**Text S1. Technical description of the mathematical model**

# **Description of the mathematical model ‘gems’**

## **General structure**

The general structure of the mathematical model is presented in the main text (Materials and Methods, Structure of the mathematical model). The structure consists of two simulations: one for the mothers, and one for their infants. The simulation of the mothers is run first, and it will inform the simulation of the infants.

## **Simulation of mothers**

The mothers’ simulation model consists of 58 states, which are shown in **Table S2**. The model includes 27 states for HIV-uninfected (states 1-27) and 27 for HIV-infected (states 28-54) women. The progress of motherhood is divided into pregnancy (states 1-6, 28-33), delivery (states 7-9, 34-36), exclusive breastfeeding (states 10-15, 37-42), mixed breastfeeding (states 16-21, 43-48) and no breastfeeding (states 22-27, 49-54). Women can be either in ANC/postnatal care or out of care because of either not yet seeking care, or because of loss to follow-up. Death is represented by four terminal states (states 55-58), split according to being in care, and reason (HIV-related or unrelated) of death.

The simulation starts at conception and continues through pregnancy and breastfeeding until 2 years after delivery, or until death, whichever occurs first. Women may either be HIV-uninfected or at an early stage of HIV infection at the beginning of the simulation. HIV-uninfected women can get infected during the simulation based on the estimated incidence of HIV during pregnancy or breastfeeding. We assumed that women may have a new HIV test three months after a negative HIV test result. After delivery, mothers start exclusive breastfeeding and later change to mixed breastfeeding. The rate of changing from exclusive to mixed breastfeeding changes over breastfeeding period **(Table S1)**; the total median duration of breastfeeding is 23 months [1] HIV-infected women who are in care start on ART according to the Malawi PMTCT guidelines [2] and the observed probability of ART uptake. Women in care may get lost to follow-up and return to care for a restricted number of times throughout the simulation.

## **Infant simulation**

The simulation for foetuses/infants covers the same time period as the mothers’ simulation. The model includes 21 states. States 1 and 8 represent the foetus, states 2 and 9 delivery, states 3-7 and 10-20 the newborn/infant, and state 21 death; in states 1-7 the foetus/infants is uninfected and in states 8-20 infected **(Table S3).** The states also account for being in care and receiving ART. At the start of the simulation, the foetus is uninfected. The foetus/infant is at risk of getting HIV infected during the time the mother is infected (see section 2.3, and the main text).

# **Parameterization**

All the input parameters and their sources are presented in **Table 1** of the main text, and **Table S1.**  The model was parameterized with literature estimates and Malawi PMTCT data.

## **Demographic parameters**

We modelled 100,000 women during the first pregnancy with median age of 19.5 years and standard deviation 3.1 years at conception based on the national ANC data (unpublished data). HIV prevalence at conception was 7.6% [3] which was consistent with the latest Spectrum projects (7.8% HIV prevalence among all pregnant women in 2014) but lower than the reported 11% HIV prevalence among pregnant women reported the 2010 ANC sentinel surveillance survey. HIV-related and HIV-unrelated mortality were modelled separately [4].

## **Access to HIV services before and after pregnancy/breastfeeding**

HIV-infected women who are neither pregnant nor breastfeeding are likely to seek HIV services when they develop symptoms. According to Hallett et al [5], we assumed that 50% of women with CD4 cell count between 350 and 150 cells/μl have symptoms. We further assumed that among those with symptoms 70% seek care within 1 year, and among those who have no symptoms no one seeks care.

## **Loss to follow-up during pregnancy and breastfeeding**

### **Description of the dataset and definitions of variables**

We extracted individual-level data from 19 health facilities in central and southern Malawi which used an electronic medical record system when the Option B+ program was launched in September 2011. We included all ART naïve women aged 16-50 years who started ART under Option B+ between September 2011 (the date Option B+ was implemented) and the date of the most recent follow-up visit in a given facility (the closing date: May 2012 – September 2012).

Our primary outcomes were “no follow-up visit after ART initiation” (NFU) and “loss to follow-up” (LTF). We defined women who missed their first follow-up visit and did not return to care for more than 60 days as women as NFU on the day of ART initiation. We assume that these women actually never started ART. Women who missed a subsequent follow-up visit and did not return to care for more than 60 days were classified as LTF on the day they were running out of dispensed drugs.

### **Statistical analysis**

Because levels of NFU and LTF are much higher among women who started ART during pregnancy compared to women who start ART while breastfeeding, we calculated separate values for the two groups of women. We calculated probability for NFU by dividing the number of women with NFU in each patient group by the total number of eligible women in each group.

Assuming that in Malawi women initiate ART on average in week 23 of gestation and deliver in week 40, we used data on the first four months of ART to estimate LTF during pregnancy. We determined a constant rate of LTF during pregnancy by dividing the number of pregnant women lost during the first four months on ART by the person-time at risk. We determined a constant rate of LTF after delivery by dividing the number of women LTF among those who started while breastfeeding by the person-time at risk. The probabilities of NFU for women who started ART while pregnancy and breastfeeding were 16.4% and 8.9%, respectively. Among women with at least one follow-up visit, rates of LTF were 0.245 and 0.131 per person-year during pregnancy and breastfeeding, respectively.

## **Mother to child transmission of HIV**

Vertical transmission of HIV occurs in utero, intrapartum, or postpartum through breastfeeding. The risk of HIV transmission ranges from 15 to 45%, depending on maternal risk factors and breastfeeding practices without ART [6]. The rate can be reduced to levels below 5% with effective interventions [7,8].

### **In utero and intrapartum transmission**

Most of the in utero transmission is believed to occur in the third trimester, based on the low rates of viral detection using HIV NAT on fetal tissue from abortions in the first and second trimester [9]. Also, a study in Thailand comparing long versus short antenatal Zidovudine prophylaxis for PMTCT reported a probability transmission of 5.1% during pregnancy when starting Zidovudine at 36 weeks gestation compared with 1.6% when starting Zidovudine at 28 weeks. This suggests that a significant proportion of transmission occur between 28 to 36 weeks [10]. Intrapartum transmission is thought to happen when the baby comes into contact with infected blood and genital secretions from the mother as it passes through the birth canal. Between 25 to 40% of the infant infections are estimated to occur in utero, about 50% around time of labour/delivery while the remainder occurs during breastfeeding period among women who are not on ART [11].

For our model, we estimated the total risk of mother-to-child transmission in utero or intrapartum in the absence of any intervention. Although several studies have reported the probability of vertical transmission in utero or intrapartum separately, they may not be able to accurately distinguish between in utero/intrapartum transmission and breastfeeding transmission: PCR does not give a positive result until a few weeks after HIV transmission has occurred. Johnson et al estimated the probability of mother-to-child transmission in utero or intrapartum based on the rate of transmission during breastfeeding and the rate at which newly infected infants develop detectable virus [12]. The average probability of mother-to-child transmission in utero or intrapartum in infants born to women who do not receive antiretroviral prophylaxis was 19.7%. In the model, we assumed that 37% of these transmissions happened before 31 weeks of gestation, to assure that they would take place before delivery. Therefore, some infections in the model may occur too early. This should not however influence the findings.

Using this probability, we modelled the risk of mother-to-child transmission starting from second trimester to delivery using Weibull distribution in the absence of any intervention. We assumed that almost 7% of the infants get infected between the weeks 18 and 31 of gestation and the remaining infections (excluding those happening through breastfeeding) occur between 31 weeks and delivery.

We use the cumulative density function for a Weibull distribution,

where *k* is the shape parameter, *λ* the scale parameter and *t* the time at risk. From this equation, we can solve *t*

Substituting *τ* = *t* – *t*0simplifies it to

Since *F* is a continuous increasing function [0,∞[ → [0,1[, each random uniform deviate *U*  corresponds to a unique time *TU* where the proportion *U* of the population have experienced the event. Now, we know the values *T*7.4% = 0.6 – 0.25 = 0.35and *T*19.7% = 0.7 – 0.25 = 0.45. Therefore, the following equations hold:

We can now solve for *k* = 4.2 and *λ* = 0.7

We used the hazard function of the Weibull distribution to parameterise the risk of infection in the model:

where *t* is the time calculated from the beginning of the second trimester. Previous studies and clinical trials suggest that viral load of maternal plasma and breast milk, acute maternal seroconversion during pregnancy or breastfeeding and advanced WHO clinical stage are important risk factors [13,14]. We assume that women are more infectious in the first 6 months of the HIV infection [15]. If the mother is treated, the risk of transmission is reduced by the factor 0.04 [16].

### **HIV transmission during breastfeeding**

HIV can be transmitted through breast milk at any time during lactating. There is evidence of increased cumulative risk of HIV transmission with continued breastfeeding [17,18]. The risk of HIV transmission during breastfeeding depends on a number of factors; maternal seroconversion, clinical, immunological factors in mothers, as well as infant feeding patterns [14,19-21]. We also modelled different risks of MTCT based on breastfeeding patterns and duration. Exclusive breastfeeding has been reported to be associated with lower postnatal HIV transmission than mixed breastfeeding [22,23]. Mixed breastfeeding was associated with 2.9 times risk of MTCT compared to exclusive breastfeeding [20]. WHO recommends exclusive breastfeeding is recommended up to 6 months of age to reduce HIV transmission from mother to child and increase the benefits of breast milk to infants.

We assumed that the risk of HIV transmission is higher during the first three months of breastfeeding than thereafter (0.35 vs 0.091 per person-years) [23, 24]. As for in-utero and intrapartum transmission, we also assumed an increased risk of transmission if the mother is in acute stage (hazard ratio 6 [15]), or, and reduced risk of transmission if she is on treatment (hazard ratio 0.04 [16]).

**Table S1. Input parameters for the mathematical model of scenarios to prevent mother-to-child transmission of HIV in Malawi. All rates are given per person-year.**

|  |  |  |
| --- | --- | --- |
| **Variable** | **Value** | **Data source** |
| **Hazard ratios of access to ANC services for 2nd pregnancy, compared to 1st pregnancy** |
| Hazard ratio of returning to ANC for second pregnancy for those who were in ANC or had a test during postnatal compared to those who were not in ANC or had not HIV test | 1.5 | Assumption |
| Hazard ratio of accessing ANC for second pregnancy for HIV positive & Advanced HIV status compared to those HIV infected or uninfected | 3 | Assumption |
| **Preterm delivery rate¥** | 0.29 | [25] |
| **Probability of returning to care after delivery** | 90% | Assumption |
| **Return rate from lost to follow-up** | 0.33 | [26] |
| **Rate of changing from exclusive to mixed breastfeeding** |  |  |
| During months 1-3 | 0.40 | [1] |
| During months 4-6 | 4.60 | [1] |
| During months 7-11 | 6.94 | [1] |
| During months 12-23 | 6.21 | [1] |
| **Rate of stopping breastfeeding (from mixed breastfeeding)** | 0.114 | [1] |
| **Mortality in women** |  |  |
| HIV free mortality | \* | [4] |
| Probability of death at delivery | 0.2% | [27] |
| HIV related mortality (Weibull shape) | 5 | \*\* |
| HIV related mortality (Weibull scale (years)) | 11 | \*\* |
| **Probability of starting ART after a confirmed positive HIV test** |  |  |
| At ANC | 93% | [3] |
| At postnatal care | 66% | Assumption  |
| **HIV testing** |  |  |
| Probability during delivery if woman was not in care | 48% | [3] |
| Probability during delivery if woman was in care | 3% | [3] |
| **Probability of false positive test result** | 0. 1% | Assumption |
| **Probability of false negative test result** | 1% | Assumption |
| **Median birth interval€** | 3 | [1] |
| **Probability of having a second pregnancy** | 98% | [1,28] |
| **Retention probability per year in ART care for women started ART for their health/ PMTCT but are now ART eligible** | 90% | [29] |
| **ART retention per year for non-ART eligible women per year** | 80% | [30] |
| **Probability of seeking care for women eligible for ART per year** | 35% | Assumption, [5] |

**¥** Preterm delivery was defined as any delivery occurring between 24 weeks and 34 weeks of gestation age.€ A birth interval is defined as the period of time between two successive live births. \*Age- and gender-specific rates (see Table S1 by Brinkhof *et al* ) [4]\*\* The median time from HIV infection to death (between 10 and 11 years) is based on the literature[5]. Because we wanted to exclude women who would have been ART eligible for their own health at the beginning of the first pregnancy, we chose a shape parameter that decreases the risk of death in the early years.

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| **Table S2. Description of states and possible transitions for women in the prevention of mother-to-child transmission of HIV mathematical model** |
| **State** |  |   | **States to which transition is possible** |
| **State no.** | **Motherhood** | **HIV testing status, treatment and care** |  |   | **Within same HIV status** | **HIV infection** | **Death** |
| **HIV uninfected** |  |  |  |  |
| 1 | Pregnancy | not in care |  | 2,5,7,8,9 | 28 | 55,57 |
| 2 | Pregnancy | at antenatal clinic |  | 3,4,6,7,8,9 | 29 | 55,57 |
| 3 | Pregnancy | tested correctly |  | 4,6,7,8,9 | 30 | 55,57 |
| 4 | Pregnancy | tested, false positive |  | 5,6,7,8,9 | 31 | 55,57 |
| 5 | Pregnancy | false positive on ART |  | 6,7 | 32 | 55,57 |
| 6 | Pregnancy | LTFU |  | 7,8,9 | 33 | 55,57 |
| 7 | Delivery | no test |  | 10,11,12,13,14 | 34 | 55,57 |
| 8 | Delivery | - test (correct) |  | 12 | 35 | 55,57 |
| 9 | Delivery | + test (false) |  | 13 | 36 | 55,57 |
| 10 | Postnatal Excl. breastfeeding | LTFU |  | 11,12,13,14,16 | 37 | 55 |
| 11 | Postnatal Excl. breastfeeding | no ART, unknown HIV status |  | 12,13,15,17 | 38 | 55,57 |
| 12 | Postnatal Excl. breastfeeding | no ART, - test (correct) |  | 13,15,18 | 39 | 55,57 |
| 13 | Postnatal Excl. breastfeeding | no ART, + test (false) |  | 14,15,19 | 40 | 55,57 |
| 14 | Postnatal Excl. breastfeeding | false posit on ART |  | 15,20 | 41 | 55,57 |
| 15 | Postnatal Excl. breastfeeding | LTFU |  | 16 | 42 | 55 |
| 16 | Postnatal Mixed breastfeeding | LTFU |  | 17,18,19,20,22 | 43 | 55 |
| 17 | Postnatal Mixed breastfeeding | no ART, unknown HIV status |  | 18,19,21,23 | 44 | 55,57 |
| 18 | Postnatal Mixed breastfeeding | no ART, - test (correct) |  | 19,21,24 | 45 | 55,57 |
| 19 | Postnatal Mixed breastfeeding | no ART, + test (false) |  | 20,21,25 | 46 | 55,57 |
| 20 | Postnatal Mixed breastfeeding | false posit on ART |  | 21,26,47 | 47 | 55,57 |
| 21 | Postnatal Mixed breastfeeding | LTFU |  | 22 | 48 | 55 |
| 22 | Postnatal No breastfeeding | LTFU |  | 23,24,25,26 | 49 | 55 |
| 23 | Postnatal No breastfeeding | no ART, unknown HIV status |  | 24,25,27 | 50 | 55,57 |
| 24 | Postnatal No breastfeeding | no ART, - test (correct) |  | 25,27 | 51 | 55,57 |
| 25 | Postnatal No breastfeeding | no ART, + test (false) |  | 26,27 | 52 | 55,57 |
| 26 | Postnatal No breastfeeding | false posit on ART |  | 27 | 53 | 55,57 |
| 27 | Postnatal No breastfeeding | LTFU |  |  | 54 | 55 |
| **HIV infected** |  |  |  |  |
| 28 | Pregnancy | not in care |   | 29,32,34,35,36 |   | 55,56,57,58 |
| 29 | Pregnancy | at antenatal clinic, unknown HIV status |   | 30,31, 33,34,35,36 |   | 55,56,57,58 |
| 30 | Pregnancy | tested, false negative |   | 31,33,34,35,36 |   | 55,56,57,58 |
| 31 | Pregnancy | tested correctly |   | 32,33,34 |   | 55,56,57,58 |
| 32 | Pregnancy | on ART |   | 33,34 |   | 55,56,57,58 |
| 33 | Pregnancy | LTFU |   | 34,35,36 |   | 55,56 |
| 34 | Delivery | no test |   | 37,38,39,40,41 |   | 55,56,57,58 |
| 35 | Delivery | - test (false) |   | 39 |   | 55,56,57,58 |
| 36 | Delivery | + test (correct) |   | 40 |   | 55,56,57,58 |
| 37 | Postnatal Excl. breastfeeding | LTFU |   | 38,39,40,41,43 |   | 55,56 |
| 38 | Postnatal Excl. breastfeeding | no ART, unknown HIV status |   | 39,40,42,44 |   | 55,56,57,58 |
| 39 | Postnatal Excl. breastfeeding | no ART, - test (false) |   | 40,42,45 |   | 55,56,57,58 |
| 40 | Postnatal Excl. breastfeeding | no ART, + test (correct) |   | 41,42,46 |   | 55,56,57,58 |
| 41 | Postnatal Excl. breastfeeding | on ART |   | 42,47 |   | 55,56,57,58 |
| 42 | Postnatal Excl. breastfeeding | LTFU |   | 43 |   | 55,56 |
| 43 | Postnatal Mixed breastfeeding | LTFU |   | 44,45,46,47,49 |   | 55,56 |
| 44 | Postnatal Mixed breastfeeding | no ART, unknown HIV status |   | 45,46,48,50 |   | 55,56,57,58 |
| 45 | Postnatal Mixed breastfeeding | no ART, - test (false) |   | 46,48,51 |   | 55,56,57,58 |
| 46 | Postnatal Mixed breastfeeding | no ART, + test (correct) |   | 47,48,52 |   | 55,56,57,58 |
| 47 | Postnatal Mixed breastfeeding | on ART |   | 48,53 |   | 55,56,57,58 |
| 48 | Postnatal Mixed breastfeeding | LTFU |   | 49 |   | 55,56 |
| 49 | Postnatal No breastfeeding | LTFU |   | 50,51,52,53 |   | 55,56 |
| 50 | Postnatal No breastfeeding | no ART, unknown |   | 51,52,54 |   | 55,56,57,58 |
| 51 | Postnatal No breastfeeding | no ART, - test (false) |   | 52,54 |   | 55,56,57,58 |
| 52 | Postnatal No breastfeeding | no ART, + test (correct) |   | 53,54 |   | 55,56,57,58 |
| 53 | Postnatal No breastfeeding | on ART |   | 54 |   | 55,56,57,58 |
| 54 | Postnatal No breastfeeding | LTFU |   |   |   | 55,56 |
| **Death** |   |   |   |   |   |   |
| 55 | Death | Non-HIV-related, unregistered |  | n/a |  | n/a |
| 56 | Death | HIV-related, unregistered |  | n/a |  | n/a |
| 57 | Death | Non-HIV-related, registered |  | n/a |  | n/a |
| 58 | Death | HIV-related, registered |   | n/a |   | n/a |
|  *LTFU= Lost to follow-up; excl. = Exclusive; ART = antiretroviral therapy; n/a= Not applicable* |  |  |

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| **Table S3. Description of states and possible transitions for infants in the prevention of mother-to-child transmission of HIV mathematical model** |
| **State** |   | **States to which transition is possible** |
| **State no.** | **Fetus/Infancy** | **HIV status & care** |   | **Within same HIV status** | **HIV infection** | **Death** |
| **HIV uninfected** |  |  |  |  |
| 1 | Fetus |  |  | 2 | 8 | 21 |
| 2 | Delivery |  |  | 3,4 | 9 | 21 |
| 3 | Infancy | No ARV Prophylaxis |  | 4,5 | 10 | 21 |
| 4 | Infancy | ARV Prophylaxis |  | 5 | 11 | 21 |
| 5 | Infancy | Confirmed at 6 weeks |  | 6 | 12 | 21 |
| 6 | Infancy | Confirmed at 12 months |  | 7 | 13 | 21 |
| 7 | Infancy | Confirmed at 24 months |  |  |  | 21 |
| **HIV infected** |   |   |   | 21 |
| 8 | Fetus |  |   |   | 9 | 21 |
| 9 | Delivery |  |   |   | 10,11 | 21 |
| 10 | Infancy | No ARV Prophylaxis |   |   | 11,14 | 21 |
| 11 | Infancy | ARV Prophylaxis |   |   | 14 | 21 |
| 12 | Infancy | Latent after negative test at 6 weeks |   |   | 14 | 21 |
| 13 | Infancy | Latent after negative test at 12 months |   |   | 14 | 21 |
| 14 | Infancy | Confirmed (anytime) |   |   | 15,17,19 | 21 |
| 15 | Infancy | on ART |   |   | 16,17 | 21 |
| 16 | Infancy | LTFU |   |   | 17,18 | 21 |
| 17 | Infancy | on ART |   |   | 18,19 | 21 |
| 18 | Infancy | LTFU |   |   | 19,20 | 21 |
| 19 | Infancy | on ART |   |   | 20 | 21 |
| 20 | Infancy | LTFU |   |   |   | 21 |
| **Death** |  |  |  |  |  |  |
| 21 | Death | Death from any cause  |   |   |   | 21 |
|  *LTFU= Lost to follow-up; ARV= antiretroviral; ART = antiretroviral therapy; n/a= Not applicable* |  |  |  |

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| **Table S4: Cost of PMTCT service delivery**  |   |
| **Item** | **Unit cost (US dollars)** | **Reference** |
| HIV testing and counselling (adults & infants) | 3.50 | MoH Malawi |
| CD4 screening | 20.00 | MoH Malawi |
| Follow-up visit management  | 2.00 | MoH Malawi |
| Infant prophylaxis (NVP six weeks) | 1.20 | MoH Malawi |
| TDF + 3TC + EFV (per year) | 193.60 | MoH Malawi |
| Early infant diagnosis | 32.50 | MoH Malawi |
| Cotrimoxazole prophylaxis for child (per year) | 5.00 | MoH Malawi |
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| **Table S5. Outcomes of in modelled cohorts of primigravida under Option B+ and Option B to prevent mother-to-child HIV transmission in Malawi.** The values in brackets represent the 6th and 195th percentiles of the results over all 200 simulated cohorts of 10,000 women. |  |  |  |  |
|  | **Option B+** | **Option B** |
| **1st pregnancy** | **2nd pregnancy** | **1st pregnancy** | **2nd pregnancy** |
|  | n | % | n | % | n | % | n | % |
| **Number of simulated pregnant women** | 10000 |  | 9715 (9678-9749) |  | 10000 |  | 9716 (9689-9748) |  |
| **Antenatal and postnatal care** |  |  |  |  |  |  |  |  |
|  Women attending ANC | 8421 (8343-8496) | 84.2 (83.4-85.0) | 8821 (8759-8880) | 90.8 (90.3-91.3) | 8423 (8350-8501) | 84.2 (83.5-85.0) | 8784 (8726-8849) | 90.4 (89.8-91.0) |
|  Women receiving HIV test in ANC (of those attending ANC) | 7959 (7879-8047) | 94.5 (94.0-95.0) | 7812 (7732-7895) | 88.6 (87.9-89.2) | 7961 (7885-8046) | 94.5 (94.0-95.0) | 8084 (8010-8163) | 92.0 (91.6-92.6) |
|  Women attending postnatal care | 7915 (7841-7993) | 79.2 (78.4-79.9) | 7797 (7724-7876) | 80.3 (79.5-81.0) | 7916 (7829-8005) | 79.2 (78.3-80.1) | 7764 (7694-7846) | 79.9 (79.2-80.7) |
|  Women getting HIV test at delivery or postnatal services (of those attending postnatal care) | 873 (824-927) | 11.0 (10.4-11.7) | 436 (398-475) | 5.6 (5.1-6.1) | 873 (811-924) | 11.0 (10.3-11.7) | 434 (395-472) | 5.6 (5.1-6.1) |
| **Pregnancy outcomes** |  |  |  |  |  |  |  |  |
|  Number of live births | 7951 (7873-8032) | 79.5 (78.7-80.3) | 7703 (7628-7788) | 79.3 (78.6-80.1) | 7954 (7871-8037) | 79.5 (78.7-80.4) | 7704 (7629-7787) | 79.3 (78.5-80.1) |
|  Number of miscarriages and stillbirths | 2039 (1958-2119) | 20.4 (19.6-21.1) | 1983 (1909-2059) | 20.4 (19.6-21.2) | 2036 (1951-2120) | 20.4 (19.5-21.2) | 1983 (1904-2054) | 20.4 (19.6-21.2) |
|  Mother died before giving birth | 10 (5-17) | 0.1 (0.1-0.2) | 29 (19-40) | 0.3 (0.2-0.4) | 10 (3-16) | 0.1 (0.0-0.2) | 29 (20-40) | 0.3 (0.2-0.4) |
| **HIV status** |  |  |  |  |  |  |  |  |
|  Women infected at the beginning of  the pregnancy | 759 (699-812) | 7.6 (7.0-8.1) | 1510 (1435-1574) | 15.5 (14.8-16.2) | 757 (706-809) | 7.6 (7.1-8.1) | 1507 (1438-1591) | 15.5 (14.8-16.4) |
| Women infected at delivery | 1029 (973-1091) | 10.3 (9.7-10.9) | 1748 (1674-1821) | 18.0 (17.2-18.8) | 1029 (967-1098) | 10.3 (9.7-11.0) | 1746 (1676-1826) | 18.0 (17.2-18.8) |
| Women infected two years after  delivery | 1575 (1503-1649) | 15.7 (15.0-16.5) | 2229 (2133-2317) | 22.9 (22.0-23.9) | 1573 (1499-1661) | 15.7 (15.0-16.6) | 2228 (2145-2303) | 22.9 (22.1-23.7) |
| **ART** |  |  |  |  |  |  |  |  |
|  Started ART during pregnancy (of those infected at delivery) | 674 (630-728) | 65.5 (61.8-69.3) | 846 (789-903)  | 48.4 (46.3-50.5) | 674 (619-728) | 65.5 (61.4-69.7) | 1089 (1029-1149) | 62.3 (59.6-65.0) |
|  Started ART at any stage (of those infected 2 years after birth)\* | 806 (750-858) | 42.8 (40.2-45.7) | 926 (865-984)  | 37.9 (36.2-39.9) | 805 (752-864) | 42.9 (40.4-45.3) | 1184 (1120-1244) | 48.9 (46.8-50.8) |
|  Women on ART at start of second  pregnancy (of those HIV infected at the  beginning)\* | n/a | n/a | 581 (531-623) | 38.5 (35.8-41.2) | n/a | n/a | 278 (245-315) | 18.4 (16.5-20.5) |
| **Loss to follow-up (LTFU)** |  |  |  |  |  |  |  |  |
|  From ANC | 1902 (1818-1981) | 22.6 (21.6-23.5) | 2158 (2077-2235) | 24.5 (23.6-25.3) | 1903 (1835-1988) | 22.6 (21.8-23.5) | 2195 (2102-2283) | 25.0 (23.9-26.0) |
|  From postnatal care | 3888 (3794-3992) | 49.1 (47.5-50.7) | 2310 (2242-2389) | 29.6 (28.6-30.9) | 3891 (3769-3983) | 49.2 (47.2-50.7) | 2347 (2279-2429) | 30.2 (29.1-31.5) |
| **MTCT of HIV in all HIV infected women** |  |  |  |  |  |  |  |  |
| Live births to HIV infected mothers (of  women infected 2 years after delivery) | 1273 (1210-1340) | 80.8 (79.0-82.8) | 1783 (1709-1865) | 80.0 (78.3-81.6) | 1272 (1200-1347) | 80.9 (79.1-82.9) | 1782 (1717-1855) | 80.0 (78.5-81.3) |
| Infants infected with HIV by 6 weeks (of live births to mothers infected) | 136 (114-160) | 10.7 (9.0-12.4) | 156 (135-183) | 8.8 (7.6-10.1) | 138 (115-163) | 10.9 (9.3-12.4) | 170 (145-193) | 9.5 (8.2-10.9) |
| Children infected with HIV by 24 months (of live births to mothers infected 2 years after delivery) | 187 (161-212) | 14.7 (12.9-16.3) | 202 (176-230) | 11.3 (9.9-12.8) | 189 (160-215) | 14.9 (13.1-16.7) | 219 (194-248) | 12.3 (11.0-13.9) |
| **MTCT in women who started ART at first ANC visit or before** |  |  |  |  |
| Live births | 594 (554-642) |  | 1185 (1118-1246) |  | 595 (545-642) |  | 1151 (1089-1213) |  |
| Children infected with HIV by 24 months (of live births to mothers who started ART) | 51 (38-65) | 8.5 (6.4-10.7) | 81 (64-99) | 6.8 (5.4-8.3) | 51 (39-65) | 8.6 (6.7-10.8) | 89 (72-107) | 7.8 (6.1-9.3) |
| **MTCT in women who started ART during pregnancy at a later visit** |  |  |  |  |
| Live births | 28 (19-39) |  | 39 (26-52) |  | 28 (18-37) |  | 50 (38-64) |  |
| Children infected with HIV by 24 months (of live births to mothers who started ART) | 4 (0-7) | 12.6 (0.0-25.0) | 6 (2-10) | 14.4 (5.1-27.0) | 3 (0-7) | 12.2 (0.0-26.1) | 7 (3-13) | 14.9 (6.3-24.5) |
| **MTCT in women who started ART during breastfeeding** |  |  |  |  |
| Live births | 133 (111-156) |  | 83 (64-99) |  | 133 (112-155) |  | 97 (79-115) |  |
| Children infected with HIV by 24 months (of  live births to mothers who started ART) | 40 (29-53) | 30.3 (23.0-39.0) | 27 (16-37) | 32.1 (21.4-41.8) | 41 (29-52) | 30.7 (22.8-38.0) | 30 (21-40) | 30.6 (22.2-39.6) |
| **Deaths** |  |  |  |  |  |  |  |  |
| Women | 88 (71-110) | 0.9 (0.7-1.1) | 213 (187-243) | 2.2 (1.9-2.5) | 86 (68-104) | 0.9 (0.7-1.0) | 213 (185-243) | 2.2 (1.9-2.5) |
| Infants | 213 (189-240) | 2.7 (2.4-3.0) | 209 (185-232) | 2.7 (2.4-3.0) | 215 (189-241) | 2.7 (2.4-3.0) | 213 (190-241) | 2. 8 (2.5-3.1) |

\*Excluding HIV uninfected women who started ART based on false positive HIV test result. ANC, antenatal care; ART, antiretroviral therapy; MTCT, mother to child transmission

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| **Table S6. Outcomes of the scenarios to prevent mother-to-child HIV transmission in Malawi in no PMTCT scenario** |
|  | **1st pregnancy** | **2nd pregnancy** |
| **Number of simulated pregnant women** | 10000 |  | 9706 |  |
| **HIV status** |  |  |  |  |
| Women infected at the beginning of simulation | 993 | 9.9% | 1727 | 17.8% |
| Women infected at the end of simulation | 1790 | 17.9% | 2425 | 25.0% |
| **Number of live births** | 8175 | 81.7% | 7861 | 81.0% |
| **HIV transmission in all HIV infected women** |  |  |  |  |
| Live births to HIV infected mothers (of women infected in the end) | 1473 | 82.3% | 1961 | 80.8% |
| Infants infected with HIV by 6 weeks (of live births to HIV infected mothers) | 289 | 16.2% | 385 | 22.3% |
| Children infected with HIV by 24 months (of live births to HIV infected mothers) | 395 | 22.0% | 506 | 29.3% |
| **Deaths** |  |  |  |  |
| Women | 97 | 1.0% | 239 | 2.5% |
| Infants | 206 | 2.5% | 212 | 2.7% |

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| **Table S7. Total costs and cost-effectiveness ratios of Option B and Option B+ in Malawi.** All values are given for a cohort consisting of 10,000 women in the first pregnancy, together with 95% prediction intervals. Costs are given in US dollars. |
|  | **PMTCT scenario** |
|  | **Option B+** | **Option B** |
|  **1st pregnancy** | **2nd pregnancy** |  **1st pregnancy** | **2nd pregnancy** |
| **Costs of prevention of mother-to-child transmission** |
| ART for mothers | 351,016 (322,750-377,696) | 579,252 (548,584-615,738) | 268,649 (246,088-287,837) | 446,864 (423,664-470,342) |
| Diagnostic tests for mothers (CD4, HIV) | 40,612 (40,192-40,973) | 36,643 (36,237-37,020) | 57,177 (55,885-58,579) | 60,861 (59,549-62,224) |
| HIV tests and ARV prophylaxis for infants | 40,283 (37,726-43,412) | 46,179 (42,861-49,280) | 40,284 (37,186-43,289) | 56,824 (53,387-59,654) |
| ***Total programme costs*** | **431,910 (402,094-457,653)** | **662,074 (630,942-696,392)** | **366,109 (340,159-389,650)** | **564,549 (538,048-592,634)** |
|  Average cost per woman\* | 43 (40-46) | 68 (65-72) | 37 (34-39) | 58 (55-61) |
|  Average cost per infection averted |  | 13,880\*\*\* |  | n/a  |
| **Treating and life expectancy of the infected children** |
| Lifelong ART cost for children  | 284,330 (207,434-355,864)  | 313,095 (242,356-377,792) | 288,994 (225,704-369,804) | 364,512 (286,123-451,335) |
| **Total DALYs** | 3,269 (2,737-3,796) | 3,109 (2,616-3,580) | 3,242 (2,818-3,785) | 3,240 (2,755-3,789) |
| **DALYs averted\*\*** |  | 133\*\*\* |  | n/a |
| **Incremental cost-effectiveness ratio (per DALY averted)\*\*** |  | 841\*\*\* |  | n/a  |

PMTCT, prevention of mother-to-child transmission; ART, antiretroviral therapy; DALY, disability-adjusted life-year; n/a, not applicable. \*Per women included in each pregnancy (1st pregnancies: n=10,000; 2nd pregnancy in Option B+: n=9,715; 2nd pregnancy in Option B+: n=9,716). \*\*To minimize the possibility of stochastic error, we excluded DALYs and ART of children from the first pregnancies.

**Table S8. Results of sensitivity analyses on loss to follow-up for second pregnancy in Option B and Option B+.** All values are given for the cohort including 10,000 women at the beginning of the first pregnancy. Costs are given in US dollars.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **90% annual retentionα** | **75% reduction in LTFUβ** | **Best-case scenarioγ** | **Reduced incidenceδ** |
|  **Option B+** | **Option B** |  **Option B+** | **Option B** |  **Option B+** | **Option B** |  **Option B+** | **Option B** |
| **New infections** |  |  |  |  |  |  |  |  |
|  Children infected with HIV by 24 months in all women | 11.9% | 12.4% | 9.0% | 10.6% | 9.1% | 9.6% | 7.8% | 9.2% |
| Children infected with HIV by 24 months in ART women | 8.9% | 10.2% | 4.7% | 6.8% | 4.4% | 5.3% | 6.8% | 8.1% |
| **Total DALYs (infants from the second pregnancy)** | 3024 | 3305 | 2688 | 2779 | 2656 | 2683 | 1001 | 1180 |
| **DALYs averted** | 2812 | n/a | 912 | n/a | 272 | n/a | 179 | n/a |
| **Incremental cost-effectiveness ratio (per DALY averted)** | 624 | n/a | 2316 | n/a | 4530 | n/a | 206 | n/a |

**α** One-year retention in care among women who started ART based on Option B+ and were not clinically eligible for ART;  **β** Loss to follow-up rates from ANC and postnatal care reduced by 75%; γIncreased access to ANC services (99% accessed ANC, of whom 20% during first trimester), increased probability of HIV status ascertainment (96% tested), and decreased LTFU (by 75% in all stages compared with the main analysis) δ Estimate for West Africa used for HIV incidence during pregnancy and breastfeeding (lowest across the regions of Sub-Saharan Africa; 0.7 per 100 person-years)

**Table S9. Results of cost-effectiveness analysis comparing Options B and B+ with either current rates of ANC attendance, HIV status ascertainment and loss to follow-up, or in the “best-case scenario” (see Table S8).** Costs are given in US dollars.

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| --- | --- | --- |
|  | **Main analysis** | **Sensitivity analysis (“best-case” scenario)** |
|  | **Option B+** | **Option B** | **Option B+** | **Option B** |
| Total eligible costs\* | 1,407,079 | 1,295,170 | 1,438,048 | 1,314,827 |
| DALYs (infants from the second pregnancy) | 3109 | 3242 | 2656 | 2683 |
| DALYs averted\*\* | s/d | n/a | 27 | 559 |
| Incremental cost-effectiveness ratio (per DALY averted)\*\*\* | s/d | n/a | 4564 | 35 |

s/d, strongly dominated; n/a, not applicable.

**Figure S1. Schematic representation of mathematical model for infants.**



**References**

1 Malawi National Statistics Office and Macro ICF. 2010 Malawi Demographic and Health Survey. Calverton,Maryland, USA: http://www.nsomalawi.mw/images/stories/data\_on\_line/demography/MDHS2010/MDHS2010%20report.pdf. Accessed on 10th April 2015

2 Malawi Ministry Of Health. 2014 Clinical Management of HIV in Children and Adults: Malawi integrated guidelines for providing HIV services. Lilongwe: Malawi Ministry of Health; 2014.

3 Malawi Ministry Of Health. Integrated HIV Program Report July -September 2014 . Lilongwe, Malawi: ; 2014.

4 Brinkhof MWG, Pujades-Rodriguez M, Egger M. Mortality of patients lost to follow-up in antiretroviral treatment programmes in resource-limited settings: Systematic review and meta-analysis. *PLoS One* 2009; **4**. doi:10.1371/journal.pone.0005790

5 Hallett TB, Gregson S, Dube S, Garnett GP. The impact of monitoring HIV patients prior to treatment in resource-poor settings: Insights from mathematical modelling. *PLoS Med* 2008; **5**:0403–0412.

6 John GC, Kreiss J. Mother-to-child transmission of human immunodeficiency virus type 1. *Epidemiol Rev* 1996; **18**:149–157.

7 Shapiro RL, Hughes MD, Ogwu A, Kitch D, Lockman S, Moffat C, *et al.* Antiretroviral regimens in pregnancy and breast-feeding in Botswana. *N Engl J Med* 2010; **362**:2282–2294.

8 Cooper ER, Charurat M, Mofenson L, Hanson IC, Pitt J, Diaz C, *et al.* Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr* 2002; **29**:484–494.

9 Ehrnst A, Lindgren S, Dictor M, Johansson B, Sonnerborg A, Czajkowski J, *et al.* HIV in pregnant women and their offspring: evidence for late transmission. *Lancet* 1991; **338**:203–207.

10 Lallemant M, Jourdain G, Le Coeur S, Kim S, Koetsawang S, Comeau AM, *et al.* A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. Perinatal HIV Prevention Trial (Thailand) Investigators. *N Engl J Med* 2000; **343**:982–991.

11 De Cock KM, Fowler MG, Mercier E, de Vincenzi I, Saba J, Hoff E, *et al.* Prevention of mother-to-child HIV transmission in resource-poor countries: translating research into policy and practice. *Jama* 2000; **283**:1175–1182.

12 Johnson LF, Davies MA, Moultrie H, Sherman GG, Bland RM, Rehle TM, *et al.* The effect of early initiation of antiretroviral treatment in infants on pediatric AIDS mortality in South Africa: a model-based analysis. *Pediatr Infect Dis J* 2012; **31**:474–480.

13 Shaffer N, Chuachoowong R, Mock PA, Bhadrakom C, Siriwasin W, Young NL, *et al.* Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Bangkok Collaborative Perinatal HIV Transmission Study Group. *Lancet* 1999; **353**:773–780.

14 Drake AL, Wagner A, Richardson B, John-Stewart G. Incident HIV during pregnancy and postpartum and risk of mother-to-child HIV transmission: a systematic review and meta-analysis. *PLoS Med* 2014; **11**:e1001608.

15 Embree JE, Njenga S, Datta P, Nagelkerke NJ, Ndinya-Achola JO, Mohammed Z, *et al.* Risk factors for postnatal mother-child transmission of HIV-1. *Aids* 2000; **14**:2535–2541.

16 Palombi L, Marazzi MC, Voetberg A, Magid NA. Treatment acceleration program and the experience of the DREAM program in prevention of mother-to-child transmission of HIV. *Aids* 2007; **21 Suppl 4**:S65–71.

17 Leroy V, Newell ML, Dabis F, Peckham C, Van de Perre P, Bulterys M, *et al.* International multicentre pooled analysis of late postnatal mother-to-child transmission of HIV-1 infection. Ghent International Working Group on Mother-to-Child Transmission of HIV. *Lancet* 1998; **352**:597–600.

18 Miotti PG, Taha TE, Kumwenda NI, Broadhead R, Mtimavalye LA, Van der Hoeven L, *et al.* HIV transmission through breastfeeding: a study in Malawi. *Jama* 1999; **282**:744–749.

19 Leroy V, Karon JM, Alioum A, Ekpini ER, van de Perre P, Greenberg AE, *et al.* Postnatal transmission of HIV-1 after a maternal short-course zidovudine peripartum regimen in West Africa. *Aids* 2003; **17**:1493–1501.

20 Becquet R, Bland R, Leroy V, Rollins NC, Ekouevi DK, Coutsoudis A, *et al.* Duration, pattern of breastfeeding and postnatal transmission of HIV: pooled analysis of individual data from West and South African cohorts. *PLoS One* 2009; **4**:e7397.

21 Coutsoudis A, Pillay K, Kuhn L, Spooner E, Tsai WY, Coovadia HM. Method of feeding and transmission of HIV-1 from mothers to children by 15 months of age: prospective cohort study from Durban, South Africa. *Aids* 2001; **15**:379–387.

22 Iliff PJ, Piwoz EG, Tavengwa N V, Zunguza CD, Marinda ET, Nathoo KJ, *et al.* Early exclusive breastfeeding reduces the risk of postnatal HIV-1 transmission and increases HIV-free survival. *Aids* 2005; **19**:699–708.

23 Coutsoudis A, Pillay K, Spooner E, Kuhn L, Coovadia HM. Influence of infant-feeding patterns on early mother-to-child transmission of HIV-1 in Durban, South Africa: a prospective cohort study. South African Vitamin A Study Group. *Lancet* 1999; **354**:471–476.

24 Ciaranello AL, Perez F, Keatinge J, Park JE, Engelsmann B, Maruva M, *et al.* What will it take to eliminate pediatric HIV? Reaching WHO target rates of mother-to-child HIV transmission in Zimbabwe: a model-based analysis. *PLoS Med* 2012; **9**:e1001156.

25 Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, *et al.* National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet* 2012; **379**:2162–2172.

26 Estill J, Tweya H, Egger M, Wandeler G, Feldacker C, Johnson LF, *et al.* Tracing of patients lost to follow-up and HIV transmission: mathematical modeling study based on 2 large ART programs in Malawi. *J Acquir Immune Defic Syndr* 2014; **65:**179-86.

27 Malawi Ministry Of Health. Integrated HIV Program Report July -September 2013. Lilongwe, Malawi: ; 2013.

28 World Bank. World development indicators. World Bank, Washington, USA; 2015. http://data.worldbank.org/indicator. [Accessed 20 May

 2015]

29 Weigel R, Estill J, Egger M, Harries AD, Makombe S, Tweya H, *et al.* Mortality and loss to follow-up in the first year of ART: Malawi national ART programme. *Aids* 2012; **26**:365–373.

30 Tweya H, Gugsa S, Hosseinipour M, Speight C, Ng’ambi W, Bokosi M, *et al.* Understanding factors, outcomes and reasons for loss to follow-up among women in Option B+ PMTCT programme in Lilongwe, Malawi. *Trop Med Int Heal* 2014; **19**:1360–1366.