}{1-x_{g,a,t}}\right) = \ln\left(\frac{H_{g,a,t}(\boldsymbol{\varphi})}{1-H_{g,a,t}(\boldsymbol{\varphi})}\right) + \varepsilon_{g,a,t}, \qquad (3.1)$$

where it is assumed that $\varepsilon_{g,a,t}$ ~ N(0, $\sigma^2_{g,a,t}$), and the variance of this normal distribution is calculated from the published 95% confidence intervals around the survey prevalence levels. It is thus assumed that if $\boldsymbol{\varphi}$ is the 'true' set of parameter values, we would not expect the difference between the model estimates and the

survey estimates of HIV prevalence to be significant relative to the standard errors around the survey estimates. The likelihood function for a single HIV prevalence estimate is calculated as

$$\frac{1}{\sqrt{2\pi}\sigma_{g,a,t}}\exp\left(-\frac{1}{2}\left(\frac{\text{logit}\left(x_{g,a,t}\right)-\text{logit}\left(H_{g,a,t}(\boldsymbol{\varphi})\right)}{\sigma_{g,a,t}}\right)^2\right). \quad (3.2)$$

The likelihood function for all the HIV seroprevalence data is then

$$L_S(\mathbf{x}\mid\boldsymbol{\varphi})\propto\prod_g\prod_a\prod_t\exp\left(-\frac{1}{2}\left(\frac{\text{logit}\left(x_{g,a,t}\right)-\text{logit}\left(H_{g,a,t}(\boldsymbol{\varphi})\right)}{\sigma_{g,a,t}}\right)^2\right), \quad (3.3)$$

where **x** is the vector of observed HIV seroprevalence levels (12 observations in total). For the purpose of weighting the different randomly sampled parameter combinations by the likelihood values, it is not important to know the constant of proportionality, and it is therefore omitted from equation (3.3).

The likelihood function in respect of the PCR data is defined in the same way. If $x_0$ represents the proportion of children under the age of 2 who had PCR-detectable HIV in their blood in the 2008 survey, $\sigma_0$ represents the standard deviation of the proportion on the logit scale, and $H_0(\boldsymbol{\varphi})$ represents the model estimate of HIV prevalence in children under the age of 2 in 2008, then the likelihood in respect of the PCR data is defined as

$$L_P(x_0\mid\boldsymbol{\varphi})\propto\exp\left(-\frac{1}{2}\left(\frac{\text{logit}\left(x_0\right)-\text{logit}\left(H_0(\boldsymbol{\varphi})\right)}{\sigma_0}\right)^2\right). \quad (3.4)$$

The total likelihood, for both the seroprevalence data and the PCR data, $L_T(\mathbf{x},x_0\mid\boldsymbol{\varphi})$, is calculated as the product of $L_S(\mathbf{x}\mid\boldsymbol{\varphi})$ and $L_P(x_0\mid\boldsymbol{\varphi})$.

## 3.3 Posterior analysis

The posterior distribution, $p(\boldsymbol{\varphi}\mid\mathbf{x})$, represents the synthesis of the prior beliefs regarding the parameters in the vector $\boldsymbol{\varphi}$ (i.e. the prior distribution discussed in section 3.1, which we represent by $p(\boldsymbol{\varphi})$), and the likelihood function, $L_T(\mathbf{x},x_0\mid\boldsymbol{\varphi})$, defined in section 3.2. By Bayes' theorem, the posterior distribution is calculated as

$$p(\boldsymbol{\varphi}\mid\mathbf{x},x_0)=k\times p(\boldsymbol{\varphi})\times L_T(\mathbf{x},x_0\mid\boldsymbol{\varphi}), \quad (3.5)$$

where *k* is a constant, calculated in such a way that the integral of the posterior distribution is 1. Because the calculation of the likelihood function requires us to run a complex mathematical model, there is no closed-form analytical solution to equation

(3.5), i.e. there is no simple formula for calculating $p(\boldsymbol{\varphi} \mid \mathbf{x}, x_0)$ for given values of $\mathbf{x}$, $x_0$ and $\boldsymbol{\varphi}$. It is therefore necessary to use numerical methods to approximate $p(\boldsymbol{\varphi} \mid \mathbf{x}, x_0)$.

The numerical method used in this analysis is Incremental Mixture Importance Sampling (IMIS) (Raftery and Bao 2010). The method we use to generate a posterior sample of parameter combinations follows these steps:

1. Randomly sample 10 000 parameter combinations from the prior distribution $p(\boldsymbol{\varphi})$.
2. For each parameter combination sampled, run the model, calculate the model estimates $H_{g,a,t}(\boldsymbol{\varphi})$ and $H_0(\boldsymbol{\varphi})$, and then calculate the likelihood.
3. Calculate weights for each of the 10 000 parameter combinations, where the weight for the $i^{\text{th}}$ parameter combination is $W_i = \dfrac{L_T(\mathbf{x}, x_0 \mid \boldsymbol{\varphi}_i)}{\sum_j L_T(\mathbf{x}, x_0 \mid \boldsymbol{\varphi}_j)}$.
4. Form a new multivariate normal sampling distribution, using the parameter combination with maximum weight from the previous step as the mean and calculating the weighted covariance matrix from the 1 000 parameter combinations that are closest to the parameter combination with maximum weight.
5. Randomly sample 1 000 parameter combinations from this multivariate normal distribution and calculate the likelihood weights in the same way as before, but adjust the weights by the ratio of the prior density to the updated sampling density.
6. Form a new multivariate normal sampling distribution based on the weights in the previous step, repeating steps 4 and 5 until such time as there is an acceptable degree of heterogeneity in the sample weights.
7. Draw a sample of 3 000 parameter combinations (with replacement) from the sets of parameter combinations generated in all previous steps, using the weights calculated in the last step as the sample weights. If the heterogeneity in the weights is adequate, the fraction of unique parameter combinations in the sample should be greater than $1-\exp(-1)=0.63$.

The set of 3 000 parameter combinations is effectively a sample from the posterior distribution, since sampling from the prior distribution and then resampling from this distribution using the likelihood values as sample weights is equivalent to sampling from the product of the prior distribution and likelihood function. A more detailed description of the method is provided by Raftery and Bao (2010). For each of the 3 000 parameter combinations, the model was run again in order to generate more detailed results. The distributions of model outputs shown in subsequent sections are the distributions of results obtained when the model is run for all 3 000 parameter combinations, with the 95% confidence intervals representing the 2.5 and 97.5 percentiles of these distributions.

## 3.4 Programming

The model was initially programmed in Excel/VBA. As this model was too slow for the purpose of the Bayesian uncertainty analysis, it was reprogrammed in Visual C++ .NET. A reconciliation of the C++ and Excel models was performed, by projecting both models for 30 years and comparing 17 arbitrarily chosen model outputs at the end of this projection period. The outputs from the two versions of the model were identical.

For the purpose of the uncertainty analysis, two libraries of C++ functions were copied into the C++ code. The DCDFLIB library (downloaded on 4 March 2005 from http://www.csit.fsu.edu/~burkardt/cpp_src/dcdflib/dcdflib.html) is used for its statistical functions, notably the cumulative beta and gamma distributions. The 'randomc' library (downloaded from http://www.agner.org/random/randomc.htm on 3 May 2005) is used to generate random numbers from the uniform (0,1) distribution. The 'Mersenne Twister' random number generator is used for this purpose.

# 4. Results

## 4.1 Model calibration

The model provides a reasonable fit to the HIV seroprevalence data that are used in likelihood function. Figure 4.1 shows that the survey estimates of HIV prevalence in 2005 tend to be slightly higher than those predicted by the model, while the survey estimates of HIV prevalence in 2008 tend to be slightly lower than the model estimates. However, the 95% confidence intervals around the survey estimates tend to be quite wide, and these differences may therefore be due only to chance.

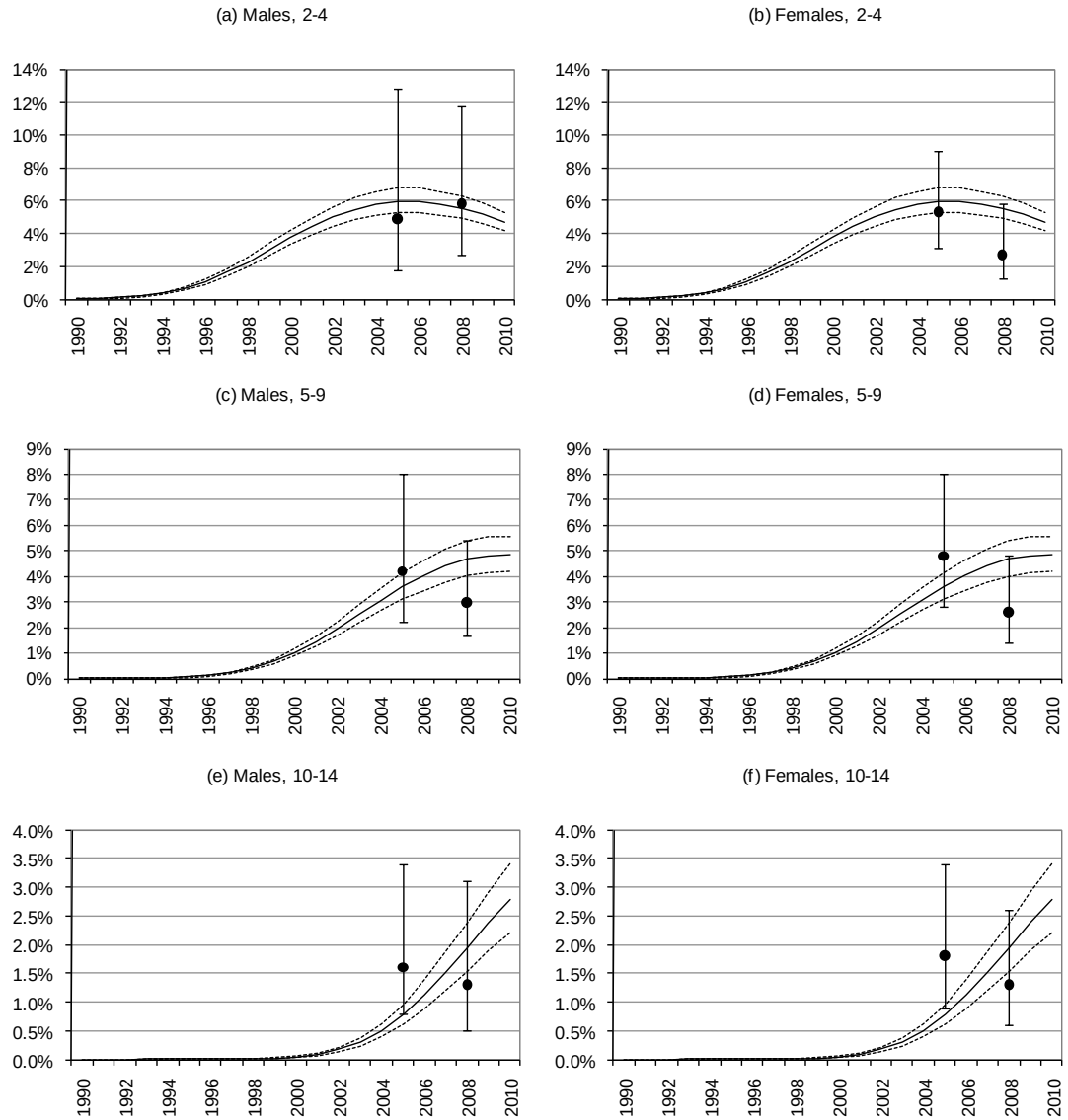


Figure 4.1: Comparison of model estimates and survey estimates of HIV prevalence
Dots represent survey estimates (with 95% confidence intervals). Solid black lines represent average prevalence levels from posterior sample of model outputs, and dashed lines represent 95% confidence intervals (i.e. 2.5 and 97.5 percentiles of distribution of model outputs).

Overall HIV prevalence in children aged 2-14 was reported to be 3.3% (95% CI: 2.3-4.8%) in the 2005 survey and 2.5% (95% CI: 1.9-3.5%) in the 2008 survey. The model estimate of HIV prevalence in children aged 2-14 in 2005 (3.1%, 95% CI: 2.7-3.5%) is reasonably consistent with the 2005 survey. However, the model estimate of HIV prevalence in 2008 (3.8%, 95% CI: 3.3-4.4%) is somewhat higher than that observed in the 2008 survey.

The model estimate of HIV prevalence in children under the age of 2 in 2008 is 4.1% (95% CI: 3.8-4.5%). This is significantly higher than the PCR positivity rate recorded in this age group in the 2008 survey (2.1%, 95% CI: 1.2-3.6%). It is possible that the survey may under-estimate the true prevalence of HIV in this age group due to the high rate of parental refusal to HIV testing in this age group (52%), although a response analysis did not find parental refusal to be significantly associated with paediatric HIV risk factors (Shisana *et al*, 2010).

Other PCR data from newborn infants correspond reasonably closely with the model estimates of vertical transmission rates at birth (Figure 4.2). Vertical transmission rates at 4-8 weeks in KwaZulu/Natal in 2004/5 (Rollins *et al*, 2007a) are estimated to be slightly higher than those predicted by the model, which may be due to the lower efficacy of nevirapine in settings where breastfeeding is widely practised (see section 2.2.2). However, vertical transmission rates at 3-4 weeks in three provinces, between 2002 and 2004 (Colvin *et al*, 2007), are slightly lower than the model estimates. The model estimates are reasonably consistent with unpublished National Health Laboratory Service (NHLS) data collected in the first 3 months of life, over the 2008/9 and 2009/10 periods, although it is possible that the NHLS data may understate the true rate of vertical transmission if women who receive sub-optimal PMTCT services are less likely to receive subsequent PCR testing.

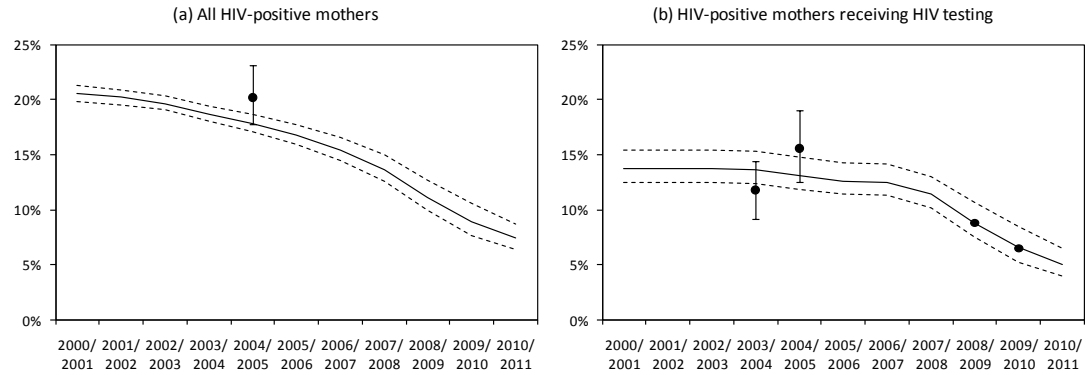


Figure 4.2: Rates of mother-to-child transmission at birth

In panel (a), the denominator is all women who are HIV-positive when they deliver, and in panel (b) the denominator is all HIV-positive women who receive antenatal HIV testing. Solid lines represent posterior model averages and dashed lines represent model 95% confidence intervals. Dots represent PCR data; the 2003/4 point represents data from the Good Start Study (Colvin *et al*, 2007), the 2004/5 point represents data from a study at immunization clinics in KwaZulu-Natal (Rollins *et al*, 2007a), and the 2008/9 and 2009/10 points represent unpublished data from the NHLS (Gayle Sherman, personal communication).

It is also possible to check the plausibility of the model estimates by comparing the model estimates of the age distribution of children starting antiretroviral treatment

(ART) with the age distribution of children starting ART in the IeDEA South Africa study, a large collaborative study that covers several different treatment programmes in urban South Africa (Cornell *et al*, 2009). Children were enrolled on ART between 2003 and 2007, and the reported numbers starting treatment in each year were used to weight the model estimates of the proportions of children in different age groups in each year, in order to obtain model estimates of the proportion of children starting antiretroviral treatment in each age group over the 2003-2007 period. These model estimates are compared with the actual age distribution in Figure 4.3. The model clearly predicts a much later average age for children starting ART than is suggested by the IeDEA data. This may be because the IeDEA Collaboration in South Africa includes a number of large tertiary care programmes, which tend to specialize in treating very young children (Davies *et al*, 2009). The difference could also be explained by the fact that the IeDEA Collaboration in South Africa represents mostly well-resourced programmes in urban settings, where transmission through breastfeeding is less common and uptake of PCR testing is likely to be higher. A number of these programmes fast-tracked infants onto ART, even before the publication of the results of the CHER study. In a rural South African programme, the average age of children starting ART has been estimated at 6 years (Janssen *et al*, 2010), and in a study of public sector programmes in four provinces, including both urban and rural areas, the median age of children starting ART was 5.8 years (Fatti *et al*, 2010). Similarly, in a collaborative study of paediatric ART programmes across Africa the median age of children starting ART was 5 years (KIDS-ART-LINC Collaboration 2008). These estimates are closer to the modelled age distribution than the IeDEA South African estimates.

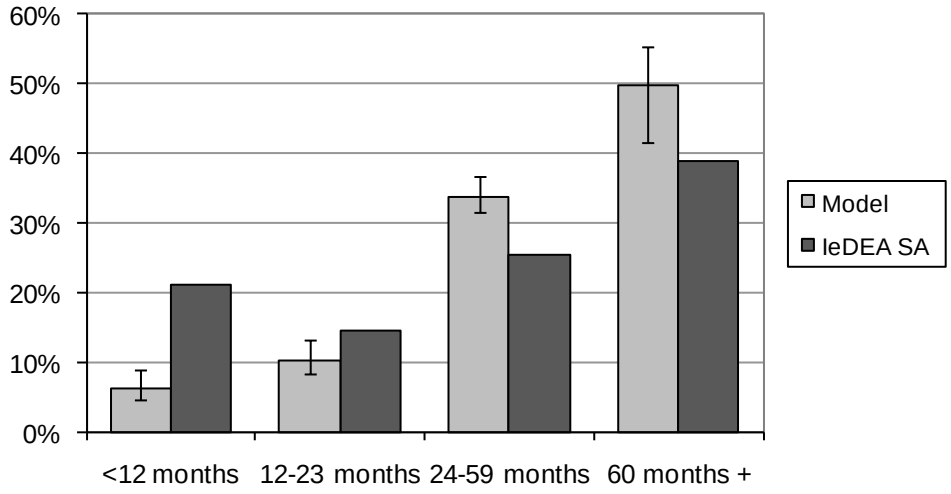


Figure 4.3 Comparison of observed and modelled age distributions of children starting antiretroviral treatment

The model validity can also be assessed by comparing the model mortality estimates with estimates of mortality from the 2007 Community Survey (Darikwa 2009). Indirect measures of mortality over the 1999-2004 period were obtained using the Children ever born/Children surviving technique, adjusted to take into account correlation between maternal and child HIV status (Ward and Zaba 2008). Due to the uncertainty regarding potential reporting biases and the appropriateness of the HIV adjustments, the indirect estimates have considerable uncertainty associated with

them. Direct measures of mortality for 2006 were also obtained based on the reporting of deaths in households over the 12 months prior to the 2007 Community Survey (Darikwa 2009). Figure 4.4 shows that although the model estimates of mortality are higher than the indirect estimates over the 1999-2004 period, the model estimates are lower than the direct estimates in 2006.

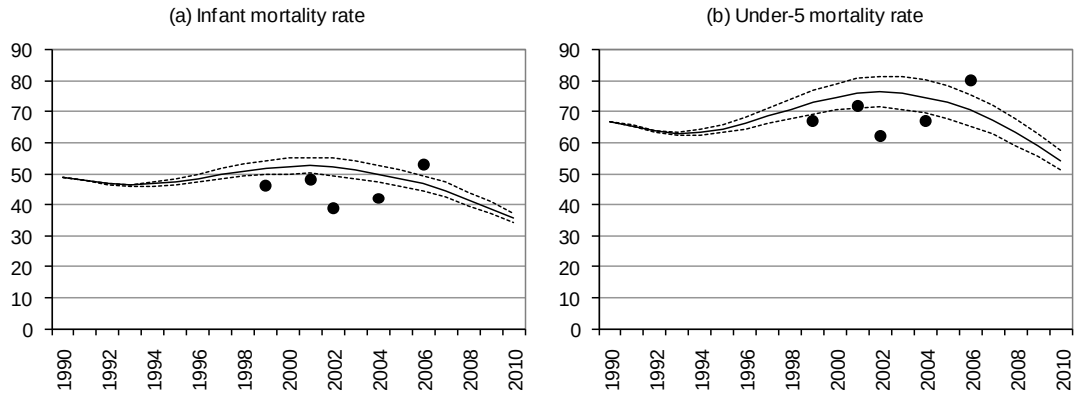


Figure 4.4: Infant and under-5 mortality rates

Solid lines represent posterior model averages and dashed lines represent model 95% confidence intervals. Dots represent indirect estimates and direct estimates from Darikwa *et al* (2009). Both infant and under-5 mortality rates are expressed as deaths per 1000 births.

## 4.2 Comparison of prior and posterior distributions

Figure 4.5 shows that in most cases, the prior and posterior distributions for the mother-to-child transmission parameters are very similar. The notable exception is the annual rate of mother-to-child transmission through mixed breastfeeding, which has a posterior mean of 11.6% (95% CI: 8.4-15.7%). This is substantially lower than the prior mean of 14%, but closer to the average annual transmission risk of 8.9% estimated by the Breastfeeding and HIV International Transmission Study Group (2004), based on data from both exclusively breastfeeding mothers and mothers practising mixed feeding.

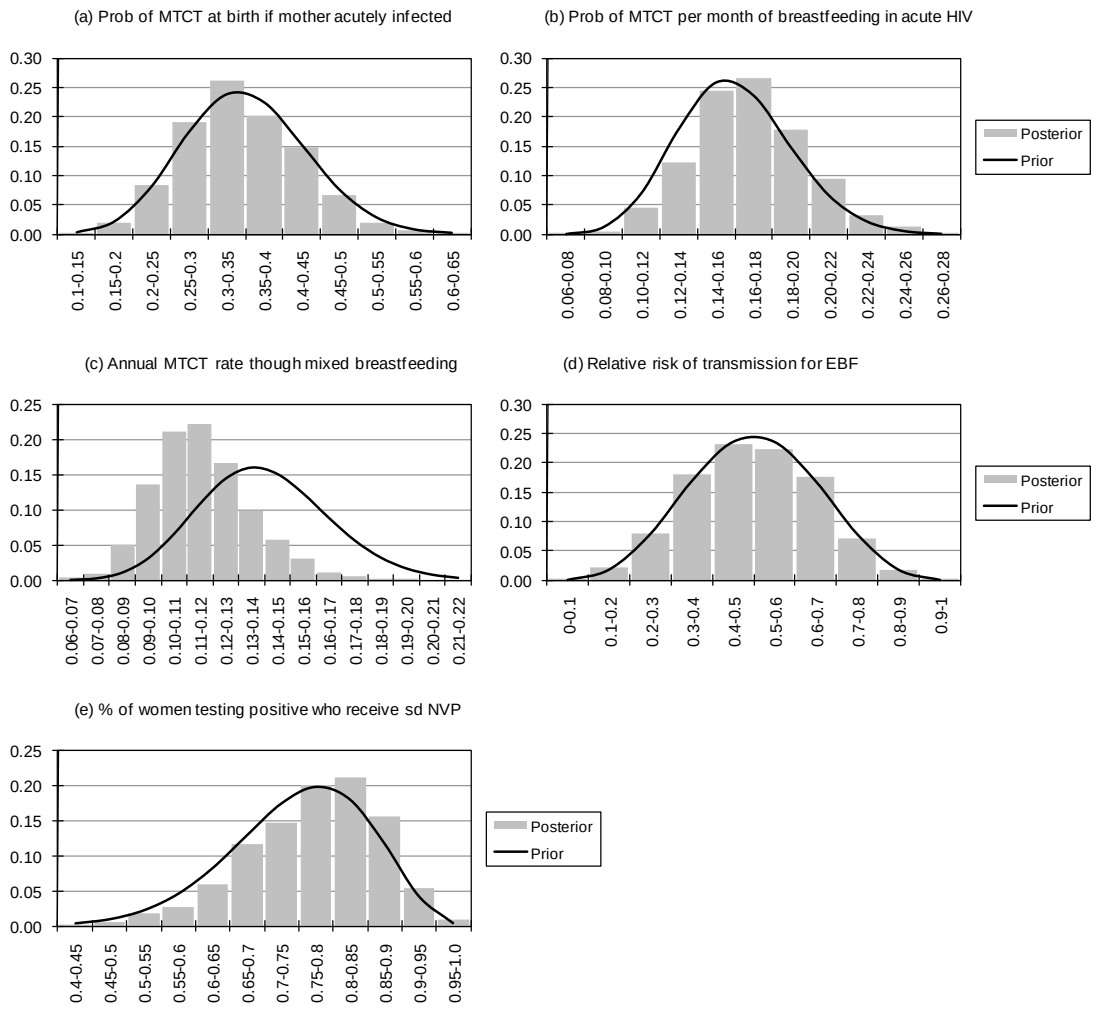


Figure 4.5: Comparison of prior and posterior distributions for mother-to-child transmission parameters

Grey bars represent proportions of posterior values in each range. Solid black lines represent beta prior distributions, scaled to be comparable with posterior distributions.

There is also a fair degree of consistency between prior and posterior estimates of paediatric HIV survival parameters (Figure 4.6). However, the posterior estimates suggest a slightly more rapid rate of progression to AIDS in the first year of life and a slightly higher rate of mortality in ART-eligible infants, when compared with the prior distributions (Figures 4.6(b) and 4.6(e) respectively). The posterior estimates also suggest a substantially slower rate of progression to ART eligibility in children infected postnatally than has been assumed a priori (Figure 4.6(c)).

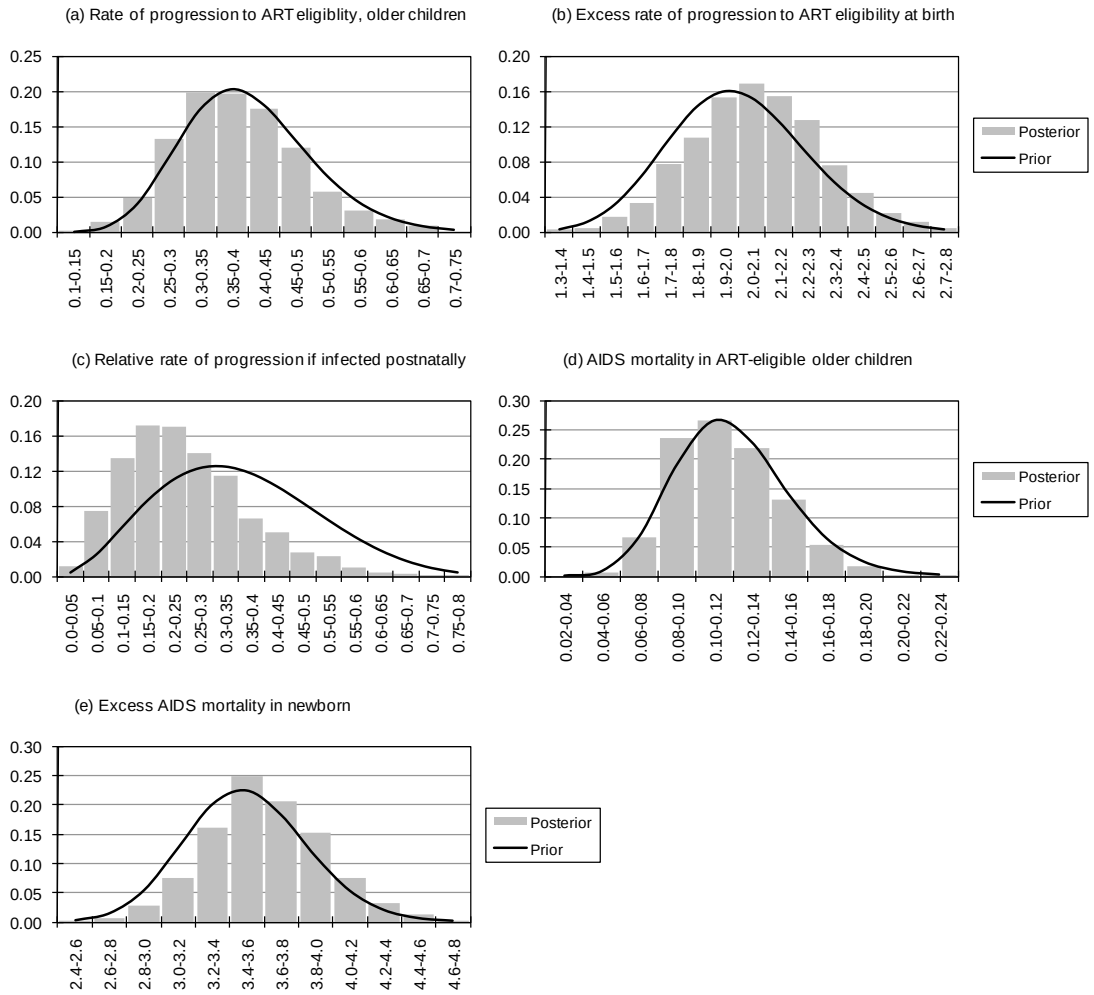


Figure 4.6: Comparison of prior and posterior distributions for paediatric HIV survival parameters

Grey bars represent proportions of posterior values in each range. Solid black lines represent prior distributions, scaled to be comparable with posterior distributions. All prior distributions are gamma distributions, except in panel (c), where the prior is a beta distribution.

## 4.3 Results in the default scenario

Figure 4.7 shows the results of the model in the default scenario, taking into account the programmes that have been introduced in the past and the policies that are currently in place. The annual number of new HIV infections in children is estimated to have reached its highest level in 2002, at 94 000 per annum (95% CI: 86 000-104 000). Since then there has been a steady decline in the annual number of new HIV infections in children, mainly as a result of the success of the PMTCT programme (Fig. 4.7(a)). In the early stages of the South African HIV epidemic, a high proportion of mother-to-child transmission occurred from mothers who were recently infected (i.e. HIV-seronegative at the time of their first antenatal visit but seroconverting thereafter), with the proportion estimated to be 60% (95% CI: 55-64%) in 1990. This proportion declined steadily during the 1990s, as the level of prevalent HIV in pregnant women rose relative to the rate of HIV incidence in pregnant women (Fig 4.5(b)). The proportion would have continued to decline, but

the introduction of PMTCT after 2000 reduced the rate of mother-to-child transmission from women who were HIV-positive at the time of antenatal screening, resulting in a slight reversal of the downward trend. Over the period from mid-2007 to mid-2008, an estimated 68 000 new HIV infections occurred in children (95% CI: 61 000-75 000), and of these 23% (95% CI: 20-27%) occurred in children whose mothers were HIV-seronegative at the time of their first antenatal visit.

The annual number of AIDS deaths peaked in 2006, at 45 000 per annum (95 CI: 35 000-56 000), and is estimated to be declining currently, mainly due to the effects of the PMTCT programme and the antiretroviral treatment programme. HIV prevalence in children under the age of 15 is estimated to be close to its maximum level, with HIV prevalence in 2008 at 3.8% (95% CI: 3.4-4.4%).

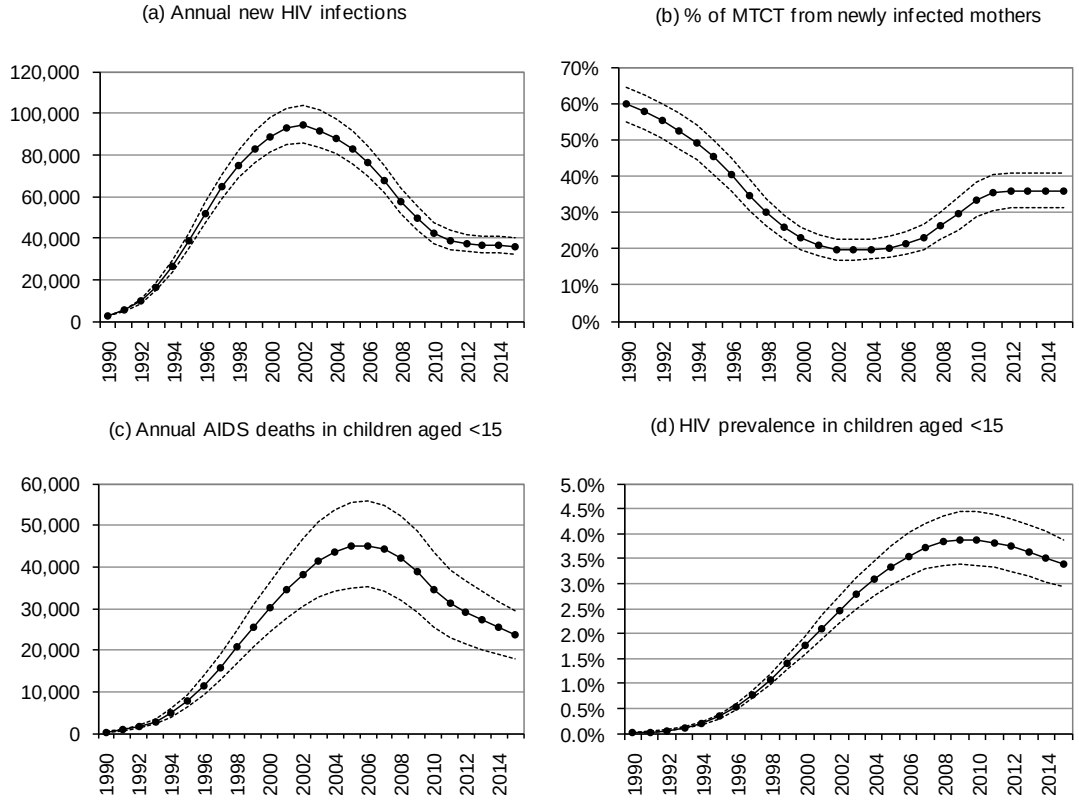


Figure 4.7: Model projections in the default scenario
Solid lines represent average results from the posterior sample. Dashed lines represent 95% confidence intervals (2.5 and 97.5 percentiles of the distribution of estimates in the posterior sample).

## 4.4 Evaluation of prevention and treatment programmes introduced up to 2010

The introduction of PMTCT programmes in South Africa has had a significant impact on the annual number of new HIV infections; over the period from mid-2007 to mid-2008, it is estimated that the annual number of new HIV infections was reduced by 34% (95% CI: 30-37%) relative to what would have been expected in the absence of a PMTCT programme (Fig. 4.8(a)). PMTCT has also had a modest impact on the

annual number of AIDS deaths, reducing the annual number of paediatric AIDS deaths by 16% (95% CI: 13-19%) relative to what would have been expected in the absence of PMTCT and ART (Fig 4.8(b)).

Access to antiretroviral treatment in children is measured in two ways: longitudinally, as the ratio of children starting ART to children becoming eligible for ART (Figure 4.8(c)), and cross-sectionally, as the proportion of children needing ART who are receiving treatment (Figure 4.8(d)). The rate of ART initiation in children has increased significantly since the start of the public sector ART programme in 2004, with the ratio of ART initiates to new ART need rising to 0.30 (95% CI: 0.27-0.32) over the 2007-8 period. However, there is a significant accumulation of unmet need, and as a result the proportion of ART-eligible children receiving ART was only 17% (95% CI: 12-24%) by the middle of 2008[4]. The impact of antiretroviral treatment on the annual number of AIDS deaths is correspondingly small, with the reduction in AIDS deaths over the 2007/2008 period estimated at only 7.2% (95% CI: 5.2-9.8%). However, the combined effect of the PMTCT and ART programmes is a more substantial 22% reduction (95% CI: 18-26%) in the number of paediatric AIDS deaths over the 2007/2008 period (Figure 4.8(f)).

Although there is a lack of reliable data with which to track the performance of the PMTCT programme after 2008, it is possible to make projections of what is likely to happen after 2008 based on assumptions about the likely rollout of new guidelines. Figure 4.9(a) shows that with the continuation of the current protocols, the annual number of new HIV infections in children is likely to decline to about 36 000 (95% CI: 32 000-40 000) per annum by 2015, a reduction of 62% (95% CI: 59-65%) when compared with what would have been expected in the absence of PMTCT. Although much of the reduction can be explained by the introduction of single-dose nevirapine and counselling on feeding options to HIV-positive mothers (the protocol originally introduced by the Department of Health), the introduction of the AZT plus nevirapine regimen in 2008 and the subsequent changes to protocols in 2010 (extended nevirapine prophylaxis to infants who are being breastfed and greater initiation of HAART in pregnant women) can be expected to achieve significant further reductions in rates of vertical transmission.

[4] Note that this measure of coverage is based on the previous guidelines for initiating ART in children, and the unmet need in the denominator therefore does not include infants who had not yet satisfied the clinical or immunological criteria for starting ART in the SA 2005 guidelines.

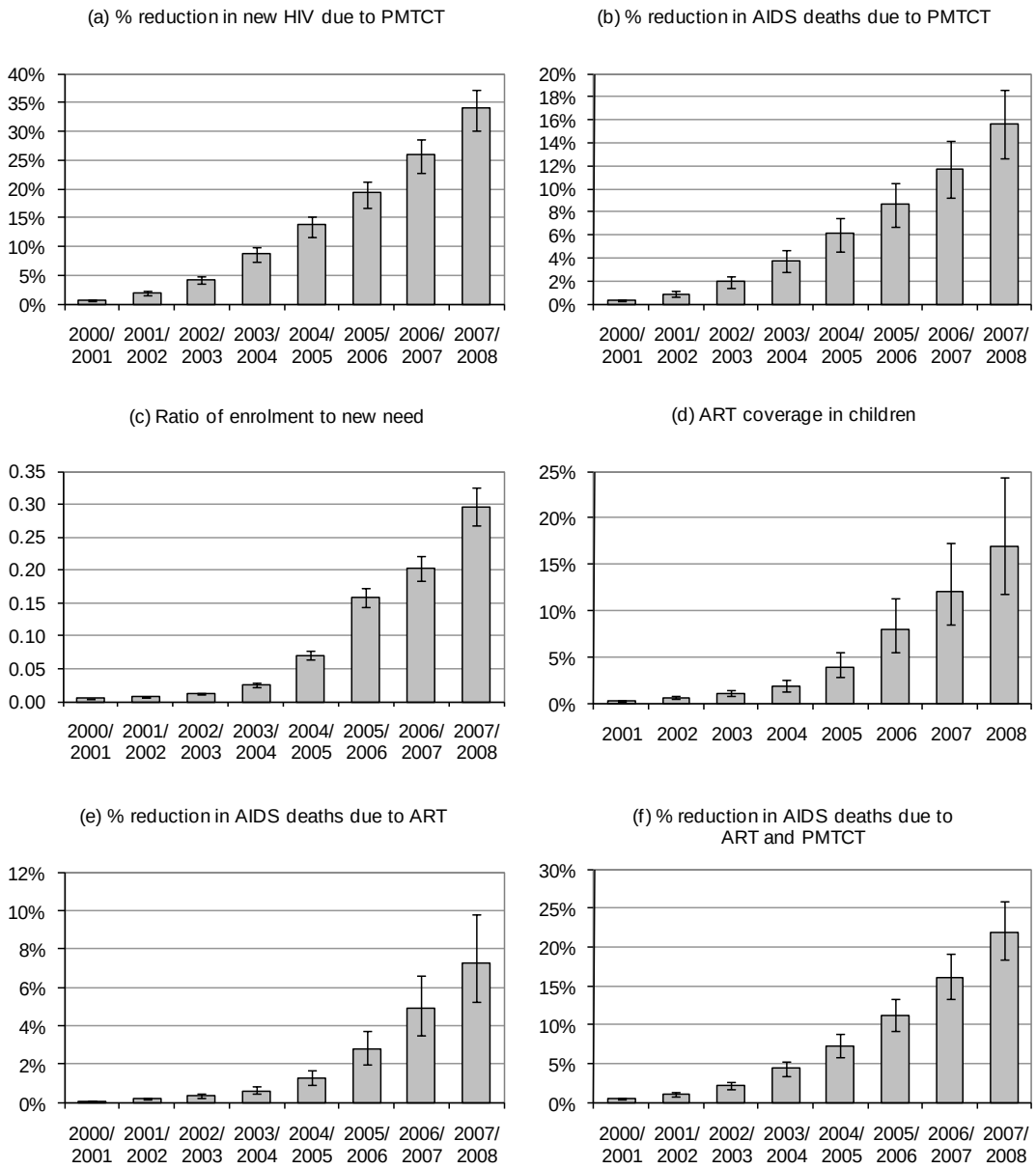


Figure 4.8: Impact of PMTCT and paediatric ART programmes introduced up to 2008, in children under the age of 15

Bars represent averages from posterior samples. Upper and lower error bars represent 95% confidence intervals (97.5 and 2.5 percentiles of distribution of posterior estimates).

The recent changes in PMTCT and ART guidelines can also be expected to lead to significant declines in AIDS mortality (Figure 4.9(b)). If current protocols continue, the annual number of AIDS deaths in children under the age of 15 is expected to drop to 24 000 (95% CI: 18 000-30 000) per annum by 2015, a reduction of 64% (95% CI: 60-68%) relative to what would have been expected in the absence of any intervention. Most of the reduction is attributable to the impact of the PMTCT programme, although antiretroviral treatment contributes significantly to the reduction. The new paediatric ART protocols, which recommend immediate initiation of ART in all HIV-infected infants ("early ART"), are expected to achieve only a modest reduction in levels of AIDS deaths.

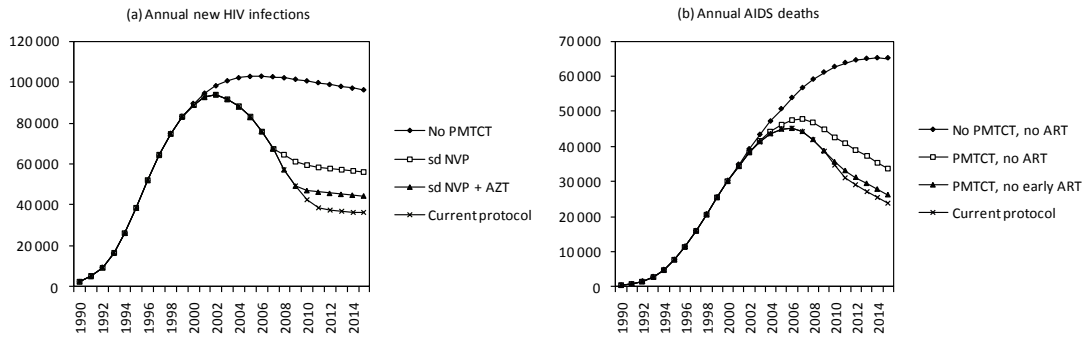


Figure 4.9: Comparison of HIV incidence trends and mortality trends in different scenarios

In panel (a), the scenarios correspond to the 'No PMTCT', 'Early PMTCT', 'Dual therapy' and 'WHO protocols, option A' scenarios described in section 4.7.6. In panel B, the 'WHO protocols, option A' assumptions about PMTCT are assumed to apply in all scenarios except the first, and the last two scenarios correspond to paediatric ART scenarios 1 and 2 described in section 4.8.

The proportion of AIDS deaths occurring in the first year of life is shown in Figure 4.10(a). Partly because of the impact of the PMTCT programme, and partly because of the ageing of HIV-positive children infected in the earlier stages of the epidemic, the proportion of AIDS deaths occurring in children under the age of 12 months has declined significantly since 2000, dropping from 54% (95% CI: 45-63%) in 2000/2001 to 32% (95% CI: 25-40%) in 2007/2008. As might be expected, PMTCT has had a relatively greater impact on numbers of AIDS deaths in the first year of life than it has had on total AIDS deaths (Fig 4.10(b)). For example, over the 2007/2008 period, the PMTCT programme is estimated to have reduced AIDS deaths in the first year of life by 30% (95% CI: 24-34%), which is double the percentage reduction in total paediatric AIDS deaths shown in Figure 4.8(b). The reduction in infant AIDS deaths due to antiretroviral treatment, on the other hand, is very small (0.6%, 95% CI: 0.4-1.0%), since the rate of ART initiation is low relative to the rate of AIDS mortality in the first year of life. The total reduction in infant AIDS deaths, due to both antiretroviral treatment and PMTCT, is therefore similar to the reduction attributable to PMTCT.

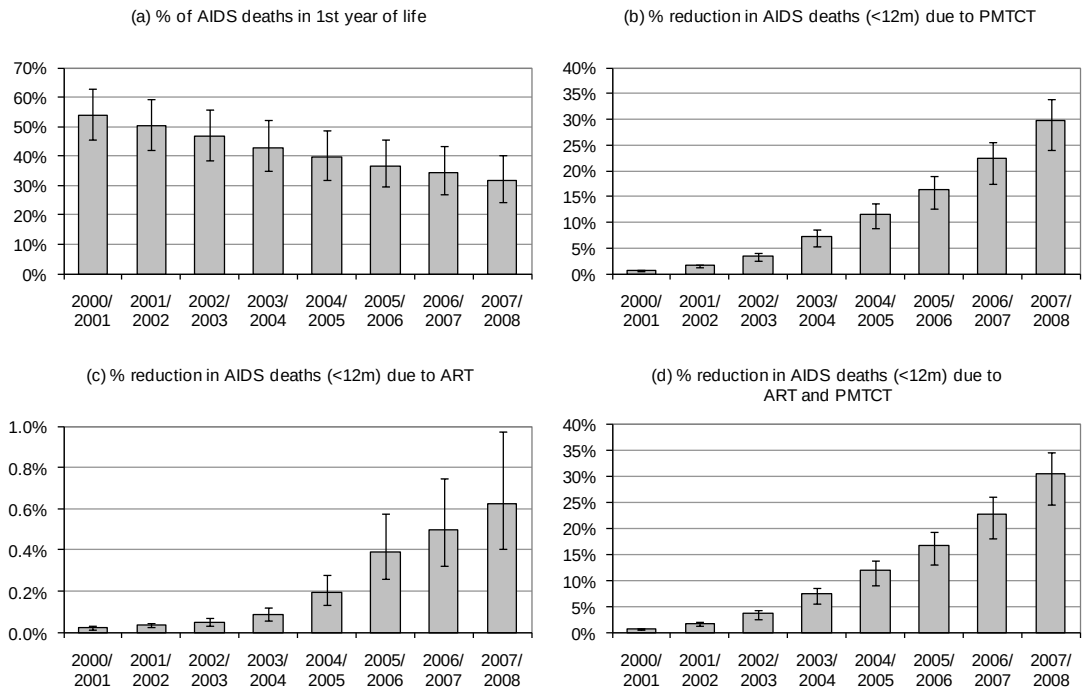


Figure 4.10: Impact of prevention and treatment programmes introduced up to 2008, on AIDS mortality in children aged <12 months

Bars represent averages from posterior samples. Upper and lower error bars represent 95% confidence intervals (97.5 and 2.5 percentiles of distribution of posterior estimates).

## 4.5 Effect of future changes to PMTCT and ART

A number of potential extensions to current protocols have been proposed. Offering HIV testing to all women bringing their infants for immunization at age 6 weeks would prevent an estimated 3.9% of new paediatric infections over the 2010-2015 period (95% CI: 3.0-4.9%), as a result of women testing positive changing their feeding practices and initiating nevirapine prophylaxis if choosing to continue breastfeeding. Initiating HAART in all pregnant women, regardless of their CD4 count, and continuing HAART for the duration of breastfeeding would achieve a 12.3% (95% CI: 9.4-15.7%) reduction in mother-to-child transmission over the 2010-2015 period, relative to what would be expected in the absence of any change to the current protocols (Figure 4.11).

Even in the absence of changes to current protocols, substantial reductions in vertical transmission could be achieved through the more effective implementation of current protocols. If all pregnant women were offered HIV re-testing in late pregnancy (in line with the current protocol), this would achieve an estimated 11.7% (95% CI: 9.9-13.3%) reduction in mother-to-child transmission over the 2010-2015 period. If it were optimistically assumed that all women received HIV testing both at their first antenatal visit and later in pregnancy, that all women testing positive received AZT and nevirapine or triple-drug therapy if eligible, and that all children breastfed by HIV-positive mothers received extended nevirapine prophylaxis, the vertical transmission rate would drop by 38% (95% CI: 34-43%).

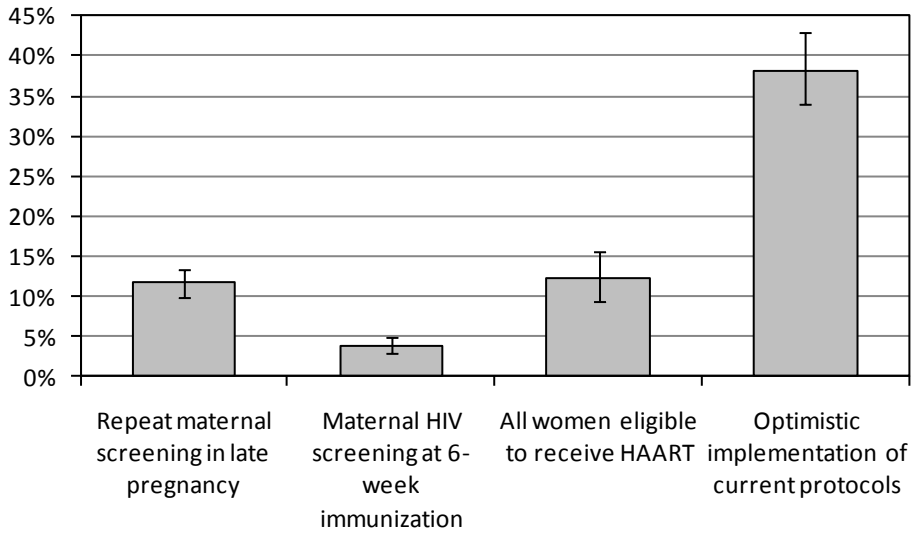


Figure 4.11: Reductions in new infections over the 2010-2015 period under different scenarios

For all scenarios, the reduction is calculated relative to the number of new infections over the period from mid-2010 to mid-2015 in the 'WHO protocols, option A' scenario. The four scenarios correspond to scenarios 6-9 described in section 4.7.6.

Figure 4.12 compares the future effect of ART in two different scenarios, described in section 4.8. The '50% ART' scenario corresponds to the default assumptions regarding ART phase-in (scenario 2 in section 2.8), while the '80% ART' scenario is an optimistic scenario in which it is assumed that the proportion of perinatally infected children starting ART by 2 months of age increases to 80%, and that the number of infected children starting ART at older ages increases to 80% of the new ART need in each period (where "new ART need" is defined according to the previous 2005 South African guidelines). In the 80% ART scenario, the number of children starting ART is expected to peak at 37 000 (95% CI: 29 000-44 000) per annum in 2013, while in the 50% ART scenario the annual numbers of children starting ART is expected to decline steadily after 2010 (Figure 4.12(a)). Because the 'backlog' of unmet need is addressed to a greater extent in the 80% ART scenario than the 50% ART scenario, the ratio of the number starting ART to the number of new infections in children rises above 1 initially, in the 80% ART scenario (Figure 4.12(b)); in both scenarios, the ratio gradually declines in the longer term as the backlog reduces. The number of children receiving ART levels off at around 152 000 (95% CI: 129 000-173 000) in 2015, in the 50% ART scenario, while in the 80% ART scenario the numbers of children on ART takes longer to plateau, reaching a level of 208 000 (95% CI: 170 000-243 000) by 2020 (Figure 4.12(c)). ART coverage (the number of children on ART divided by the number of children needing treatment, according to the 2010 Department of Health guidelines) is expected to rise to 64% (95% CI: 52-76%) by 2020 in the 50% ART scenario, and to 81% (95% CI: 70-92%) by 2020 in the 80% ART scenario (Figure 4.12(d)). As a result of this extension of ART coverage in children, AIDS deaths in children are expect to drop substantially, relative to the levels of AIDS mortality that would have been expected in the absence of ART (Figure 4.12(e)). Over the period from mid-2010 to mid-2025 the number of AIDS deaths in children is expected to reduce by 29% (95% CI: 26-33%) and by 38% (95% CI: 34-43%) in the 50% ART and 80% ART scenarios respectively.

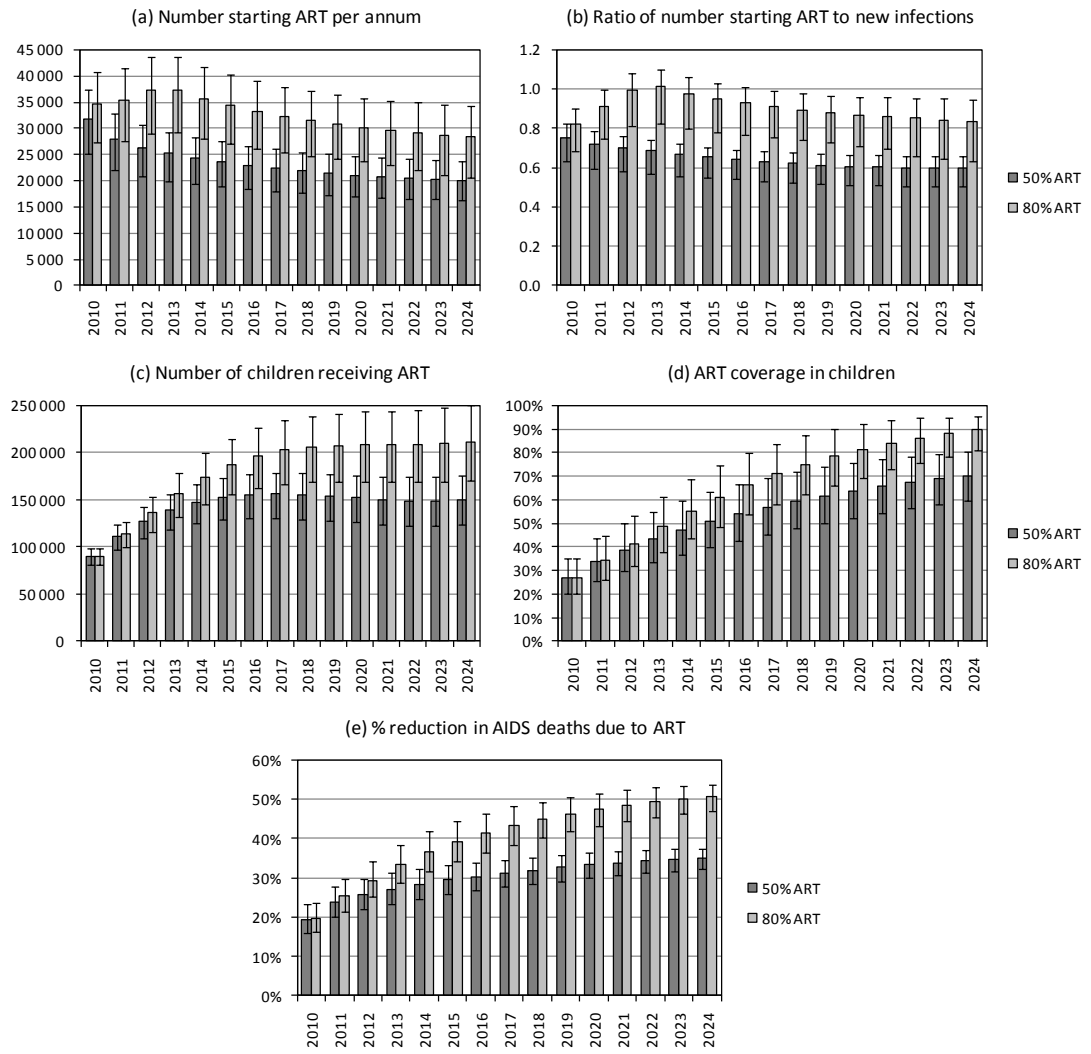


Figure 4.12: Future rollout of paediatric ART

Bars represent averages from posterior samples. Upper and lower error bars represent 95% confidence intervals (97.5 and 2.5 percentiles of distribution of posterior estimates).

## 4.6 Non-vertical transmission

Table 4.1 compares the default model described in previous sections, in which there is assumed to be no non-vertical transmission, and two alternative models that allow for different types of non-vertical transmission in children. These two models correspond to the models of nosocomial transmission and sexual abuse described in section 2.10. Of the three models, the model with the highest integrated likelihood is the model in which there is non-vertical transmission due to sexual abuse. Although the three models produce similar estimates of overall HIV prevalence in children aged less than 15, the model of sexual abuse provides the best fit to the available HIV prevalence data because its estimate of HIV prevalence in children aged 10-14 in 2005 is closest to that measured in the 2005 HSRC survey (1.7%, 95% CI: 1.0-2.8), and the other two models depart significantly from this estimate.

Both models of non-vertical transmission estimate an HIV incidence rate in the 2-14 age group in 2004 that is substantially lower than the 0.5% annual rate estimated by

Rehle *et al* (2007), on which the prior distribution is based. Nevertheless, the annual numbers of new HIV infections due to non-vertical transmission are very high in both models, at 16 000 (95% CI: 2 000-37 000) per annum in the nosocomial transmission model and at 22 000 (95% CI: 7 000-39 000) per annum in the sexual abuse model. This is equivalent to 17% and 19% respectively of all new HIV infections in children in 2004. However, confidence intervals around these estimates are extremely wide, indicating that there is substantial uncertainty regarding the significance of non-vertical transmission.

Table 4.1: Characteristics of different models

| | No non-vertical transmission | Nosocomial transmission | Transmission due to sexual abuse |
|---|---|---|---|
| Log of integrated likelihood | -16.01 | -18.02 | -13.19 |
| HIV prevalence in 2005 | 3.3% (3.0-3.8%) | 3.4% (3.0-3.9%) | 3.4% (3.0-3.8%) |
| HIV prevalence in 2005, ages 10-14 | 0.8% (0.6-1.0%) | 0.9% (0.7-1.2%) | 1.4% (0.4-2.0%) |
| Posterior estimate of non-vertical HIV | | | |
| HIV incidence in 2004, ages 2-14 | 0% | 0.08% (0.01-0.17%) | 0.17% (0.05-0.30%) |
| New HIV cases in 2004, ages 0-14 | 0 | 16 000 (2 000-37 000) | 22 000 (7 000-39 000) |
| All new infections in 2004, ages 0-14 | 88 000 (80 000-97 000) | 102 000 (86 000-123 000) | 109 000 (92 000-128 000) |
| % of new infections in 2004 due to non-vertical transmission, ages 0-14 | 0% | 17% (3-34%) | 19% (8-31%) |
| % of HIV-infected children in health facilities, aged 2-9, with HIV due to non-vertical transmission, in 2004* | 0% | 12.1% (1.8-27.0%) | 4.0% (1.1-7.8%) |
| AIDS deaths in 2005, ages 0-14 | 45 000 (35 000-55 000) | 54 000 (40 000-71 000) | 59 000 (44 000-75 000) |
| Ratio of progression to ART eligibility, postnatal compared to perinatal | 0.25 (0.07-0.53) | 0.36 (0.12-0.66) | 0.41 (0.16-0.71) |

* Calculated on the assumption that children who are eligible to receive ART attend health facilities at a frequency of 6.5 times that in children who are HIV-negative. The fraction is calculated by comparing the estimate of prevalence in children aged 2-9 attending health facilities with the prevalence that would be expected with exactly the same model assumptions but setting the non-vertical HIV incidence rate to zero.

The models can be assessed using data from a study conducted in health facilities in the Free State in 2004 (Shisana *et al*, 2005a). If it is assumed that HIV-positive children who are eligible to receive antiretroviral treatment attend health services 6.5 times as frequently as children who are HIV-negative (an assumption that appears plausible based on rates of hospitalization in HIV-positive and HIV-negative South African children (Shisana *et al*, 2010)), the model estimates of HIV prevalence by age are reasonably consistent with the survey estimates for all three models (Figure 4.13(a)). However, the survey estimate of the proportion of HIV-positive children with HIV-negative mothers (1.4%, 95% CI: 0.3-2.5%) is substantially lower than the estimated proportion of infections due to non-vertical transmission: 4.0% in the sexual abuse model and 12.1% in the nosocomial transmission model (Table 4.1).

Estimates of AIDS mortality are substantially higher in the models that allow for non-vertical transmission than in the model that allows only for vertical transmission, as the same prevalence can be sustained with higher HIV incidence only if AIDS mortality is also higher. The posterior estimates of HIV survival rates in children are

therefore lower in the models that allow for non-vertical transmission (Figure 4.13(b)). Most of this difference can be explained by the difference in the relative rate of progression to ART eligibility in postnatally-infected children when compared with perinatally-infected children. In the model of sexual abuse, this ratio is relatively high (0.41, 95% CI: 0.16-0.71) compared to the model in which there is only vertical transmission (0.25, 95% CI: 0.07-0.53).

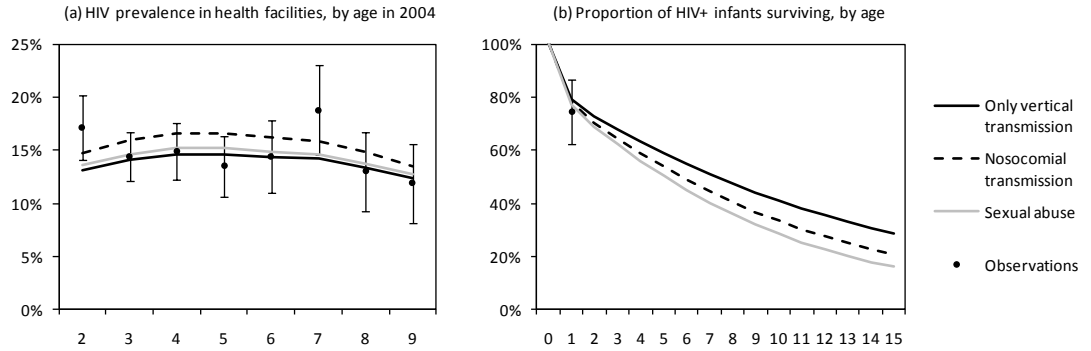


Figure 4.13: Comparison of HIV transmission models

In both panels, posterior model averages are displayed. In panel (a), observations are from a study conducted in the Free State in 2004 (Shisana *et al*, 2005a). In panel (b), the single observation is from a study of children born to HIV-positive mothers in Durban (Bobat *et al*, 1999), and has been adjusted to remove the effect of non-AIDS mortality (assumed to be 50 per 1000 in the first year of life). The model estimates in panel (b) are calculated on the assumption that 60% of children infected in the first year of life are infected at or before birth, and the remaining 40% are infected postnatally at the age of 6 months.

## 4.7 Results for KwaZulu-Natal and Western Cape

Figure 4.14 compares the model results for KwaZulu-Natal and the Western Cape in the baseline scenario. As a result of the higher levels of antenatal HIV prevalence in KwaZulu-Natal, the incidence and prevalence of paediatric HIV in KwaZulu-Natal is substantially higher than in the Western Cape. In spite of the higher levels of breastfeeding in KwaZulu-Natal, the proportion of new infections attributable to postnatal transmission is higher in the Western Cape. This may be a reflection of the later development of the HIV epidemic in the Western Cape, since in early epidemics the ratio of maternal HIV incidence to maternal HIV prevalence is relatively high, and incident maternal HIV is more significant as a source of postnatal vertical transmission than as a source of intrapartum and intrauterine transmission. This could also explain why the proportion of vertical transmission from newly-infected mothers is higher in the Western Cape than in KwaZulu-Natal prior to 2000 (Figure 4.14(c)). After 2000, the more rapid rollout of PMTCT in the Western Cape also accounts for the higher proportion of vertical transmission from newly-infected mothers, since PMTCT interventions reduce the transmission from chronically-infected mothers but have little effect on transmission from acutely-infected mothers.

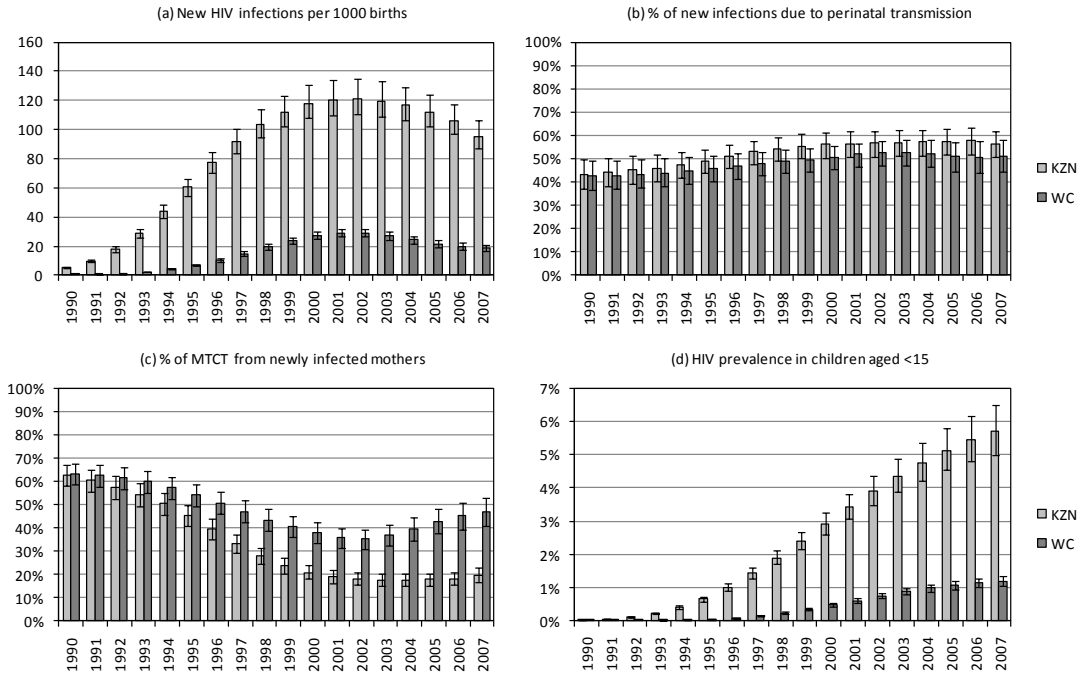


Figure 4.14: HIV incidence and prevalence in KwaZulu-Natal and Western Cape
Bars represent averages from posterior samples. Upper and lower error bars represent 95% confidence intervals (97.5 and 2.5 percentiles of distribution of posterior estimates).

Figure 4.15 shows that the Western Cape has achieved a much more rapid rollout of PMTCT and paediatric ART than KwaZulu-Natal. Over the period from mid-2007 to mid-2008, the Western Cape averted 57% (95% CI: 52-61%) of new paediatric infections through its PMTCT programme and averted 55% (95% CI: 48-64%) of paediatric AIDS deaths through the combined effect of its ART and PMTCT programmes. Corresponding proportions for KwaZulu-Natal were 25% (95% CI: 22-27%) and 17% (95% CI: 14-20%) respectively. In the same period, the ratio of the number of children starting ART to the number of children becoming infected (i.e. new need for ART in terms of current WHO guidelines) was 0.74 (95% CI: 0.65-0.84) in the Western Cape and 0.26 (95% CI: 0.23-0.28) in KwaZulu-Natal. ART coverage, defined as the proportion of children eligible to receive ART who were on therapy, was 54% (95% CI: 38-75%) in the Western Cape and 16% (95% CI: 11-23%) in KwaZulu-Natal, by the middle of 2008.

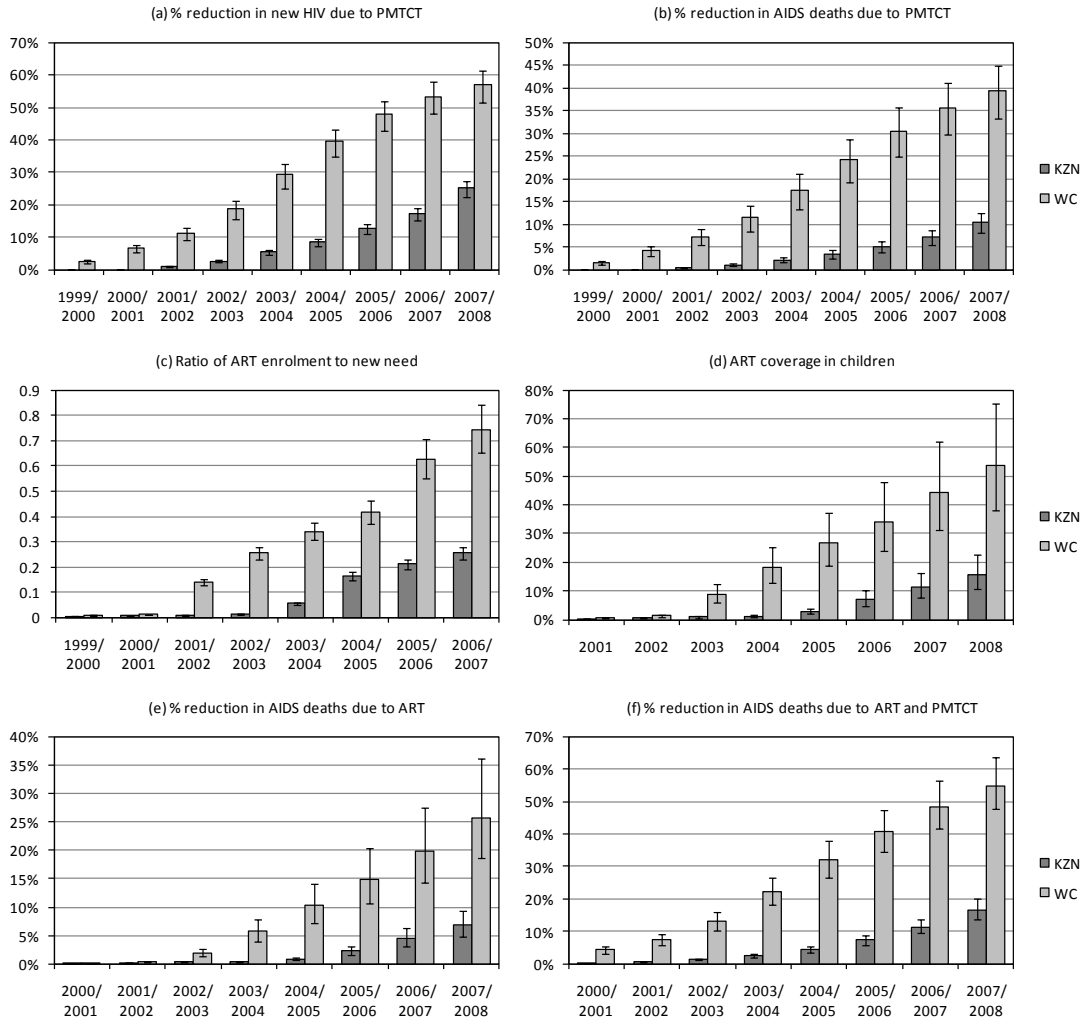


Figure 4.15: Impact of PMTCT and paediatric ART programmes introduced up to 2008, in KwaZulu-Natal and the Western Cape

Bars represent averages from posterior samples. Upper and lower error bars represent 95% confidence intervals (97.5 and 2.5 percentiles of distribution of posterior estimates).

## 4.8 Sensitivity testing of mortality assumptions

To assess the sensitivity of the model results to changes in mortality assumptions, two alternative scenarios are considered. In the first scenario, it is assumed that HIV-negative children who are not breastfed have a higher non-AIDS mortality rate than HIV-negative children who are breastfed. It is conservatively assumed that the multiples by which the non-AIDS mortality rates are increased are the same as those estimated by the WHO Collaborative Study Team on the Role of Breastfeeding on the Prevention of Infant Mortality (2000), although these estimates are likely to overstate the true effect of not breastfeeding (as discussed in section 2.5). The non-AIDS mortality rate in HIV-infected children is assumed to be the same as that in HIV-negative children of the same age who are being breastfed, regardless of whether the HIV-positive child is being breastfed or not.

In the second scenario, it is assumed that children who become infected with HIV at or before birth, after having been exposed to ARV prophylaxis, have a higher rate of AIDS mortality than children who become infected at or before birth in the absence of ARV prophylaxis (as discussed in section 2.4). It is optimistically assumed that the rate of progression to ART eligibility in children who are infected in the absence of any ARV prophylaxis is 0.65 times that in children who are infected in spite of ARV prophylaxis. It is unlikely that this ratio would be less than 0.6, since only 40% of vertical transmission is prevented by single-dose nevirapine.

The results for the two alternative scenarios are compared with the results for the baseline model in Table 4.2. The results for the three scenarios are almost identical in 1990, when the HIV epidemic is in its early stage. However, over time the results diverge, and by 2007/8 the IMR and U5MR are both higher in the scenario that allows for differences in non-AIDS mortality according to feeding practices, and lower in the scenario that allows for differences in AIDS mortality according to PMTCT exposure. In both of the alternative scenarios, the percentage reduction in mortality due to PMTCT and ART is significantly lower than in the baseline scenario, since PMTCT programmes lead to increases in the proportions of children who are formula-fed and increases in the proportions of infected children who are exposed to ARV prophylaxis.

Table 4.2: Sensitivity to changes in mortality assumptions

| | Baseline scenario | Higher non-AIDS mortality in children not breastfed | Higher AIDS mortality in children who fail PMTCT |
|---|---|---|---|
| Infant mortality rate in 2007/8 | 44.6 (42.3-47.1) | 48.3 (46.0-50.8) | 42.6 (40.7-44.7) |
| % reduction in IMR due to PMTCT and ART in 2007/8 | 11.1% (8.8-13.2%) | 3.0% (0.5-5.3%) | 6.3% (4.9-7.7%) |
| % reduction in IMR due to EBF support (scenario 10) by 2015 | 0.03% (-0.01-0.10%) | 0.61% (0.57-0.68%) | 0.02% (0.00-0.07%) |
| Under 5 mortality rate in 2007/8 | 67.4 (62.8-72.2) | 71.2 (66.6-76.0) | 64.2 (60.1-68.5) |
| % reduction in U5MR due to PMTCT and ART in 2007/8 | 11.7% (9.5-13.6%) | 6.3% (3.9-8.5%) | 8.1% (6.5-9.9%) |
| % reduction in U5MR due to EBF support (scenario 10) by 2015 | 0.03% (-0.07-0.14%) | 0.45% (0.36-0.56%) | 0.02% (-0.05-0.11%) |

95% confidence intervals are given in brackets.

The effect of changes in infant feeding practices can also be assessed in each of the three scenarios, as described in section 2.7.6 (scenario 10). If it is assumed that from 2010 onwards, the proportion of diagnosed HIV-positive mothers electing to practise exclusive breastfeeding (EBF) increases from 34.6% to 45%, and the median duration of EBF increases from 2 months to 6 months, there would be a 0.61% reduction in the IMR and a 0.45% reduction in the U5MR by 2015, in the scenario in which breastfeeding is assumed to reduce non-AIDS mortality. However, in the other two scenarios, the impact of the change in feeding practices on mortality is negligible. The change in feeding practices may in fact lead to increases in numbers of new HIV infections due to longer durations of breastfeeding, which could potentially lead to

increases in infant and under-5 mortality in the scenarios in which breastfeeding is assumed to have no effect on non-AIDS mortality.

## 4.9 Comparisons with other models

Figure 4.16 compares the model estimates with estimates from the 'lite' version of the ASSA2003 AIDS and Demographic model, a widely used model of the South African HIV epidemic (Dorrington *et al*, 2006). The ASSA2003 model estimates of HIV prevalence in children under the age of 15 are substantially lower than the prevalence levels estimated in the present analysis, with the level in 2005 (1.8%) roughly half of that estimated by the new model (3.3%, 95% CI: 3.0-3.8%). This is partly because the new model estimates a substantially greater level of postnatally-transmitted HIV (Figure 4.16(d)), since it allows for mothers who are HIV-negative at the time of their child's birth to subsequently seroconvert and transmit the virus to their child while breastfeeding. The difference in HIV prevalence between the two models is also partly due to the difference in survival assumptions, since the new model generally allows for longer survival of HIV-infected children (discussed below). As a result of the longer HIV survival in the new model, the new model estimates slightly lower levels of AIDS mortality up to 2003 (Figure 4.16(b)). There follows a period in which the two models appear to converge, but after 2006, the new model estimates a lower level of AIDS mortality than the ASSA2003 model. This pattern can be explained in terms of the difference in trends in annual numbers of HIV infections occurring at or before birth (Figure 4.16(c)). Over the 2002-2005 period, the ASSA2003 model assumes a more rapid rate of PMTCT phase-in than in the new model, and thus produces a lower initial estimate of the annual number of new HIV infections. However, the ASSA2003 model does not allow for the phase-in of the new PMTCT protocols after 2008 (i.e. AZT in addition to nevirapine), and therefore produces a higher ultimate estimate of the annual number of new paediatric HIV infections.

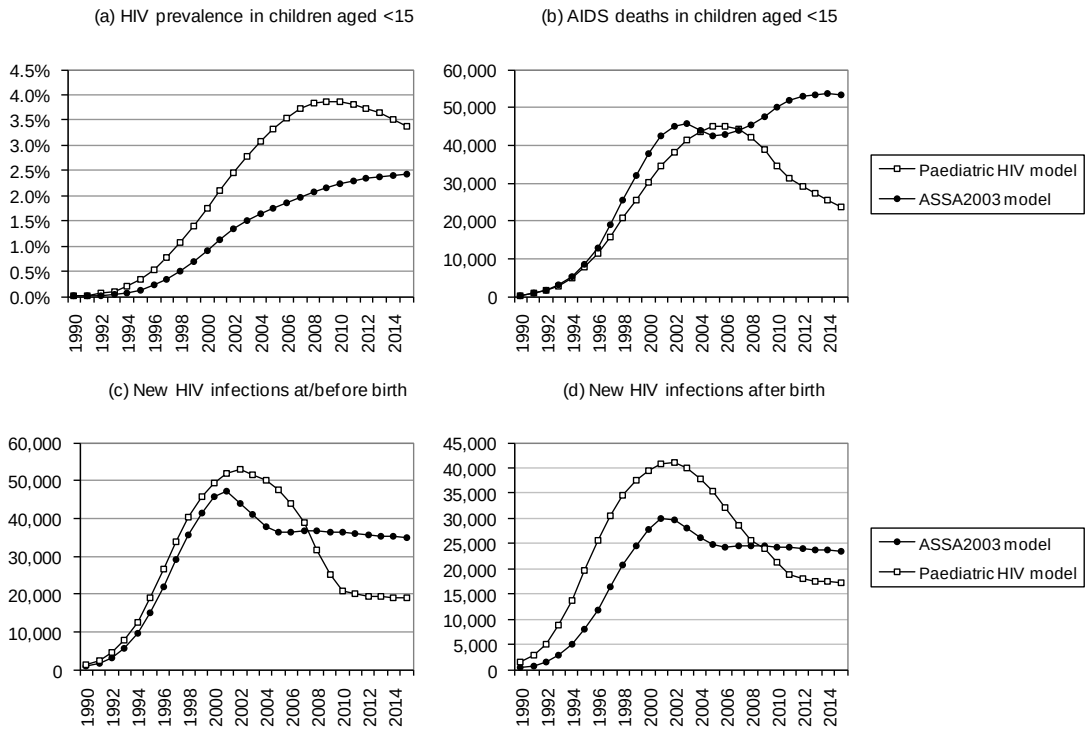


Figure 4.16: Comparison with estimates from the ASSA2003 lite model
Open squares represent the means from the posterior distributions shown in previous sections.

The new model estimates a much longer survival with HIV infection than the ASSA2003 model, in the absence of antiretroviral treatment, both for children infected at birth (Figure 4.17(a)) and for children infected after birth (Figure 4.17(b)). This partly explains the lower estimate of HIV prevalence in the ASSA2003 model (Figure 4.16(a)).

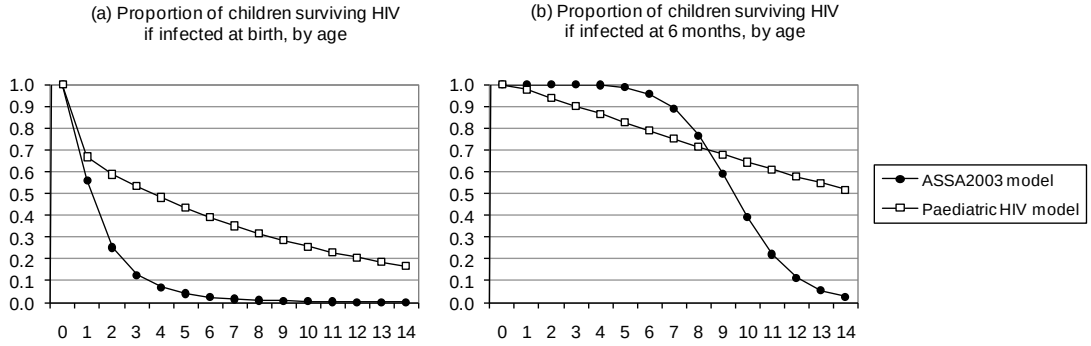


Figure 4.17: Comparison with survival assumptions in the ASSA2003 model
Open squares represent the means from the posterior distributions. Non-AIDS mortality is ignored in all calculations, and it is assumed that children do not have access to antiretroviral treatment.

The new model can also be compared with the results of a model developed by Little *et al* (2007), which has been applied to South Africa. The model of Little *et al* produces similar estimates of the total number of HIV-infected children aged <10 in 2002 (385 000) when compared with the new model estimate of the total number of HIV-positive children in 2002 (384 000, 95% CI: 345 000-431 000). However, Little

*et al* estimate a substantially lower level of antiretroviral need in 2002 (45 000 children) when compared with the new model (171 000, 95% CI: 120 000-235 000). This is likely to be due to differences in the assumptions regarding mortality of ART-eligible children in the two models.

The new model also estimates a considerably higher number of paediatric HIV infections than is estimated by UNAIDS using the Spectrum model (UNAIDS 2008). The UNAIDS estimate of the number of paediatric HIV cases in South Africa in 2007 (280 000, 95% CI: 230 000-320 000) is less than half the number estimated by the new model (580 000, 95% CI: 510 000-660 000). This difference is partly due to vertical transmission from mothers who seroconvert after delivery, which is not allowed for in the Spectrum model, and partly due to differences in survival assumptions. Although Spectrum appears to assume a similar rate of survival for children infected after birth (a median survival time of 14 years in the absence of antiretroviral treatment (Stover *et al*, 2006)), the Spectrum assumptions about mortality in children who are infected at or before birth are much higher than those estimated in our model. The Spectrum assumptions are based on the 'fast progressor' component of the double Weibull distribution estimated by Marston *et al* (2005), which means that children infected at or before birth are assumed to have a median survival of approximately one year in the absence of antiretroviral treatment, substantially shorter than the survival assumed in our model (Figure 4.17(a)).

# 5. Discussion

A major finding of this analysis is that HIV prevalence in South African children appears to be substantially higher than previous models have estimated (Dorrington *et al,* 2006; UNAIDS 2008), and the unmet need for antiretroviral treatment in children is also much greater than previously thought (Little *et al,* 2007). There are a number of explanations for this finding.

The first explanation is that in most previous models, vertical transmission from mothers who seroconvert after delivery has been ignored. A few previous models have allowed for this transmission (Del Fante *et al,* 1993; Hu *et al,* 1992; Dube *et al,* 2008; Lu *et al,* 2009). In the most recent of these modelling exercises, Lu *et al* (2009) estimated that 43% of all mother-to-child transmission in Botswana was from mothers who had been HIV-seronegative at the time of their antenatal screening visit. This is higher than the proportion of one third that we have estimated for South Africa at the current time, possibly because of the more extensive PMTCT programme in Botswana. As PMTCT programmes expand and deal more effectively with mothers who are chronically infected with HIV, the relative contribution of acutely-infected mothers to vertical transmission can be expected to increase.

The second explanation for the relatively high HIV prevalence estimated in our model is the relatively low rate of HIV-related mortality in HIV-positive children. As shown in section 4.9, other models tend to assume substantially higher rates of AIDS mortality in HIV-infected children, and hence there are fewer children surviving to older ages. Most of these models are based, directly or indirectly, on the estimates of HIV-related mortality produced by Marston *et al* (2005), based on pooling of untreated HIV survival data from a number of African paediatric HIV cohorts. Although there were no data beyond 5 years of follow-up, and this limits the reliability of the long-term paediatric HIV survival estimates, the discrepancy between our estimates of survival at young ages and those estimated by Marston and others (Sutcliffe *et al,* 2008) is a cause for concern.

It is possible that paediatric HIV survival in South African may be better than that in other African countries, and some experts have observed that paediatric HIV survival in South Africa appears to be intermediate between that in other African countries and that in developed countries (van Kooten Niekerk *et al,* 2006). This could be because of better access to cotrimoxazole in South Africa, as well as better quality of paediatric healthcare when compared with other African countries. Healthcare is provided free of charge for indigent patients using the South African public health sector. South Africa is also one of the few African countries that provides a child support grant, and this could have a significant impact on the wellbeing of HIV-infected children. South African children with HIV are generally less malnourished than children with HIV in other African countries (De Baets *et al,* 2008), and malnutrition has been shown to be associated with rapid disease progression (Cross Continents Collaboration for Kids 2008; van Kooten Niekerk *et al,* 2006; Bobat *et al,* 2001). Differences in survival could perhaps also be due to differences between HIV-1 viral subtypes (Church *et al,* 2008). Individuals infected with subtype C, the most common subtype in South Africa, develop the synctium-inducing HIV phenotype less frequently than individuals infected with other subtypes, and this phenotype is

associated with more rapid disease progression (Morris *et al*, 2000; Peeters *et al*, 2003). In addition, comparison of non-synctium-inducing isolates suggests that subtype C is less fit than subtype B, which has fitness comparable to subtypes A, D and E (Ball *et al*, 2003).

It is possible to obtain a similar or better model fit to paediatric HIV prevalence data if it is assumed that there is significant paediatric HIV incidence associated with sexual abuse, as shown in section 4.6. This also produces lower estimates of HIV survival, closer to those estimated by Marston *et al* (2005). However, the resulting estimate of the proportion of HIV in children aged 2-9 attending health facilities, that can be attributed to non-vertical transmission (4.0%, 95% CI: 1.1-7.8%), is higher than the 1.4% of HIV-infected children in the same age group whose mothers were HIV-negative, in a survey conducted in Free State health facilities (Shisana *et al*, 2005a). In addition, the study of Free State health facilities noted that the most significant risk factors associated with paediatric HIV in children of HIV-negative mothers were breastfeeding by non-biological mothers and mothers making use of stored expressed breast milk (which might not be the mother's own milk, due to mislabelling in hospital milk rooms). The evidence regarding the significance of sexual abuse as a source of HIV infection in children is therefore mixed, and further data are needed in order to assess the role of sexual abuse in paediatric HIV.

This analysis strongly suggests that nosocomial transmission is not contributing significantly to paediatric HIV incidence in South Africa. When extended to allow for nosocomial transmission, the model produced a significantly poorer fit to the HIV prevalence data than that obtained using the standard model that allows only for vertical transmission. In addition, the model estimate of the proportion of HIV-positive children in health facilities, aged 2-9, who had HIV due to nosocomial transmission was 12.1% (95% CI: 1.8-27.0%), substantially higher than the observed 1.4% of HIV-infected children with HIV-negative mothers. Evidence from case reports suggests that the number of paediatric HIV cases in which nosocomial transmission is suspected is very small relative to the total number of paediatric HIV cases (Hiemstra *et al*, 2004).

Although we cannot rule out the possibility that we may have under-estimated AIDS mortality rates in HIV-infected South African children, it is important to note that we would not have been able to fit the observed levels of HIV prevalence in the HSRC household surveys if we had assumed substantially higher rates of AIDS mortality. It is possible that the HSRC prevalence estimates may themselves be problematic, for example, due to poor test specificity (Human Sciences Research Council 2008). However, it is unlikely that false positive reactions are the explanation for the high HIV prevalence observed in children in the HSRC household survey; in both the 2005 and 2008 surveys, confirmatory HIV testing was performed on all specimens that were initially reactive, and the specificity of the testing algorithm would therefore have been very high. It is also possible that the HSRC prevalence survey estimates may be affected by non-response bias, which could be particularly significant if parents/guardians are reluctant to consent to blood being drawn from children who are in poor health, or who are suspected of being HIV-positive. However, this would tend to lead to HIV prevalence being under-estimated, and it would not explain why the survey estimates of HIV prevalence in children are higher than predicted by previously published models.

Another key finding from this analysis is that the PMTCT programme has had a significant impact on HIV incidence in South Africa, reducing the number of paediatric HIV infections over the 2007/2008 period by 34% (95% CI: 30-37%), and reducing the number of AIDS deaths over the same period by 16% (95% CI: 13-19%). The impact of PMTCT has been extremely variable between South Africa's provinces: in the Western Cape, the PMTCT programme achieved a 57% reduction in HIV incidence and a 39% reduction in AIDS deaths over the 2007/2008 period, while the corresponding reductions in KwaZulu-Natal were only 25% and 10% respectively, over the same period. With the implementation of the new PMTCT protocols, the reduction in HIV incidence can be expected to rise to 62% (95% CI: 59-65%) by 2015. Further reductions in HIV incidence would be possible through the introduction of routine HIV testing at immunization clinics and through the implementation of the WHO 'Option B' guidelines, which recommend the provision of highly active antiretroviral treatment to all HIV-positive women, for the duration of their pregnancy and while breastfeeding. However, the most substantial reductions in vertical transmission are likely to come from better implementation of current protocols. In particular, it is important to ensure that all pregnant women are offered repeat HIV testing in late pregnancy, to ensure that all HIV-positive mothers receive antiretroviral prophylaxis, and to ensure that all ART-eligible mothers start treatment early in pregnancy, with proper follow-up of them and their infants. The problem of substantial proportions of HIV-positive mothers failing to receive appropriate antiretroviral prophylaxis is common to other African countries (Stringer *et al,* 2010), and there is an urgent need for better implementation of existing guidelines.

Although PMTCT programmes have been successful in preventing transmission from mothers who are HIV-positive at their first antenatal visit, a major concern is that programmes are having little effect on transmission from mothers who seroconvert after their first antenatal screening visit. As HIV testing at the first antenatal visit has approached universal coverage, the latter source of transmission has become relatively more significant. Our simulations suggest that HIV retesting in late pregnancy and at the 6-week immunization visit would only slightly reduce this transmission. Regular HIV testing of HIV-negative women who are breastfeeding might help to further reduce postnatal transmission. However, the fundamental problem is that the high viral load in the first few weeks after maternal HIV acquisition is associated with an intense vertical transmission risk, and if women are only identified with HIV after the primary HIV infection phase has passed, the effect of changes in feeding practices is likely to be small. Creative solutions to this problem will need to be sought, and HIV counselling and testing of male partners may be necessary in order to limit maternal HIV incidence (Musiime *et al,* 2007). However, integrating men into antenatal HIV testing is challenging, and in African studies that have attempted to provide HIV testing to male partners of pregnant women, typically only 10-20% of male partners have sought HIV testing at the antenatal clinic (Msuya *et al,* 2008; Katz *et al,* 2009).

Linked to the need for more frequent HIV testing is the need for more regular CD4 monitoring in those women who are identified as HIV-positive. This would ensure that women who qualify for ART start treatment as early as possible, thus limiting their risk of transmission to their infants. Ideally women should start ART prior to pregnancy, for the greatest reductions in vertical transmission to occur.

Although the PMTCT programme in South Africa has been moderately successful, the impact of the paediatric antiretroviral treatment programme has been disappointing. The number of paediatric AIDS deaths in 2007/2008 was reduced by only 7.2% (95% CI: 5.2-9.8%) as a result of antiretroviral treatment, which compares with an estimated 23% reduction in adult AIDS mortality over the same period, based on an updated analysis of the ASSA2003 model. Antiretroviral coverage is also much lower in children than in adults; our model suggests that by the middle of 2008, only 17.0% (95% CI: 11.8-24.4%) of children eligible to receive ART were on treatment – this compares with a coverage rate of 40% in adults (Adam and Johnson 2009). Factors that could account for the relatively low rate of antiretroviral coverage in children include the lower rates of VCT in children (linked to the poor follow-up of infants in the PMTCT programme), the greater difficulty associated with diagnosing HIV infection in children (PCRs are required in young children), and the more complex nature of paediatric antiretroviral treatment (Meyers *et al*, 2007; Kellerman and Essajee 2010). However, it should also be recognized that criteria for starting ART in adults are fundamentally different from the criteria for starting ART in children, and to some extent the differences in antiretroviral coverage in adults and children may be a reflection of the earlier average duration of infection at which children are considered eligible for ART, when compared with adults.

As antiretroviral coverage increases in future, greater reductions in AIDS mortality can be expected as a result of antiretroviral treatment. However, the adoption of the new WHO protocols for initiating ART in infants is likely to have only a modest impact on AIDS deaths if PCR coverage remains at current levels: initiating ART in children diagnosed with HIV soon after birth would reduce the number of AIDS deaths in children over the 2010-15 period by only 6.3% (95% CI: 4.8-8.4%), relative to what would have been expected in the absence of any change in paediatric ART guidelines. There are a number of reasons why the impact is relatively small. Firstly, it is assumed that only 53% of children infected at or before birth are diagnosed at their six-week immunization, based on observed rates of HIV testing in HIV-exposed infants and observed rates of receipt of HIV test results by HIV-positive mothers. Secondly, it is assumed that children infected postnatally would not be diagnosed at six-week immunization, and the new WHO protocol is therefore assumed to have no effect on mortality in these children. Lastly, 50% of children eligible to receive ART are assumed to initiate ART in the absence of the new protocols, and the new protocols are assumed not to influence the mortality of these children except in the first years of life when there is a significantly increased mortality risk. The marginal effect of introducing the new protocols is therefore relatively small. However, the combined effect of increasing PCR coverage at the six-week visit to 80%, and increasing the fraction on newly eligible children starting ART to 80% at older ages is a 38% reduction in AIDS deaths (95% CI: 34-43%) over the 2010-25 period, relative to what would be expected in the absence of ART. Substantial improvements in mortality are therefore possible if PCR coverage is improved and access to ART at older ages is also improved.

A strength of this analysis is that it incorporates evidence regarding differences in vertical transmission rates between CD4 categories. This is important when assessing the impact of the new WHO and South African guidelines, which recommend different forms of antiretroviral prophylaxis or treatment depending on the mother's

CD4 count. However, the model does not take into consideration that CD4 distributions in HIV-positive mothers are likely to be changing over time, and that an increasingly high proportion of HIV-positive pregnant women will be on ART at the time of conception. Modelling these dynamics would require a more detailed model of fertility in HIV-positive women, which allows for changes in CD4 distributions and ART initiation over the course of the epidemic, as well as differences in fertility rates between CD4 and ART categories. Such a model is currently being developed, and it is hoped that this will be integrated with the current paediatric HIV model in order to produce more accurate estimates of levels of vertical transmission.

The model presented here does not link the survival of children to the survival of their mothers. This is a limitation, as several African studies have found that child mortality rates are significantly higher in children whose mothers have died than in children whose mothers are alive, even after controlling for maternal HIV status (Nakiyingi *et al,* 2003; Crampin *et al,* 2003; Ng'weshemi *et al,* 2003; Zaba *et al,* 2005) and child HIV status (Newell *et al,* 2004). To the extent that maternal death does indeed lead to increased mortality risk in children, our model may understate the increase in child mortality attributable to maternal HIV. Our model may also understate the reduction in child mortality attributable to maternal ART, which by reducing AIDS mortality in HIV-infected mothers should reduce mortality in their children (Ndirangu *et al,* 2010).

Greater accuracy could be achieved by allowing separately for maternal and infant adherence to antiretroviral prophylaxis. However, to do so would require information on the proportions of mother-infant pairs in which both mother and infant are adherent, only the mother is adherent, only the infant is adherent, or neither mother nor infant is adherent. Information would also be needed to estimate the relative efficacy of the different forms of prophylaxis under the different permutations of infant and maternal adherence. Since South Africa lacks reliable data on the relative proportions of mother-infant pairs in the different adherence categories, and since there are limited data concerning the relative efficacy of different forms of prophylaxis under different adherence patterns, we have chosen to model the efficacy of antiretroviral prophylaxis only as a function of maternal adherence. The implicit assumption is that if women adhere to antiretroviral prophylaxis, their children will also adhere, and conversely, that if women do not receive antiretroviral prophylaxis their children will also not receive prophylaxis. This leads to some loss of accuracy, although the bias is likely to be relatively small if the difference between maternal and child adherence is modest. We have also not allowed for the effect of maternal ART on vertical transmission to vary according to the timing of maternal ART initiation, although women who start ART later in pregnancy are known to have a higher transmission risk (Hoffman *et al,* 2010; Black *et al,* 2008).

A further limitation of this analysis is that it does not address the uncertainty regarding the maternal HIV prevalence and incidence estimates from the ASSA2003 model, which have been used as inputs in the current analysis. The ASSA2003 model is calibrated to survey estimates of HIV prevalence in pregnant women attending public antenatal clinics, with adjustment to allow for lower prevalence in pregnant women attending private antenatal clinics. However, there is substantial uncertainty regarding the magnitude of the adjustment required to allow for private sector differences (Johnson *et al,* 2007). As mentioned in section 2.7.1, unbooked

pregnancies may lead to some under-estimation of HIV prevalence in mothers of newborn infants. However, it is also possible that because of the relatively high rates of miscarriage and stillbirth in HIV-positive pregnant women (Brocklehurst and French 1998), which are not allowed for in the ASSA2003 model, the model may over-estimate HIV prevalence in mothers of live births.

Another limitation of our analysis is that we have assumed that the District Health Information System provides reliable estimates of the proportions of women who receive HIV testing. Recent studies conducted in KwaZulu-Natal suggest that there are significant problems with the completeness and accuracy of District Health Information System data (Mate *et al*, 2009; Garrib *et al*, 2008), although it is believed that the reported proportions of women tested for HIV probably do not overstate the true proportions tested (Kedar Mate, personal communication). It is not clear whether data quality is similarly poor in other provinces, although concerns regarding data quality have been raised in the Eastern Cape (Rispel *et al*, 2009). These questions will need to be investigated more thoroughly in future. An associated problem is that there is a lack of recent data on the extent to which the 2008 PMTCT guidelines have been implemented, and this increases the uncertainty regarding the trends in paediatric HIV incidence. The NHLS PCR testing data from infants aged less than three months is more recent, but it provides only indirect information on the success of the PMTCT programme, as it is not clear how representative the tested infants are of all infants born to mothers diagnosed HIV-positive. There is also a lack of nationally-representative data on feeding practices in mothers who are diagnosed HIV-positive, and better data on feeding practices are required if the model is to be applied to all nine of South Africa's provinces.

The model allows for the effect of the recent change in the paediatric ART guidelines by assuming that all children who are diagnosed PCR-positive at their six-week immunization visit would be started on ART at the age of two months. However, the guidelines also recommend PCR testing six weeks after breastfeeding has ceased (Department of Health 2010), and the potential for infants to start ART following diagnosis soon after weaning has not been considered in the model. This may lead to some under-estimation of numbers of children starting ART, although it is not clear to what extent infants are indeed HIV-tested after weaning. The model assumes that at other ages, the numbers of children starting ART in each period is proportional to the unmet need for treatment at that age, where 'unmet need' is defined according to the previous 2005 South African guidelines for starting ART. The model therefore does not allow for the possibility that untreated ART-eligible children at young ages may initiate ART at a higher rate than untreated ART-eligible children at older ages. This could be a problem if ART-eligible infants are more likely to be fast-tracked for ART than ART-eligible children at older ages, or if infants are more likely to be diagnosed than older children.

The accuracy of the model could be substantially enhanced if the likelihood function used in the uncertainty analysis was based on mortality data as well as HIV prevalence data. Although Statistics South Africa has published numbers of deaths in children by age (Statistics South Africa 2008), we have not used these data in calibrating the model, due to uncertainty regarding the completeness of vital registration in children. Preliminary attempts to calibrate the model to reported death data suggest that the level of completeness has not increased monotonically over time,

and it is possible that the phased implementation of the Child Support Grant may have influenced the reporting of deaths. Due to the uncertainty regarding the completeness of reporting, the model estimates of mortality need to be treated with caution. Our model estimates of mortality are quite sensitive to changes in the assumed effect of breastfeeding on non-AIDS mortality, the assumed difference in mortality between HIV-infected infants who are ARV-exposed and unexposed, and the assumed extent of non-vertical transmission. None of these three parameters can be determined accurately. In addition, there is substantial uncertainty regarding non-AIDS mortality in children born to HIV-negative mothers, particularly the extent of the improvement in non-AIDS mortality over time. There is thus a need for further research to quantify infant and child mortality trends in South Africa more accurately.

## Acknowledgements

This research was funded through postdoctoral research fellowships from the William and Flora Hewlett Foundation (administered through the Centre for Actuarial Research at the University of Cape Town) and the South African Medical Research Council. Leigh Johnson thanks all members of the scientific advisory group for their help in setting the model assumptions and in adding to the discussion of the model results.

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# Appendix A: Estimation of proportions of vertical transmission from women in different CD4 categories

This appendix describes the method used to estimate the proportion of pregnant HIV-positive women in different CD4 categories, the relative rates of vertical transmission from HIV-positive mothers in different CD4 categories, and the proportion of all vertical transmission from women in different CD4 categories. The CD4 categories that are considered in this analysis are <200, 200-349, 350-500 and >500.

## A.1 Estimation of the proportion of pregnant HIV-positive women in different CD4 categories

To estimate the average proportion of pregnant HIV-positive women in different CD4 categories, we reviewed data on CD4 distributions in pregnant HIV-positive women from various African studies, and fitted a random effects model to these data. Table A1 summarizes the data that have been used in this analysis. Eleven independently-conducted studies were identified. Studies were excluded if they used unusual CD4 cut-offs, or if they duplicated results reported in those studies already included in Table A.1.

Suppose that our model estimates that the proportion of pregnant HIV-positive women in CD4 group $i$ is $\pi_i$ ($i$ = 1, 2, 3, 4). Further suppose that the observed numbers of infected women in the $j^{\text{th}}$ study, who are in stage $i$ is $n_{ij}$. It could then be assumed that the $n_{ij}$ terms are multinomially distributed, so that the likelihood function in respect of the $j^{\text{th}}$ study is equal to

$$\binom{n_j}{n_{1j}\ n_{2j}\ n_{3j}\ n_{4j}} \pi_1^{n_{1j}} \pi_2^{n_{2j}} \pi_3^{n_{3j}} \pi_4^{n_{4j}}, \qquad \text{(A1)}$$

where $n_j$ is the total number of HIV-positive women in the $j^{\text{th}}$ study. In most of the studies, certain CD4 groups are combined together, but the method generalizes easily to situations in which there are fewer than four CD4 groups. For example, if study $j$ reports only on the number of women with CD4 counts of 200-500, $n_{*j}$, then the likelihood for this study would be

$$\binom{n_j}{n_{1j}\ n_{*j}\ n_{4j}} \pi_1^{n_{1j}} \left(\pi_2 + \pi_3\right)^{n_{*j}} \pi_4^{n_{4j}}.$$

Table A.1: African studies of CD4 distributions in pregnant HIV-positive women

| Study | Location | n | CD4 group | % in CD4 group |
|---|---|---|---|---|
| Brown *et al* (2009) | Kenya | 481 | <200 | 10.6% |
| | | | 200-350 | 24.5% |
| | | | >350 | 64.9% |
| Coovadia *et al* (2007) | South Africa | 1299 | <200 | 11.2% |
| | | | 200-500 | 46.7% |
| | | | >500 | 42.1% |
| Coutsoudis *et al* (1999b) | South Africa | 572 | <200 | 9.6% |
| | | | 200-499 | 50.9% |
| | | | >=500 | 39.5% |
| Dabis *et al* (2005) | Côte d'Ivoire | 986 | <200 | 14.9% |
| | | | 200-350 | 23.5% |
| | | | 350-500 | 24.7% |
| | | | >=500 | 36.8% |
| Fawzi *et al* (2001) | Tanzania | 685 | <200 | 12.8% |
| | | | 200-499 | 58.4% |
| | | | >=500 | 28.8% |
| Geddes *et al* (2008) | South Africa | 262 | <200 | 25.6% |
| | | | >=200 | 74.4% |
| Gray *et al* (2005a) | South Africa | 967 | <500 | 57.0% |
| | | | >=500 | 43.0% |
| Iliff *et al* (2005) | Zimbabwe | 1809 | <200 | 11.9% |
| | | | 200-349 | 24.5% |
| | | | 350-499 | 27.4% |
| | | | >=500 | 36.2% |
| Moodley *et al* (2003) | South Africa | 1294 | <200 | 14.5% |
| | | | >=200 | 85.5% |
| Shapiro *et al* (2006) | Botswana | 651 | <=200 | 18.3% |
| | | | >200 | 81.7% |
| Stinson *et al* (2008) | South Africa | 3401 | <=200 | 15.2% |
| | | | 201-350 | 29.0% |
| | | | >350 | 55.9% |

This is a fixed effects model, i.e. it is assumed that the CD4 distribution is the same for all samples of pregnant African women that we might choose to study. The assumption of a fixed effects framework is probably unrealistic, since the effect of HIV on fertility may differ between populations (Lewis *et al*, 2004), CD4 distributions may naturally vary between populations even in the absence of HIV (Williams *et al*, 2006), and some populations may be experiencing more advanced epidemics than others. To account for variation in proportions between populations, we define $\rho_{ij}$ as the true proportion of infected women in CD4 group $i$, in the $j^{th}$ study population. Then it would be natural to assume that the $\rho_{ij}$ terms are Dirichlet-distributed, i.e.

$$p(\boldsymbol{\rho}_j \mid \boldsymbol{\pi}, \varphi) = \Gamma(\varphi) \prod_{i=1}^{4} \left( \rho_{ij}^{\varphi\pi_i - 1} \right) \Big/ \Gamma(\varphi\pi_i), \qquad \text{(A2)}$$

where $\boldsymbol{\rho}_j$ and $\boldsymbol{\pi}$ represent the vectors of $\rho_{ij}$ and $\pi_i$ values respectively. Note that from the properties of the Dirichlet distribution,

$$\mathrm{E}\left[\rho_{ij}\right] = \pi_i$$
$$\mathrm{Var}\left[\rho_{ij}\right] = \frac{\pi_i(1-\pi_i)}{\varphi+1}$$

so that the $\varphi$ variable controls the variance of the random effects. The likelihood function for study *j* is then

$$p(\mathbf{n}_j \mid \boldsymbol{\pi}, \varphi) = \int_{\boldsymbol{\rho}_j} p(\mathbf{n}_j \mid \boldsymbol{\rho}_j) p(\boldsymbol{\rho}_j \mid \boldsymbol{\pi}, \varphi) d\boldsymbol{\rho}_j \qquad \text{(A3)}$$

where $\mathbf{n}_j$ represents the vector of $n_{ij}$ values. The likelihood in equation (A3) can be more fully expressed as

$$\int_{\rho_{ij}} \int_{\rho_{2j}} \int_{\rho_{3j}} \int_{\rho_{4j}} \Gamma(\varphi) \binom{n_j}{n_{1j}\ n_{2j}\ n_{3j}\ n_{4j}} \prod_{i=1}^{4} \frac{\rho_{ij}^{n_{ij}+\varphi\pi_i-1}}{\Gamma(\varphi\pi_i)} d\rho_{4j} d\rho_{3j} d\rho_{2j} d\rho_{1j}.$$

Note that after factoring out the terms that are independent of $\rho_{ij}$ in the above equation, the integral is itself of a Dirichlet form, and therefore integrates to 1 with the multiplication of an appropriate constant term. Hence

$$p(\mathbf{n}_j \mid \boldsymbol{\pi}, \varphi) = \frac{\Gamma(\varphi)}{\Gamma(n_j+\varphi)} \binom{n_j}{n_{1j}\ n_{2j}\ n_{3j}\ n_{4j}} \prod_{i=1}^{4} \frac{\Gamma(n_{ij}+\varphi\pi_i)}{\Gamma(\varphi\pi_i)}. \qquad \text{(A4)}$$

The total likelihood is obtained by multiplying the values of the likelihood for each individual study (equation A4). We maximize the natural log of this likelihood with respect to $\pi_1$, $\pi_2$, $\pi_3$ and $\varphi$, and hence the combination factor can be omitted from equation (A4). The expression we maximize is thus

$$\sum_{j=1}^{11} \left( \ln(\Gamma(\varphi)) - \ln(\Gamma(n_j+\varphi)) + \sum_{i=1}^{4} \ln(\Gamma(n_{ij}+\varphi\pi_i)) - \ln(\Gamma(\varphi\pi_i)) \right). \qquad \text{(A5)}$$

(For ease of representation, equation (A5) does not reflect the complication that arises when there are fewer than four CD4 groups in a particular study.) The maximum likelihood estimates of the proportions of HIV-positive pregnant women in the different stages are shown in Table A.2. The maximum likelihood estimate of $\varphi$ (not shown in Table A.2) is 128.1.

Table A.2: Maximum likelihood estimates of proportions of pregnant women in different CD4 stages

| Symbol | Definition | Estimate (95% CI) |
|---|---|---|
| $\pi_1$ | % of pregnant women with CD4 of <200 | 14.0% (12.0-16.1%) |
| $\pi_2$ | % of pregnant women with CD4 of 200-349 | 24.9% (21.3-28.6%) |
| $\pi_3$ | % of pregnant women with CD4 of 350-500 | 24.5% (20.2-28.7%) |
| $\pi_4$ | % of pregnant women with CD4 of >500 | 36.6% (33.1-40.0%) |

**A.2 Estimation of relative rates of vertical transmission from HIV-positive mothers in different CD4 categories**

As in section A.1, the procedure followed in estimating the relative rates of vertical transmission in different CD4 categories is to review estimates of rates of mother-to-child transmission in different CD4 categories, and to fit a statistical model to the pooled data. Table A3 summarizes the data that are used in this analysis. Studies were excluded if they focused exclusively on postnatal transmission of HIV, since our primary interest is in the effect of maternal CD4 count on vertical transmission at or before birth. Studies were also excluded if they used unusual CD4 cut-offs, or if they duplicated results reported in those studies already included in Table A.3.

As in section A.1, suppose that in study *j*, the number of pregnant HIV-positive women with CD4 counts in CD4 band *i* is $n_{ij}$. Further suppose that the number of HIV-positive women in study *j* and CD4 band *i* who transmit HIV to their infants is $x_{ij}$, and that the expected transmission rate in these women is $\beta_j r_i$, where $\beta_j$ is the expected transmission rate in study *j*, among women with CD4 counts <200, and $r_i$ is the ratio of the transmission rate in CD4 band *i* to that in women with CD4 counts <200 (so that $r_1 = 1$ by definition). Although it may seem natural to assume that the value of $\beta_j$ is the same in all studies, the studies differ in terms of the way in which vertical transmission is measured and the extent of the PMTCT regimens (see Table A.3). It is therefore not appropriate to pool the data from the different studies without allowing for the differences between studies in the overall transmission rates.

Table A.3: Studies of vertical transmission rates according to maternal CD4 counts

| Study | Location | Definition of transmission | PMTCT regimen | CD4 group | # women in CD4 group | MTCT rate |
|---|---|---|---|---|---|---|
| Coutsoudis *et al* (1999b) | South Africa | Transmission up to 3 months | Vitamin A | <500 | 176 | 24.5% |
| | | | | >=500 | 115 | 14.7% |
| | | | Placebo | <500 | 170 | 26.0% |
| | | | | >=500 | 111 | 17.7% |
| Dabis *et al* (2005) | Côte d'Ivoire | Transmission up to 6 weeks | ZDV, 3TC, NVP | <200 | 147 | 15.6% |
| | | | | 200-350 | 232 | 9.1% |
| | | | | 350-500 | 244 | 7.5% |
| | | | | >=500 | 363 | 4.6% |
| European Collaborative Study (1997) | Europe | Perinatal | Some ZDV | <500 | 160 | 20.6% |
| | | | | >=500 | 108 | 12.0% |
| Fawzi *et al* (2001) | Tanzania | Intrauterine (pos. at birth) | Vitamin A, multivitamins or placebo | <200 | 88 | 14.8% |
| | | | | 200-499 | 400 | 8.0% |
| | | | | >=500 | 197 | 6.1% |
| | | Transmission up to 6 weeks (neg. at birth) | Vitamin A, multivitamins or placebo | <200 | 40 | 25.0% |
| | | | | 200-499 | 198 | 17.2% |
| | | | | >=500 | 108 | 10.2% |
| Lallemant *et al* (2004) | Thailand | Perinatal | ZDV, NVP | <=200 | 219 | 5.0% |
| | | | | >200 | 1019 | 1.8% |
| Rollins *et al* (2007b) | South Africa | Transmission up to 8 weeks | NVP | >=500 | 420 | 9.0% |
| | | | | 201-500 | 433 | 17.6% |
| | | | | <=200 | 109 | 24.8% |
| Shaffer *et al* (1999) | Thailand | Perinatal | ZDV | <200 | 17 | 23.5% |
| | | | | 200-499 | 105 | 9.5% |
| | | | | >=500 | 65 | 6.2% |
| | | | Placebo | <200 | 24 | 37.5% |
| | | | | 200-499 | 104 | 18.3% |
| | | | | >=500 | 67 | 13.4% |
| Shapiro *et al* (2006) | Botswana | Transmission up to 1 month | ZDV, NVP | <=200 | 119 | 5.0% |
| | | | | >200 | 532 | 3.8% |
| Sperling *et al* (1996) | USA | Perinatal | Placebo | 200-349 | 32 | 40.6% |
| | | | | 350-499 | 52 | 15.4% |
| | | | | >=500 | 119 | 21.0% |
| | | | ZDV | 200-349 | 31 | 9.7% |
| | | | | 350-499 | 49 | 6.1% |
| | | | | >=500 | 117 | 7.7% |

It is assumed that the number of women in study *j* and CD4 band *i* who transmit HIV to their infants is binomially distributed with parameters $n_{ij}$ and $\beta_j r_i$. This means that the likelihood in respect of the data for study *j* is

$$L\left(\mathbf{x}_j \mid \beta_j, \mathbf{r}\right) = \prod_{i=1}^{4} \binom{n_{ij}}{x_{ij}} \left(\beta_j r_i\right)^{x_{ij}} \left(1-\beta_j r_i\right)^{n_{ij}-x_{ij}}, \qquad \text{(A6)}$$

where $\mathbf{x}_j$ is the vector of $x_{ij}$ values and **r** is the vector of $r_i$ values. Equation (A6) can be extended to the case in which there are fewer than four CD4 groups, if we assume that the CD4 distribution in the groups that have been combined is the same as that in Table A.3. For example, if study *j* reports the number of women transmitting HIV to their infants in the CD4 200-500 group ( $x_{*j}$ out of $n_{*j}$ ), then the likelihood in respect of this number is

$$L\left(x_{*j} \mid \beta_j, \mathbf{r}\right) = \binom{n_{*j}}{x_{*j}} \left(\beta_j \left(\frac{\pi_2 r_2 + \pi_3 r_3}{\pi_2 + \pi_3}\right)\right)^{x_{*j}} \left(1 - \beta_j \left(\frac{\pi_2 r_2 + \pi_3 r_3}{\pi_2 + \pi_3}\right)\right)^{n_{*j} - x_{*j}}.$$

We maximize the log of the likelihood for all observations with respect to the parameters $r_2$, $r_3$ and $r_4$. Terms independent of $\beta_j$ and $r_i$ can therefore be omitted, so that the expression to be maximized is

$$\sum_{j=1}^{13} \sum_{i=1}^{4} x_{ij} \ln\left(\beta_j r_i\right) + \left(n_{ij} - x_{ij}\right) \ln\left(1 - \beta_j r_i\right). \qquad \text{(A7)}$$

(For ease of representation, equation (A7) does not reflect the complication that arises when there are fewer than four CD4 groups in a particular study.) This expression is maximized using the downhill simplex algorithm (Press *et al*, 1986). Prior to each evaluation of the likelihood in equation (A7), the values of the $\beta_j$ terms are updated by maximizing equation (A6) with respect to $\beta_j$, for each value of $j$.

The resulting estimates of $r_2$, $r_3$ and $r_4$ are 0.74 (95% CI: 0.54-0.93), 0.43 (95% CI: 0.28-0.59) and 0.38 (95% CI: 0.30-0.47) respectively. The confidence intervals around $r_2$ and $r_3$ are relatively wide because there are relatively few studies that report on HIV transmission rates separately for the 200-349 and 350-500 CD4 groups.

Combining these results with the results in Table A.2, we estimate that 24.8% of all vertical transmission is from mothers with CD4 counts less than 200, 32.2% of transmission is from mothers who have CD4 counts of 200 to 349, 18.7% of transmission is from mothers who have CD4 counts of 350 to 500, and the remaining 24.4% of transmission is from mothers who have CD4 counts greater than 500. If it assumed that in the absence of PMTCT, the average probability of transmission at or before birth is 20%, the implied rates of transmission in the different CD4 stages are 35.0% for women with CD4 less than 200, 25.8% for women with CD4 counts of 200 to 349, 15.2% for women with CD4 counts of 350 to 500, and 13.4% for women with CD4 counts greater than 500.

# Appendix B: Mathematical approach

This appendix provides the mathematical detail underlying the modelling of HIV transmission and HIV survival in children.

### B.1 Modelling of HIV transmission at birth

Define the following symbols:

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

$J_1(t)$ = number of births, in month $t$, to women who were HIV-positive 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 who are offered HIV rescreening in late pregnancy, in month $t$;

$\nu_0$ = proportion of pregnant women who agree to retesting in late pregnancy if they previously tested negative;

$\nu_1$ = proportion of pregnant women who agree to testing in late pregnancy if they weren't offered testing (or refused testing) at their first antenatal visit;

$J_{1,1}(t)$ = 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-negative 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 $t$;

$$J_{0,0}(t) = J_0(t)\left(1 - I(t)\left(T_3 - T_1 + 5\right)/52\right)$$
$$J_{0,1,1}(t) = J_0(t)\left(I(t)\left(T_2 - T_1\right)/52\right)Z(t)\nu_0 Se$$
$$J_{0,1,0}(t) = J_0(t)\left[\left(I(t)\left(T_2 - T_1\right)/52\right)\left(1 - Z(t)\nu_0 Se\right) + \left(I(t)\left(T_3 - T_2 + 5\right)/52\right)\right]$$

The 5 in the first and third equations is the assumed window period on standard antibody tests. The period of 5 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.

In the interests of simplicity, we have calculated the births in month $t$ using the rates of HIV screening and rescreening in month $t$, though in fact screening and rescreening are assumed to occur some 16 weeks and 5 weeks prior to delivery, respectively. This will lead to a slight over-estimation of the impact of the PMTCT programme, since rates of HIV screening have been increasing over time.

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

$\pi$ = 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;

$\pi_i$ = 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 $i$;

$\chi_i$ = proportion of pregnant HIV-positive women in CD4 stage $i$;

$\pi^*$ = 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;

$\pi^H$ = probability of mother-to-child transmission at or before birth, if the mother initiated HAART prior to delivery;

$\alpha_0$ = proportion of diagnosed HIV-positive pregnant women, not initiating long-term HAART, who receive single-dose nevirapine;

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

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

$U(t)$ = proportion of antenatal clinics from which HAART is readily accessible, in month $t$;

$\alpha_1(t)$ = 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);

$\Lambda_i(t)$ = indicator variable determining whether pregnant HIV-positive women in CD4 stage $i$ are eligible to start HAART in year $t$ (1 = yes, 0 = no);

$\zeta_0$ = efficacy of single-dose NVP in preventing mother-to-child transmission at birth;

$\zeta_1$ = efficacy of single-dose NVP, together with short-course AZT, in preventing mother-to-child transmission at birth;

$\zeta_2$ = efficacy of short-course AZT in preventing mother-to-child transmission at birth;
$Y_{0,i}(t)$ = 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 exposed to ARV prophylaxis ($i$ = 1) or not exposed ($i$ = 0);

The method used to estimate the $\pi_i$ and $\chi_i$ values is described in Appendix A. The values have been calculated such that

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

The formulas used to calculate the numbers of births according to the HIV status of the child, at birth, and the maternal antenatal history, are as follows:

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

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

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

$$Y_{0,3}(t) = \left(J_{1,1}(t) + J_{1,0,1}(t) + J_{1,2,1}(t)\right) \sum_{i=1}^{4} \chi_i \Lambda_i(t) U(t) \alpha_1(t) \left(1 - \pi^H\right)$$

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

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

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 – or if they did initiate HAART, the effect would be no different from the effect that would be expected if they initiated short-course ARV prophylaxis. The assumption only becomes slightly problematic in the scenario in which we consider the effect of HAART initiation in *all* pregnant HIV-positive women ('Option B' in the most recent WHO protocols, or scenario 8 described in section 2.7.6). In the other model scenarios, it is reasonable to assume that women who have recently seroconverted would not yet have reached the immunological criteria for starting HAART.

## B.2 Modelling 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 gender *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 = 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 gender *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;

$E_{v,i}$ = 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;

$SR_g$ = proportion of births that are of gender *g*;

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

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

From the way that $N^0_{g,i,v}(0,t)$ is calculated, it is clear that 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. However, 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 have now progressed to the 'chronic' stage of infection and are no longer in the highly infectious acute phase of infection. It may seem more correct to include some fraction of $J_{0,1,0}(t)$ and $J_{0,1,1}(t)$. However, since the average interval in which women can acquire HIV during late pregnancy without being seropositive at their first antenatal visit is 21 weeks ($T_3 - T_1 + 5$), these recently infected women will have been infected for an average of 10.5 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 very close to the average of 10.5 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 months after delivery, and will be at a very high risk of transmitting the virus while breastfeeding.

The following symbols are defined:

$\delta_{v,i}(a)$ = 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 before age $a + 1$;

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

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

$h_i$ = 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 method used to calculate $\delta_{v,i}(a)$ is explained in section 2.7.6, and the method used to calculate $q_g(a, t)$ is explained in section 2.1. Probabilities such as $\delta_{v,i}(a)$ and $I(t)$ 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 a mother who is breastfeeding discontinues breastfeeding in the next month, *before* becoming infected with HIV, is calculated as

$$C\left(\delta_{1,0}(t),1-\left[1-I(t)\right]^{1/12}\right)=\left(1-\left(1-\delta_{1,0}(t)\right)\left[1-I(t)\right]^{1/12}\right)\frac{\ln\left(1-\delta_{1,0}(t)\right)}{\ln\left(\left(1-\delta_{1,0}(t)\right)\left[1-I(t)\right]^{1/12}\right)}$$

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:

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

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

Further suppose that we define $C^T(\Delta_1,\Delta_2,...,\Delta_n)$ 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:

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

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

$$N^0_{g,0,2}(a+1,t+1)=0$$

Note that we are assuming mothers would not practise exclusive breastfeeding unless they knew they were HIV-positive. 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-AIDS mortality. Non-AIDS mortality is not treated as a competing decrement in the way that the other decrements are because the same non-AIDS mortality probability is assumed to apply to all children of a given age and sex.

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

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

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.

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

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 scenario 8 in section 2.7.6.) 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.

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

$$Q^0_{g,3,1}(a,t) = N^0_{g,3,2}(a,t)C\left(\delta_{2,1}(a,t), h_2\left(1-X(t)z_1\right)\right)\left(1-w(a)\right)$$

$$
\begin{aligned}
N^0_{g,3,0}(a+1,t+1) &= \Big[N^0_{g,3,0}(a,t) + N^0_{g,3,1}(a,t)C\big(\delta_{1,1}(a,t), h_1\big(1-X(t)z_1\big)\big) \\
&\quad + N^0_{g,3,2}(a,t)C\big(\delta_{2,1}(a,t), h_2\big(1-X(t)z_1\big)\big)w(a) \\
&\quad + Q^0_{g,3,1}(a,t)C^*\big(\delta_{1,1}(a,t), h_1\big(1-X(t)z_1\big)\big)\Big]\big(1-q_g(a,t)\big) \\
N^0_{g,3,1}(a+1,t+1) &= N^0_{g,3,1}(a,t)\big(1-\delta_{1,1}(a,t)\big)\big(1-h_1\big(1-X(t)z_1\big)\big)\big(1-q_g(a,t)\big) \\
&\quad + Q^0_{g,3,1}(a,t)\Big[1-C^T\big(\delta_{1,1}(a,t), h_1\big(1-X(t)z_1\big)\big)\Big]\big(1-q_g(a,t)\big) \\
N^0_{g,3,2}(a+1,t+1) &= N^0_{g,3,2}(a,t)\big(1-\delta_{2,1}(a,t)\big)\big(1-h_2\big(1-X(t)z_1\big)\big)\big(1-q_g(a,t)\big)
\end{aligned}
$$

Note that $h_2$ is calculated as $h_1\xi$, where $\xi$ is the relative rate of postnatal transmission, per month of breastfeeding, if the HIV-positive mother practises exclusive breastfeeding. Also note that the above formulas are modified in the case $a$ = 1, if there is screening of mothers at immunization:

$$
\begin{aligned}
N^0_{g,3,0}(2,t+1) &= \Big[N^0_{g,3,0}(1,t) + N^0_{g,3,1}(1,t)C\big(\delta_{1,1}(1,t), h_1\big(1-X(t)z_1\big)\big) \\
&\quad + N^0_{g,3,2}(1,t)C\big(\delta_{2,1}(1,t), h_2\big(1-X(t)z_1\big)\big)w(a) \\
&\quad + Q^0_{g,3,1}(1,t)C^*\big(\delta_{1,1}(1,t), h_1\big(1-X(t)z_1\big)\big)\Big]\big(1-q_g(1,t)\big) \\
&\quad + N^0_{g,2,0}(1,t)\big(1-q_g(1,t)\big)u(t) + \Big\{N^0_{g,2,1}(1,t)\big(1-\delta_{1,0}(1,t)\big)\big(1-h_1\big) \\
&\quad + Q^0_{g,2,1}(1,t)\Big[1-C^T\big(\delta_{1,0}(1,t), h_1\big)\Big]\Big\}\big(1-q_g(1,t)\big)u(t)E_{0,1} \\
N^0_{g,3,1}(2,t+1) &= N^0_{g,3,1}(1,t)\big(1-\delta_{1,1}(1,t)\big)\big(1-h_1\big(1-X(t)z_1\big)\big)\big(1-q_g(1,t)\big) \\
&\quad + Q^0_{g,3,1}(1,t)\Big[1-C^T\big(\delta_{1,1}(1,t), h_1\big(1-X(t)z_1\big)\big)\Big]\big(1-q_g(a,t)\big) \\
&\quad + \Big\{N^0_{g,2,1}(1,t)\big(1-\delta_{1,0}(1,t)\big)\big(1-h_1\big)\big(1-q_g(1,t)\big) \\
&\quad + Q^0_{g,2,1}(1,t)\Big[1-C^T\big(\delta_{1,0}(1,t), h_1\big)\Big]\big(1-q_g(1,t)\big)\Big\}u(t)\big(1-E_{0,1}\big)
\end{aligned}
$$

In these equations, $E_{0,1}$ is the proportion of breastfeeding women who discontinue breastfeeding if they discover they are HIV-positive. 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). The proportion who discontinue breastfeeding is assumed to be the same as the proportion of women who would elect not to breastfeed if diagnosed HIV-positive prior to birth ($E_{0,1}$).

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 $X(t)z_1$:

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

$$N^0_{g,4,1}(a+1,t+1) = N^0_{g,4,1}(a,t)\left(1-\delta_{1,1}(a,t)\right)\left(1-h_1\left(1-z_2\right)\right)\left(1-q_g(a,t)\right)$$
$$+ Q^0_{g,4,1}(a,t)\left[1-C^T\left(\delta_{1,1}(a,t),h_1\left(1-z_2\right)\right)\right]\left(1-q_g(a,t)\right)$$
$$N^0_{g,4,2}(a+1,t+1) = N^0_{g,4,2}(a,t)\left(1-\delta_{2,1}(a,t)\right)\left(1-h_2\left(1-z_2\right)\right)\left(1-q_g(a,t)\right)$$

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 gender *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

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

**B.3 Modelling of survival of HIV-infected children in the absence of ART**

To model disease progression and mortality in untreated HIV-positive children, it is necessary to define the following symbols:

$\lambda^*_0(a)$ = the probability that a child who is aged exactly *a* months, who has been HIV infected since birth, but has not yet experienced the clinical or immunological conditions that originally determined ART eligibility, meets the clinical or immunological criteria within the next month;

$\lambda^*_1(a)$ = the same as $\lambda^*_0(a)$, except that this applies only to those children who became infected at birth after having been exposed to PMTCT;

$\lambda^*_2(a)$ = the same as $\lambda^*_0(a)$, except that this applies only to those children who became infected *after* birth;

$\theta_0$ = the relative rate of progression to ART eligibility in children who were infected at birth, in the absence of PMTCT exposure (compared to children who were PMTCT-exposed);

$\theta_2$ = the relative rate of progression to ART eligibility in children who were infected after birth (compared to children who were infected before birth, in the absence of PMTCT);

$\mu^*(a)$ = the probability that a child who is aged exactly *a* months, who is eligible to receive ART but not receiving ART, dies from AIDS within the next month;

$\rho^*(a,t)$ = the probability that a child who is aged exactly *a* months at time *t*, who is eligible to receive ART but not receiving ART, begins ART within the next month

These variables are similar to the $\lambda$, $\mu$ and $\rho$ parameters defined in sections 2.4 and 2.8, but they differ in that they are discrete probabilities rather than continuous hazards, and they are expressed as monthly rates rather than annual rates. Using the symbols defined in section 2.4, the variables are calculated as follows:

$$\lambda_0^*(a) = 1 - \exp\left(-\int_{a/12}^{(a+1)/12} \theta_0\left(G_p + H_p c^s\right) ds\right)$$

$$= 1 - \exp\left(-\frac{\theta_0 G_p}{12} - \frac{\theta_0 H_p}{\ln(c)}\left(c^{(a+1)/12} - c^{a/12}\right)\right)$$

$$\lambda_1^*(a) = 1 - \exp\left(-\frac{G_p}{12} - \frac{H_p}{\ln(c)}\left(c^{(a+1)/12} - c^{a/12}\right)\right)$$

$$\lambda_2^*(a) = 1 - \exp\left(-\frac{\theta_0\theta_2 G_p}{12} - \frac{\theta_0\theta_2 H_p}{\ln(c)}\left(c^{(a+1)/12} - c^{a/12}\right)\right)$$

$$\mu^*(a) = 1 - \exp\left(-\frac{G_m}{12} - \frac{H_m}{\ln(d)}\left(d^{(a+1)/12} - d^{a/12}\right)\right)$$

Now suppose that we define the following symbols:

$N_{g,i}^1(a,t)$ = number of infected children of gender *g* (0 = male; 1 = female), aged exactly *a* months at the start of month *t*, who are in HIV stage *i*;

$Q_{g,i}^1(a,t)$ = number of children of gender *g*, aged exactly *a* months at the start of month *t*, who enter the HIV stage *i* between time *t* and time *t* + 1

The different HIV-positive states are defined as follows:

0: infected at birth in the absence of PMTCT exposure, not yet eligible for ART in terms of clinical or immunological status;

1: infected at birth after having been exposed to PMTCT, not yet eligible for ART in terms of clinical or immunological status;

2: infected after birth, not yet eligible for ART in terms of clinical or immunological status;

3: eligible for ART but not receiving ART

4: receiving ART, having initiated ART prior to meeting clinical or immunological criteria;

5: receiving ART, having recently initiated ART after having developed clinical or immunological criteria, and currently still at a high mortality risk;

6: receiving ART, having initiated ART after having developed clinical or immunological criteria, and having stabilized at a low mortality risk;

7: discontinued ART but still alive

The numbers of untreated HIV-positive children at birth are calculated as follows:

$$N_{g,0}^1(0,t) = Y_{1,0}(t-1)SR_g$$

$$N_{g,1}^1(0,t) = Y_{1,1}(t-1)SR_g$$

$$N^1_{g,2}(0,t) = 0$$
$$N^1_{g,3}(0,t) = 0$$

The changes in the numbers of untreated HIV-positive children at older ages are calculated as follows:

$$N^1_{g,0}(a+1,t+1) = N^1_{g,0}(a,t)\left(1-\lambda^*_0(a)\right)\left(1-q_g(a,t)\right)$$
$$N^1_{g,1}(a+1,t+1) = N^1_{g,1}(a,t)\left(1-\lambda^*_1(a)\right)\left(1-q_g(a,t)\right)$$
$$N^1_{g,2}(a+1,t+1) = N^1_{g,2}(a,t)\left(1-\lambda^*_2(a)\right)\left(1-q_g(a,t)\right) + Q^1_{g,2}(a,t)\left(1-C^T\left(\lambda^*_2(a)\right)\right)\left(1-q_g(a,t)\right)$$

In the scenarios that assess the impact of the new ART guidelines, which recommend the initiation of ART in infants independent of their clinical or immunological status, the first two formulas are modified when calculating the numbers at two months of age, on the assumption that infected children would be identified through the PCR screening at 6 weeks and then initiated on ART at two months (on average). The third formula is not modified, as it is assumed that postnatally-infected infants would for the most part not have detectable viraemia at the age of 2 months. If $A(t)$ is the proportion of perinatally-infected infants who are diagnosed HIV-positive at the 6 week follow-up visit in month $t$, and who initiate ART soon thereafter, then the modifications to the first and second formulas are as follows:

$$N^1_{g,0}(2,t+1) = N^1_{g,0}(1,t)\left(1-\lambda^*_0(1)\right)\left(1-q_g(1,t)\right)\left(1-A(t)\right)$$
$$N^1_{g,1}(2,t+1) = N^1_{g,1}(1,t)\left(1-\lambda^*_1(1)\right)\left(1-q_g(1,t)\right)\left(1-A(t)\right)$$

To assess the change in the number of untreated children who are eligible to receive ART in terms of clinical or immunological criteria, the following formulas are used:

$$Q^1_{g,3}(a,t) = N^1_{g,0}(a,t)\lambda^*_0(a) + N^1_{g,1}(a,t)\lambda^*_1(a) + N^1_{g,2}(a,t)\lambda^*_2(a) + Q^1_{g,2}(a,t)C^T\left(\lambda^*_2(a)\right)$$
$$N^1_{g,3}(a+1,t+1) = N^1_{g,3}(a,t)\left(1-\rho^*(a,t)\right)\left(1-\mu^*(a)\right)\left(1-q_g(a,t)\right) + Q^1_{g,3}(a,t)\left(1-C^T\left(\mu^*(a)\right)\right)\left(1-q_g(a,t)\right)$$

Note from the second formula that individuals who progress to the ART eligible state are assumed not to begin ART in the same month that they become eligible. As explained in section 2.8, this is because of the time it would typically take to process the laboratory test results and prepare the patient for ART. If ART is initiated according to the new WHO and South African guidelines, the second equation is modified at two months:

$$N^1_{g,3}(2,t+1) = \left\{N^1_{g,3}(1,t)\left(1-\rho^*(1,t)\right)\left(1-\mu^*(1)\right)\left(1-q_g(1,t)\right) + Q^1_{g,3}(1,t)\left(1-C^T\left(\mu^*(1)\right)\right)\left(1-q_g(1,t)\right)\right\}\left(1-A(t)\right)$$

**B.4 Modelling of survival of HIV-infected children after ART initiation**

The number of children starting ART between time t and time t + 1 is broken into two components: those who start ART prior to having met clinical and immunological criteria for starting ART ($Q^1_{g,4}(a,t)$) and those who have met clinical and immunological criteria for starting ART ($Q^1_{g,5}(a,t)$). The former applies only at the age of 2 months, on the assumption that children who have not progressed to ART eligibility would only be identified as HIV-infected at the 6-week PCR test. At all other ages, the number of individuals starting ART is calculated as

$$Q^1_{g,4}(a,t) = 0$$
$$Q^1_{g,5}(a,t) = N^1_{g,3}(a,t)C\left(\rho^*(a,t),\mu^*(a)\right).$$

To allow for the effect of the new ART guidelines at 2 months, we set

$$Q^1_{g,4}(1,t) = \left[N^1_{g,0}(1,t)\left(1-\lambda^*_0(1)\right)+N^1_{g,1}(1,t)\left(1-\lambda^*_1(1)\right)\right]A(t)$$
$$Q^1_{g,5}(1,t) = N^1_{g,3}(1,t)\left[C\left(\rho^*(1,t),\mu^*(1)\right)+\left(1-\rho^*(1,t)\right)\left(1-\mu^*(1)\right)A(t)\right]$$
$$+Q^1_{g,3}(1,t)\left[1-C^T\left(\rho^*(1,t),\mu^*(1)\right)\right]A(t)$$

To model mortality and treatment discontinuation in children on ART, it is necessary to define the following symbols:
$\psi_i(a)$ = monthly probability of death due to AIDS in treated children aged exactly *a* months, who are in stage *i*;
$\varsigma_0$ = monthly probability of discontinuing ART in children who recently started ART, after having been clinically or immunologically eligible to start ART, and who are still considered to be at a high mortality risk;
$\varsigma_1$ = monthly probability of discontinuing ART in children who started ART after having been clinically or immunologically eligible to start ART, and who are now considered to be stabilized on ART;
$\varsigma^*(a)$ = monthly probability of discontinuing ART in children aged *a*, who started ART prior to meeting clinical or immunological criteria

These parameters are calculated in terms of the symbols defined in sections 2.4 and 2.6:

$$\psi_4(a) = 1-\exp\left(-\int_{a/12}^{(a+1)/12}\Phi_1\left(G_m+0.4\times H_m d^s\right)ds\right)$$
$$= 1-\exp\left(-\frac{\Phi_1 G_m}{12}-\frac{0.4\times\Phi_1 H_m}{\ln(d)}\left(d^{(a+1)/12}-d^{a/12}\right)\right)$$
$$\psi_5(a) = 1-\exp\left(-\frac{\Phi_0 G_m}{12}-\frac{\Phi_0 H_m}{\ln(d)}\left(d^{(a+1)/12}-d^{a/12}\right)\right)$$
$$= 1-\left(1-\mu^*(a)\right)^{\Phi_0}$$
$$\psi_6(a) = 1-\left(1-\mu^*(a)\right)^{\Phi_1}$$
$$\varsigma_0 = 1-\exp\left(-\kappa_0/12\right)$$
$$\varsigma_1 = 1-\exp\left(-\kappa_1/12\right)$$

$$\varsigma^*(a) = 1 - \exp\left(-\kappa_a^{'}/12\right)$$

The number of children who remain on ART after having started ART prior to meeting clinical or immunological criteria for eligibility is calculated according to the following formulas:

$$N_{g,4}^1(2,t+1) = Q_{g,4}^1(1,t)\left(1-q_g(1,t)\right)$$
$$N_{g,4}^1(a+1,t+1) = N_{g,4}^1(a,t)\left(1-\psi_4(a)\right)\left(1-\varsigma^*(a)\right)\left(1-q_g(a,t)\right) \qquad \text{for } a \geq 2$$

The children who are on ART, having started after meeting clinical or immunological criteria for eligibility, are split into two groups: those who are still at a high mortality risk, and those who have stabilized on ART and are now considered to be at a low mortality risk. Children are assumed to remain in the high risk phase for an average of 3 months after starting ART, before progressing to the low risk phase. The number in the 'high risk' group is calculated according to the following formula:

$$\begin{aligned} N_{g,5}^1(a+1,t+1) = {} & N_{g,5}^1(a,t)\left(1-\psi_5(a)\right)\left(1-\varsigma_0(a)\right)\exp\left(-1/3\right)\left(1-q_g(a,t)\right) \\ & + Q_{g,5}^1(a,t)\left[1-C^T\left(\psi_5(a),\varsigma_0(a),1-\exp\left(-1/3\right)\right)\right]\left(1-q_g(a,t)\right) \end{aligned}$$

The number progressing to the 'low risk' group is

$$\begin{aligned} Q_{g,6}^1(a,t) = {} & N_{g,5}^1(a,t)C\left(1-\exp\left(-1/3\right),\psi_5(a),\varsigma_0(a)\right) \\ & + Q_{g,5}^1(a,t)C^*\left(1-\exp\left(-1/3\right),\psi_5(a),\varsigma_0(a)\right) \end{aligned}$$

The formulas are modified at the age of 2 months if ART is initiated early:

$$\begin{aligned} N_{g,5}^1(2,t+1) = {} & N_{g,5}^1(1,t)\left(1-\psi_5(1)\right)\left(1-\varsigma_0(1)\right)\exp\left(-1/3\right)\left(1-q_g(1,t)\right) \\ & + N_{g,3}^1(1,t)C\left(\rho^*(1,t),\mu^*(1)\right)\left[1-C^T\left(\psi_5(1),\varsigma_0(1),1-\exp\left(-1/3\right)\right)\right]\left(1-q_g(1,t)\right) \\ & + N_{g,3}^1(1,t)\left(1-\rho^*(1,t)\right)\left(1-\mu^*(1)\right)A(t)\left(1-q_g(1,t)\right) \\ & + Q_{g,3}^1(1,t)\left(1-C^T\left(\rho^*(1,t),\mu^*(1)\right)\right)A(t)\left(1-q_g(1,t)\right) \\ Q_{g,6}^1(1,t) = {} & N_{g,5}^1(1,t)C\left(1-\exp\left(-1/3\right),\psi_5(1),\varsigma_0(1)\right) \\ & + N_{g,3}^1(1,t)C\left(\rho^*(1,t),\mu^*(1)\right)C^*\left(1-\exp\left(-1/3\right),\psi_5(a),\varsigma_0(a)\right) \end{aligned}$$

The number in the low risk group is

$$\begin{aligned} N_{g,6}^1(a+1,t+1) = {} & N_{g,6}^1(a,t)\left(1-\psi_6(a)\right)\left(1-\varsigma_1(a)\right)\left(1-q_g(a,t)\right) \\ & + Q_{g,6}^1(a,t)\left[1-C^T\left(\psi_6(a),\varsigma_1(a)\right)\right]\left(1-q_g(a,t)\right) \end{aligned}$$

The number of children who discontinue ART, for reasons other than death, is

$$
\begin{aligned}
Q^1_{g,7}(a,t) = {} & N^1_{g,4}(a,t)C\left(\varsigma^*(a),\psi_4(a)\right) + N^1_{g,5}(a,t)C\left(\varsigma_0,1-\exp(-1/3),\psi_5(a)\right) \\
& + N^1_{g,6}(a,t)C\left(\varsigma_1,\psi_6(a)\right) + Q^1_{g,5}(a,t)C^*\left(\varsigma_0,1-\exp(-1/3),\psi_5(a)\right) \\
& + Q^1_{g,6}(a,t)C^*\left(\varsigma_1,\psi_6(a)\right)
\end{aligned}
$$

The fourth term on the right hand side of the above equation is modified if ART is initiated early:

$$
\begin{aligned}
Q^1_{g,7}(1,t) = {} & N^1_{g,4}(1,t)C\left(\varsigma^*(1),\psi_4(1)\right) + N^1_{g,5}(1,t)C\left(\varsigma_0,1-\exp(-1/3),\psi_5(1)\right) \\
& + N^1_{g,6}(1,t)C\left(\varsigma_1,\psi_6(1)\right) + N^1_{g,3}(1,t)C\left(\rho^*(1,t),\mu^*(1)\right)C^*\left(\varsigma_0,1-\exp(-1/3),\psi_5(1)\right) \\
& + Q^1_{g,6}(1,t)C^*\left(\varsigma_1,\psi_6(1)\right)
\end{aligned}
$$

Children who have discontinued ART for reasons other than death are assumed not to resume ART. They are also assumed to experience the same rate of AIDS mortality as untreated children of the same age who are eligible to receive ART. The formula that is used to calculate the number of untreated surviving children who have discontinued ART is therefore

$$
\begin{aligned}
N^1_{g,7}(a+1,t+1) = {} & N^1_{g,7}(a,t)\left(1-\mu^*(a)\right)\left(1-q_g(a,t)\right) \\
& + Q^1_{g,7}(a,t)\left(1-C^T\left(\mu^*(a)\right)\right)\left(1-q_g(a,t)\right)
\end{aligned}
$$

The total number of AIDS deaths in children aged between $a$ and $a$ + 1 months, between time $t$ and time $t$ + 1 (in months), is calculated as

$$
\begin{aligned}
& \left\{N^1_{g,3}(a,t)C\left(\mu^*(a),\rho^*(a,t)\right) + N^1_{g,4}(a,t)C\left(\psi_4(a),\varsigma^*(a)\right) + N^1_{g,5}(a,t)C\left(\psi_5(a),\varsigma_0,1-\exp(-1/3)\right)\right. \\
& \quad + N^1_{g,6}(a,t)C\left(\psi_6(a),\varsigma_1\right) + N^1_{g,7}(a,t)\mu^*(a) + Q^1_{g,3}(a,t)C^*\left(\mu^*(a),\rho^*(a,t)\right) \\
& \quad + N^1_{g,3}(a,t)C\left(\rho^*(a,t),\mu^*(a)\right)C^*\left(\psi_5(a),\varsigma_0,1-\exp(-1/3)\right) + Q^1_{g,6}(a,t)C^*\left(\psi_6(a),\varsigma_1\right) \\
& \quad \left. + Q^1_{g,7}(a,t)C^T\left(\mu^*(a)\right)\right\}\left(1-q_g(a,t)\right)
\end{aligned}
$$

The total number of non-AIDS deaths in children of gender $g$, aged between $a$ and $a$ + 1 months, between time $t$ and time $t$ + 1 (in months), is calculated as

$$
q_g(a,t)\left\{\sum_{i=0}^{4}\sum_{v=0}^{2}N^0_{g,i,v}(a,t) + \sum_{i=0}^{7}N^1_{g,i}(a,t)\right\}.
$$

In these two equations, we are effectively calculating the non-AIDS deaths before we calculate the AIDS deaths. This is not strictly correct, as the AIDS and non-AIDS mortality rates should ideally be treated as competing decrements. However, since the monthly non-AIDS mortality probability is extremely low, it makes very little difference to the relative number of AIDS and non-AIDS deaths – and it makes no difference to the number of survivors. Allowing for non-AIDS mortality as a competing decrement would add considerably to the complexity of the calculations without changing the results materially.