Comparative cost-effectiveness of Option B+ for prevention of mother-to-child transmission of HIV in Malawi

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Objective: To estimate the cost-effectiveness of prevention of mother-to-child transmission (MTCT) of HIV with lifelong antiretroviral therapy (ART) for pregnant and breastfeeding women ('Option B+') compared with ART during pregnancy or breastfeeding only unless clinically indicated ('Option B').

Design: Mathematical modelling study of first and second pregnancy, informed by data from the Malawi Option B+ programme.

Methods: Individual-based simulation model. We simulated cohorts of 10 000 women and their infants during two subsequent pregnancies, including the breastfeeding period, with either Option B+ or B. We parameterized the model with data from the literature and by analysing programmatic data. We compared total costs of antenatal and postnatal care, and lifetime costs and disability-adjusted life-years of the infected infants between Option B+ and Option B.

Results: During the first pregnancy, 15% of the infants born to HIV-infected mothers acquired the infection. With Option B+, 39% of the women were on ART at the beginning of the second pregnancy, compared with 18% with Option B. For second pregnancies, the rates MTCT were 11.3% with Option B+ and 12.3% with Option B. The incremental cost-effectiveness ratio comparing the two options ranged between about US$ 500 and US$ 1300 per DALY averted.

Conclusion: Option B+ prevents more vertical transmissions of HIV than Option B, mainly because more women are already on ART at the beginning of the next pregnancy. Option B+ is a cost-effective strategy for PMTCT if the total future costs and lost lifetime of the infected infants are taken into account.

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Introduction

About 240 000 children acquired HIV from their mothers in 2013 [1]. In the absence of preventive interventions, the risk of mother-to-child transmission of HIV (MTCT) is estimated at 15–45% [2]. Antiretroviral therapy (ART) for pregnant and breastfeeding women infected with HIV and their infants reduces the risk of MTCT to less than 2% [3–5].

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In 2011, Malawi was the first country to introduce a prevention of mother-to-child transmission (PMTCT) programme known as 'Option B+': all HIV-infected pregnant and breastfeeding women start lifelong ART regardless of their $CD4^+$ cell count or HIV clinical stage. Infants receive daily nevirapine over 6 weeks [6]. Since 2013, Option B+ has been recommended by the WHO as one of two PMTCT strategies. The alternative strategy, 'Option B', recommends ART only for the duration of pregnancy or breastfeeding, unless women qualify for ART for their own health [7].

Option B+ has potential advantages over Option B for mothers, infants and programme delivery. Most studies evaluating the benefits of Option B+ have only considered the clinical benefits to the mother through early initiation of lifelong ART [8,9]. However, Option B+ may also prevent more MTCT than Option B. In Malawi, the fertility rate is high (5.5 births per woman) [10], and many women breastfeed for 2 years or longer [11]. With Option B+, most HIV-infected women are already on ART when they become pregnant the next time, whereas with Option B they need to restart therapy. We estimated the risk of MTCT with Options B+ and B in two subsequent pregnancies, and compared their cost-effectiveness.

Materials and methods

Mathematical model

We developed a mathematical model for MTCT of HIV that simulates the progression of HIV infection. The progression of individuals across healthcare interventions and stages of the disease is represented by a sequence of states and transitions. Transition times are sampled from time-to-event distributions. We used the R package 'gems' [12] which is described in detail elsewhere [13]. Supplementary Text S1, http://links.lww.com/QAD/A862, details the implementation of the model in gems.

We simulated cohorts of 10 000 primigravida, used the results to simulate their infants from conception to 2 years after delivery and, finally, updated mothers' simulation based on the infants' simulation. In Malawi about 98% of women who survive their first pregnancy become pregnant with a second child [10,14]. We sampled 98% of surviving women and repeated the procedure, modelling the mother and her second infant. The model was parameterized with data from a recent analysis of retention in care under Option B+ in Malawi [15], relevant literature on HIV incidence rates of miscarriage, stillbirth and mortality, MTCT, information on demographic characteristics, HIV testing, access to antenatal (ANC) and postnatal care, [16–22], and national HIV prevalence data from Malawi Ministry of Health [23,24] (Table 1; supplementary Table S1, http://links.lww.com/QAD/A862). For the main analysis, we simulated 200 cohorts, and present the mean over all cohorts as well as the 95% prediction interval (6th and 195th value of the individual cohorts, ordered from smallest to greatest). The results for a cohort of 10 000 women are expected to lie within this interval with a 95% probability. For secondary analyses, we ran 10 cohorts, and report the means.

Simulation of pregnant and breastfeeding women

The model consisted of 58 states (Fig. 1, supplementary Table S2, http://links.lww.com/QAD/A862). The simulation starts at conception with each woman proceeding through the stages of pregnancy, delivery and breastfeeding, of HIV infection, and ANC and postnatal care. Women may either be HIV negative, or at an early stage of HIV infection (HIV infection within last 5 years) at the first conception. We did not include women who were at a late stage of HIV infection, or who started ART before the first conception, because the outcomes for these women would not differ between Option B+ and Option B. Women were either in ANC or postnatal care, or out of care if they did not seek care or were lost to follow-up, and could die at any stage.

Simulation of infants

The model included 21 states, representing the development (fetus/infant), HIV status and ART status (supplementary Table S3, http://links.lww.com/QAD/A862, and supplementary Figure S1, http://links.lww.com/QAD/A862). The simulation starts with an HIV-uninfected fetus that becomes at risk of HIV infection if the mother is HIV positive. The risk of MTCT depends on the stage (pregnancy, delivery or postnatal), type of breastfeeding (exclusive or mixed), phase of mother's HIV infection (acute or chronic) and the mother's treatment (ART or no ART). A child receives HIV tests, nevirapine, cotrimoxazole prophylaxis and, if necessary, ART, according to the national guidelines, as long as the mother is alive and in care [25].

Prevention of mother-to-child transmission strategies

We modelled Option B+, Option B and a third scenario wherein no PMTCT services or ART were provided. In the Option B/B+ scenarios, ART was offered to all HIV-positive women in care. In Option B, ART was discontinued after stopping breastfeeding, except for women who were eligible for ART based on their clinical or immunological status at ART initiation. In Option B+, we calculated the cumulative risk of loss to follow-up (LTFU) up to the second pregnancy, to estimate the number of women who were on ART at the beginning of the second pregnancy. In addition to ART, PMTCT services included HIV testing and counselling for pregnant and breastfeeding women attending ANC or postnatal care, and antiretroviral prophylaxis for infants

Table 1. Selected input parameters for the mathematical model of scenarios to prevent mother-to-child transmission of HIV in Malawi.

Variable	Value	Data source
Baseline characteristics		
Age [mean (SD), in years]	19.5 (3.1)	National antenatal data (unpublished data)
HIV prevalence in pregnant women at the beginning of first pregnancy	7.6%	[24]
Rate of access to ANC services for first pregnancy (per person-year)		
Within first trimester of pregnancy	0.38	[24]
Within second trimester of pregnancy	7.2	[24], National antenatal data (unpublished data)
After 6 months of pregnancy	5.7	[24], National antenatal data (unpublished data)
HIV incidence (per person-year)		
During pregnancy	0.047	[16]
Postpartum	0.029	[16]
LTFU in antenatal care		
Probability of no follow-up visit after ART initiation	16.4%	[15]
Rate of LTFU (per person-year)	0.245	[15]
LTFU in postnatal care		
Probability of no follow-up visit after ART initiation	8.9%	[15]
Rate of LTFU with exclusive breastfeeding (per person-year)	0.131	[15]
Hazard ratio of LTFU during mixed breastfeeding compared with exclusive breastfeeding	1.5	Assumption
HIV testing		
Probability of HIV test at ANC first visit	81%	[24], National antenatal data (unpublished data)
Cumulative probability of HIV test after first ANC visit, if no test at first visit	11%	[24], National antenatal data (unpublished data)
Rate during postnatal care if no test before	5	Assumption
HIV transmission during pregnancy and delivery		
In chronic stage without ART: Weibull scale	0.7	See section 2.3, supplementary Text S1, http://links.lww.com/QAD/A862
In chronic stage without ART: Weibull shape	4.2	See section 2.3, supplementary Text S1, http://links.lww.com/QAD/A862
In acute stage (hazard ratio compared with chronic stage)	6	[17]
On ART (hazard ratio compared with no ART)	0.04	[17]
HIV transmission from mother to child during breastfeeding		
During first 3 months of exclusive breastfeeding without ART (rate per person-year)	0.35	[18]
After first 3 months exclusive breastfeeding without ART (rate, after 3 months)	0.09	[19]
In acute stage (hazard ratio compared with chronic stage)	6	[20]
On ART (hazard ratio compared with no ART)	0.04	[21]
During mixed breastfeeding (hazard ratio compared with exclusive breastfeeding)	2.9	[22]

ANC, antenatal care; ART, antiretroviral therapy; LTFU, loss to follow-up.

born to HIV-infected women. Overall 93% of the HIV-infected women started ART [23].

Outcomes

The main outcome was MTCT of HIV (the proportion of infants born to HIV-infected mothers who acquired the infection). We also calculated the proportions of women who were HIV positive at the beginning and at the end of the first and second pregnancy, the proportion of women who attended ANC or postnatal care, and the proportions of HIV-positive women who started ART, and who were on ART at the beginning of the second pregnancy.

Cost-effectiveness analysis

We compared Option B+ with Option B. We included the costs (in US$) of PMTCT services (including HIV tests, consultations and ARVs), and the costs of $CD4^+$ cell counts to determine eligibility for lifelong ART under Option B. For HIV-exposed infants, we itemized the costs of early infant diagnosis (6 weeks after birth), rapid HIV tests (12 and 24 months after birth), ARV prophylaxis and cotrimoxazole prophylaxis (supplementary Table S4, http://links.lww.com/QAD/A862). For future costs of treatment of the infected infants, we considered a range between US$ 50 and US$ 300 per year. We estimated the total disability-adjusted life years (DALYs) and total costs for managing the HIV-infected infants. We assumed that the life expectancy of an uninfected infant would be 60 years [26], but 2 years for an untreated infant infected during pregnancy or delivery, and 10 years for an infant infected during breastfeeding. For the life expectancy of treated infected infants, we considered a range between 20 and 60 years. We assumed that all infants who started ART remain on ART for the

rest of their life. We applied a constant disability weight of 0.135 for all untreated HIV-infected infants, which accounts for HIV and related conditions [27]. We calculated the incremental cost-effectiveness ratio (ICER) between the two scenarios, defined as the additional cost per DALY averted. All costs and DALYs were discounted annually by 3%.

Sensitivity analyses

We performed sensitivity analyses to explore the effect of key model parameters. Retention in care among women who start ART for PMTCT is lower than in general ART programmes [28]. We explored how improved retention would affect MTCT in Options B+ and B. First, we reduced LTFU from ANC and postnatal care by 75%. Second, we increased the 1-year retention in care among women who started ART based on Option B+ and were not clinically eligible for ART from 80% to 90%. Third, we conducted a best-case scenario wherein we increased the rates of attending ANC to 99% (20% of women attending during the first trimester) and HIV testing probability to 96%, and decreased the rates of LTFU by 75%. We also conducted a cost-effectiveness analysis where two scenarios of both Option B+ and Option B were included (one using the parameters of the main analysis, and one from this 'best-case' sensitivity analysis). Finally, we conducted a sensitivity analysis where we applied a lower HIV incidence rate, based on an estimate from West Africa (0.7 per 100 person-years) [16].

Results

Among women who attended ANC, about 95% received an HIV test during the first pregnancy (Fig. 2, supplementary Table S5, http://links.lww.com/QAD/A862). The proportion of women receiving an HIV test was lower in the second pregnancy: 89% with Option B+ and 92% with Option B. About 16% of women were infected with HIV at the end of the first pregnancy, with about half of them having been infected before conception of the second pregnancy. At the end of the second pregnancy 23% of women were infected. About 43% of the women who were HIV positive at the end of the first simulation, had started ART by 2 years after delivery. With Option B+, 68% of the HIV-positive women received ART during the second pregnancy: 39% of the infected women were already on ART at the beginning of the second pregnancy. For Option B, the corresponding percentages were lower: 66 and 18%, respectively.

About 190 (15%) of around 1270 infants born to HIV-positive mothers (including both mothers who started and who did not start ART) were HIV-infected by 24 months after the first pregnancy (Fig. 2). The risk of HIV transmission was lower among women who started ART during pregnancy or breastfeeding (around 13%). After the second pregnancy 202 (11.3%) of 1783 infants born to HIV-positive mothers were infected by 24 months with Option B+, compared with 219 (12.3%) of 1782 with Option B. Among women who started ART at the first ANC visit or were already on ART, the risk of transmission was 8.6% (first pregnancy), 6.8% (second pregnancy, Option B+) or 7.8% (second pregnancy, Option B).

In the scenario with no PMTCT or ART, 22.0 and 29.3% of infants born to infected mothers were infected after 24 months in the first and second pregnancies, respectively (supplementary Table S6, http://links.lww.com/QAD/A862).

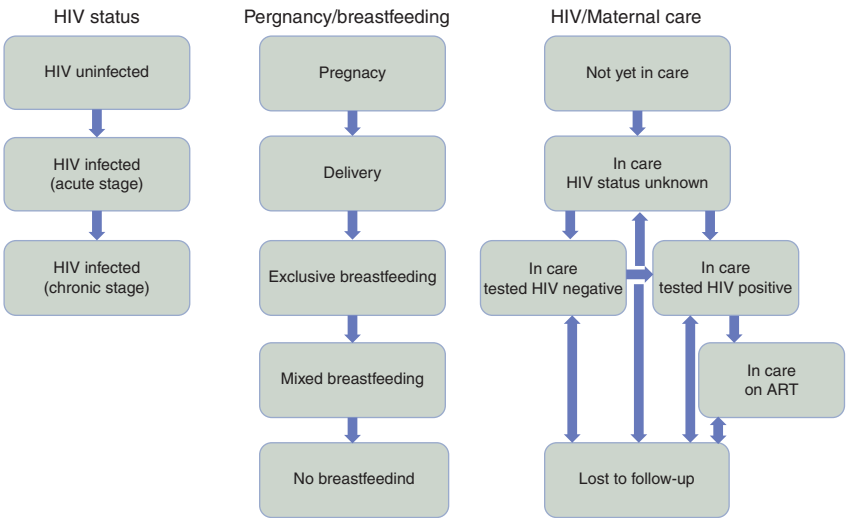

Fig. 1. Schematic representation of the mathematical simulation model for pregnant women. Women progress simultaneously across the stages of HIV status, pregnancy/breastfeeding and HIV/maternal care.

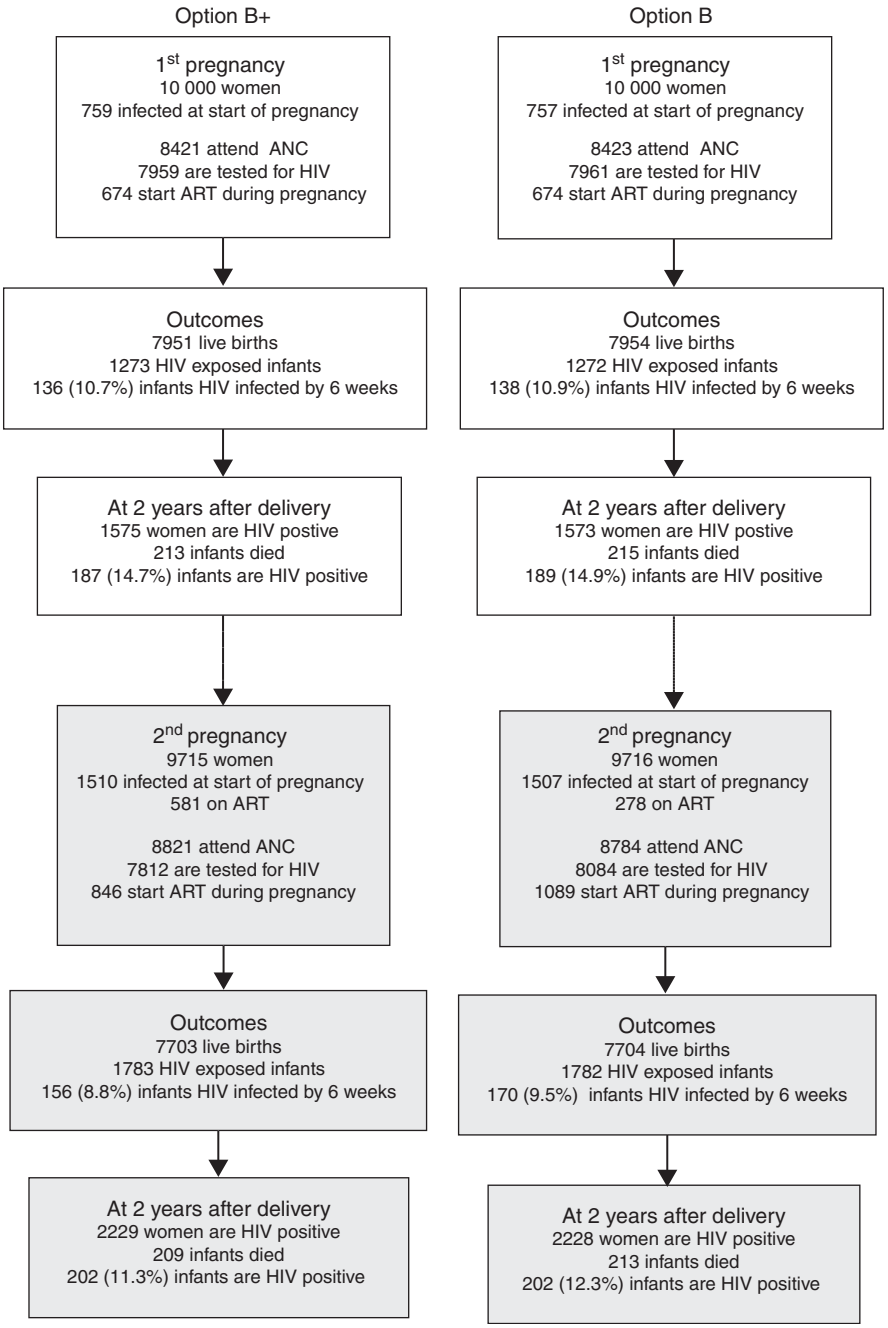

Fig. 2. Main outcomes of the model in Option B+ and Option B prevention of mother-to-child transmission strategies. Differences between Option B+ and Option B during the first pregnancy are because of random variation.

Cost-effectiveness

Figure 3 shows the cost-effectiveness of Option B+ compared with Option B for the cohort of 10 000 women with a first pregnancy, as a function of the annual costs of HIV care and the life expectancy of the treated HIV-infected infants. Assuming that the annual cost is US$ 193.60 (the current price of first-line ART) and the treated HIV-infected infants live for 50 years, the total costs for PMTCT in the first pregnancy for Option B+ and Option B were US$ 431 910 and US$ 366 109, respectively (supplementary Table S7, http://links.lww.com/QAD/A862). During the second pregnancy, the costs were US$ 662 074 (Option B+) and US$ 564 549 (Option B). The cost of averting one HIV infection by Option B+ was US$ 13 880. We estimated that under the assumptions on life expectancy and future HIV care costs mentioned above, lifelong HIV services for the infants from the second pregnancies would cost US$ 313 095 (Option B+) or US$ 364 512 (Option B). The total number of DALYs in the infected infants under these assumptions for the second pregnancy were 3109 (Option B+) and 3240 (Option B), and the ICER of Option B+

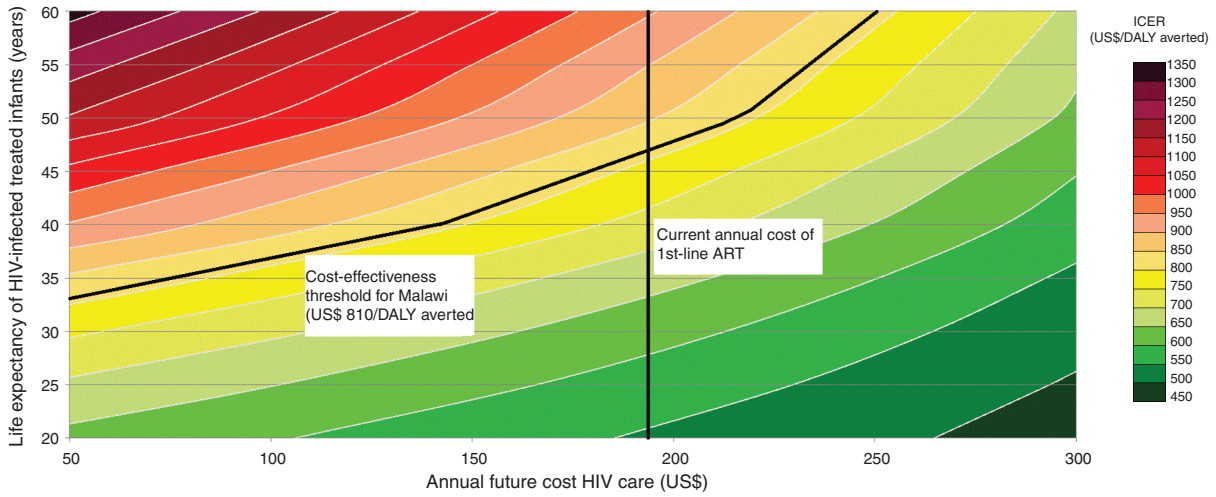

Fig. 3. Cost-effectiveness of Option B+ compared with Option B for preventing mother-to-child transmission. The colour represents the incremental cost-effectiveness ratio, depending on the assumed life expectancy of vertically infected infants who receive treatment (vertical axis), and the assumed annual cost of HIV care in the future (horizontal axis). ICER, incremental cost-effectiveness ratio; DALY, disability-adjusted life year.

compared with Option B was US$ 841 per DALY averted. The cost-effectiveness improved with decreasing life expectancy of the treated infants, and with increasing annual costs of HIV care. With a life expectancy of 20 years for the treated infants and annual HIV care cost of US$ 300, the ICER was less than US$ 500 per DALY averted. With a life expectancy of 60 years for the treated infants and annual HIV care cost of US$ 50, the ICER was over US$ 1300 per DALY averted.

Sensitivity analyses

When LTFU was reduced by 75% during ANC and postnatal services, the risk of MTCT for the second infant was 10.6% in Option B, and 9.0% in Option B+ (supplementary Table S8, http://links.lww.com/QAD/A862). The ICER was US$ 2316 per DALY averted, assuming 50-year life expectancy for infected and treated infants, and annual cost of US$ 193.60 per year. Improved retention between the end of breastfeeding of the first infant and the beginning of the second pregnancy did not influence the risk of MTCT (supplementary Table S8, http://links.lww.com/QAD/A862). In the best-case scenario, the risk of MTCT was 9.1% with Option B+ and 9.6% with Option B (Fig. 4, supplementary Table S8, http://links.lww.com/QAD/A862). Option B+ was less cost-effective compared with Option B than in the main analysis (ICER US$ 4530 per DALY averted). In the cost-effectiveness analysis comparing four scenarios (Options B+ and B with either current standard of care, or 'best-case' scenario), Option B+ with current standard of care was strongly dominated by Option B with 'best-case' scenario (supplementary Table S9, http://links.lww.com/QAD/A862). However, we did not include the possible additional costs of interventions that would be needed to improve the access to ANC, rates of HIV testing, and retention. In the sensitivity analysis with a low HIV incidence rate, the risk of MTCT was even lower (7.8 and 9.2% in Option B+ and B, respectively, during the second pregnancies), and the ICER was substantially lower than in the main analysis (US$ 206 per DALY averted; supplementary Table S8, http://links.lww.com/QAD/A862).

Discussion

This modelling study for Malawi showed that compared with Option B, Option B+ averts one additional vertical infection of HIV per 200 HIV-infected pregnant women if we consider both the first and second pregnancy. The difference is largely explained by the higher proportion of women on ART at the time of the second conception (39%) with Option B+, compared with Option B (18%). Implementing Option B+ costs more than Option B because of the greater need for ART, but the additional costs required under Option B+ are largely offset by the decreased future health costs because of the averted infections.

In Malawi, 682 000 children were estimated to be born in 2014 [29], of whom at least 50 000 to HIV-infected mothers. If we conservatively assume that HIV-positive women give birth to two to three children during the time they are infected, about 20 000 HIV-infected women are expected to have their first child after their HIV seroconversion each year. We can, therefore, expect Option B+ to prevent about 100 additional vertical HIV infections every year.

Malawi has a high fertility rate (5.5 births per woman) [10], which is similar in HIV-infected women [30].

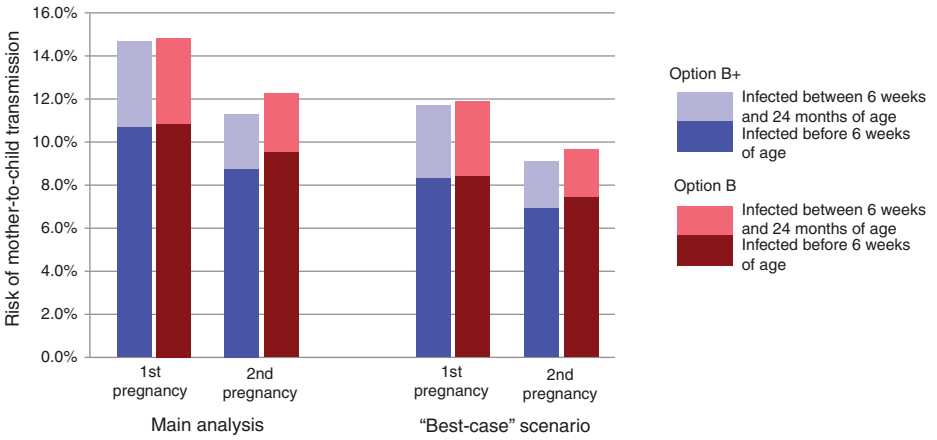

Fig. 4. Risk of mother-to-child transmission in the main analysis and a sensitivity analysis representing the 'best-case' scenario. In the 'best-case' sensitivity analysis, we assumed that 99% of all women attend antenatal care (20% within the first trimester), 96% of women attending ANC will be tested for HIV, and LTFU is reduced by 75% from the level of the main analysis. LTFU, loss to follow-up.

Women become pregnant soon after stopping breastfeeding, and 38% of women do not access ANC services until 24 weeks of gestation [11]. The women tend to access ANC only later when the pregnancy is already visible [31]. The late enrolment into ANC in combination with the high fertility rate reduces the effectiveness of Option B because early vertical transmission is not prevented. Several factors influence the women's decision on when to seek antenatal care. Some women do not understand the importance of ANC beyond the first visit [32,33]. Health programmes should involve communities by disseminating information about the importance of early ANC. Other studies reported that fear of witchcraft [31,32], religion [34], education [31,34] and economic security [31,32] are associated with access to ANC. Educating and economically empowering women could improve early access to ANC and utilization of health services. However, we also showed that even if access to ANC can be accelerated, Option B+ performs better than Option B. In this case, Option B+ is however less cost-effective.

Although the total costs of the implementation of Option B+ are clearly higher than those of Option B, Option B+ can improve survival and quality of life in the long term, and reduce the costs of HIV care in the future, by preventing new infections. Depending on the assumptions on the long-term survival and care of the infected infants, the ICER of Option B+ compared with Option B ranged between less than US$ 500 and more than US$ 1300 per DALY averted. If we assume that the life expectancy is no more than 45 years, and that the annual cost of treating an infected person is at least US$ 200, the ICER is less than US$ 810 (three times the per-capita gross domestic product of Malawi) [10], and Option B+ can be considered cost-effective [35]. In many sub-Saharan African countries, US$ 1300 per DALY averted would be below per-capita gross domestic product and therefore, very cost-effective. In settings, where the HIV incidence is lower than in southern Africa, Option B+ could also be considerably more cost-effective, since the number of acutely infected pregnant women is lower, and most infected women can therefore benefit from the early PMTCT. Previous studies have reported other benefits of Option B+ such as promotion of maternal health through early uptake of ART [8,9]. Option B+ will also prevent sexual transmissions of HIV because the women remain on ART after the breastfeeding period [36]. These benefits were not considered in our study.

The high LTFU has raised concerns about the effectiveness of Option B+. Currently, up to 24% of women who initiate ART as part of Option B+ in high volume clinics are lost to follow-up by 6 months after ART initiation [15]. About 47% of pregnant women lost to follow-up received antiretroviral drugs only once and never returned for their subsequent appointment [28], indicating that they never started ART. Our results showed that improving retention during pregnancy and breastfeeding could further reduce the risk of MTCT under both PMTCT strategies. The difference in the number of HIV infections between strategies remained relatively stable across the sensitivity analyses assuming different rates of LTFU. These analyses thus suggest that the suboptimal retention among women who start life-long ART only for PMTCT does not affect the comparative effectiveness of Option B+. Reducing LTFU made Option B+ less cost-effective because of the greater need for ART, but this does not account for the benefits that better retention has for the women's own health.

Few modelling studies have compared Option B+ with Option B from the point of view of PMTCT. An analysis of the cost-effectiveness of Option B+ in Kenya, Zambia, South Africa and Vietnam found that Option B+ prevents more vertical transmissions than Option B [37].

The studies were based on a simple deterministic model and did not consider the changing risk of MTCT during pregnancy, delivery and breastfeeding. Other mathematical modelling studies have explored the benefits and cost-effectiveness of Option B+ [8,9], but these studies have focused on the maternal outcomes, and ignored the potential of Option B+ to prevent additional vertical transmissions of HIV. Fasawe *et al.* [8] found that Option B+ substantially improves the mothers' survival in Malawi, making it a cost-effective strategy. Ciaranello *et al.* [9] found that the life expectancy of the mothers in Zimbabwe is higher in Option B+ than other PMTCT strategies. A cost-effectiveness analysis based on that study further supported the implementation of Option B+. These studies were also conducted before empirical data from routine Option B+ programmes became available to inform modelling studies.

Our study has several potential limitations. First, we did not model the viral load trajectories explicitly and used time since infection to determine the risk of HIV infection. Second, the model focused only on prevention of new vertical HIV infections. We did not model the effect of the start–stop approach implemented in Option B on the mother's health, the potential adverse effects associated with starting and stopping ART, or the effect of Option B+ on horizontal transmission. Third, we did not model subsequent pregnancies beyond two. However, we would expect that most women who were infected with HIV during or before their first pregnancy would be receiving ART for their own health at the time of the third pregnancy. We also excluded women who were already on ART or in a late stage of HIV infection at the first pregnancy, but the cascade of PMTCT care for these women does not differ between the PMTCT strategies, and excluding them should not influence our results.

The cost-effectiveness analysis was based on approximations about the long-term cost-savings and benefits of PMTCT. The true lifetime costs and loss of life among newly infected infants depend on the future of HIV treatment and care. In our main analysis, we assumed that the life expectancy of treated HIV-infected children is 10 years less than that of uninfected children. This may be overoptimistic based on the current situation of HIV care in resource-limited settings, but realistic when we take into account the likely improvements in the future. The life expectancy assumption was tested in a sensitivity analysis, where we found that the assumed life expectancy did not importantly influence the cost-effectiveness of Option B+ compared with Option B.

In conclusion, our results support the implementing of the Option B+ strategy. Despite the higher costs, Option B+ will likely become a cost-effective strategy in the long term. Although LTFU reduces the benefit of PMTCT, the effectiveness of Option B+, compared with Option B, did not depend on assumptions regarding retention. Option B+ should be considered the preferred strategy to prevent MTCT of HIV in resource-limited settings with high fertility rate.

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H.T., O.K., M.E. and J.E. planned the study. H.T. and J.E. developed the mathematical model, and H.T., A.D.H. and L.T. conducted the statistical analyses. H.T. wrote the first draft of the manuscript, which was revised by M.E. and J.E. All authors contributed to the interpretation of the results and the final version of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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