

https://dspace.org/

Costeffectiveness of intervention combinations towards the elimination of vertical transmission of HIV in limitedresource settings a mathematical modelling study

J Chevalier; M Hasen; E Coskun; K Sy; E et al ...

https://hdl.handle.net/10539/43580
WOS

Downloaded from a DSpace repository. https://dspace.org/

Cost-effectiveness of intervention combinations towards the elimination of vertical transmission of HIV in limited-resource settings: a mathematical modelling study

Joshua M Chevalier, Megan A Hansen*, Elif Coskun, Karla Therese L Sy, Janeen Drakes, Stephanie Dowling, Amanda Williams, Sarah Jenkins, Carolyn Amole, Prudence Haimbe, Felton Mpasela, Hilda Shakwelele, Brooke E Nichols*

Summary

Background Since 2000, there has been a substantial global reduction in the vertical transmission of HIV. Despite effective interventions, gaps still remain in progress towards elimination in many low-income and middle-income countries. We developed a mathematical model to determine the most cost-effective combinations of interventions to prevent vertical transmission.

Methods We developed a 12-month Markov model to follow a cohort of women of childbearing age (aged 15–49 years) in Zambia (n=1 107 255) who were either pregnant, in delivery, or breastfeeding; the population included in the model reflects the estimated number of pregnant women in Zambia from the 2018 Zambia Demographic and Health Survey. The model incorporated nine interventions: infant prophylaxis; three different HIV retesting schedule options; oral pre-exposure prophylaxis; maternal peer-support groups; regimen shift; tracing of loss to follow-up; and point-of-care viral load testing. We analysed incident HIV infections among mothers and infants, intervention costs, and evaluated 190 scenarios of different combinations of inventions to calculate the incremental cost-effectiveness ratios (ICERs) over 1 year.

Findings Three interventions with the greatest reduction in vertical transmission, individually, were support groups for 80% of those in need (35% reduction in infant infections), HIV retesting schedules (6·5% reduction), and infant prophylaxis (4·5% reduction). Of all 190 scenarios evaluated, eight were on the cost-effectiveness frontier (ie, were considered to be cost-effective); all eight included increasing infant prophylaxis, regimen shift, and use of support groups. Excluding the highest-cost scenarios, for a 1–22% increase in total budget, 23–43% of infant infections could be prevented, producing ICERs between US$244 and $16 242.

Interpretation Using the interventions modelled, it is possible to reduce vertical transmission and to cost-effectively prevent up to 1734 infant HIV infections (43% reduction) in Zambia over a period of 1 year. To optimise their effect, these interventions must be scaled with fidelity. Future work is needed to incorporate evidence on additional innovative interventions and HIV risk factors, and to apply the model to other country contexts to support targeted implementation and resource use.

Funding The ELMA Foundation.

Copyright © 2024 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

Lancet Glob Health 2024; 12: e457–66

See **Comment** page e354

*Contributed equally

Department of Global Health, Boston University School of Public Health, Boston, MA, USA (J M Chevalier MPH, M A Hansen MPH, E Coskun MPH, K T L Sy PhD, B E Nichols PhD); **Department of Medical Microbiology, Amsterdam University Medical Center, Amsterdam, Netherlands** (J M Chevalier, M A Hansen, B E Nichols); **Clinton Health Access Initiative, Boston, MA, USA** (J Drakes MPH, S Dowling MPH, A Williams MPH, S Jenkins BS, C Amole BA); **Clinton Health Access Initiative, Lusaka, Zambia** (P Haimbe MPhil, F Mpasela BA, H Shakwelele MSc); **FIND, Geneva, Switzerland** (B E Nichols); **Health Economics and Epidemiology Research Office, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa** (B E Nichols)

Correspondence to:
Assoc Prof Brooke Nichols, Department of Medical Microbiology, Amsterdam University Medical Center, 1105AZ Amsterdam, Netherlands
b.e.nichols@amsterdamumc.nl

Introduction

Progress in the prevention of childhood HIV transmission has been substantial since the year 2000, largely because of the scale-up of antiretroviral therapy (ART) and targeted programmes for the prevention of mother-to-child transmission (PMTCT). In 2000, there were 520 000 new HIV infections among children aged 0–14 years worldwide, which decreased to 200 000 new infections in 2015.[1] However, it is estimated that 160 000 incident HIV infections occurred among children aged 0–14 years in 2021, which is far more than the global target of an incidence of less than 20 000 HIV infections by 2020.[1–3] To encourage advancements in paediatric HIV prevention and treatment, in 2022, global partners launched the Global Alliance to End AIDS in Children by 2030.[4]

Much of the remaining childhood HIV infection is driven by vertical transmission (sometimes called mother-to-child transmission) in resource-limited settings. HIV is transmitted vertically through several pathways: pregnant and breastfeeding women living with HIV who have high viral loads can transmit the virus during pregnancy, labour, delivery, or breastfeeding.[5] Vertical transmission results from pregnant and breastfeeding women with HIV not being diagnosed or initiated on ART, discontinuing treatment, or becoming incidentally infected with HIV during pregnancy or breastfeeding.[6]

Zambia's extensive PMTCT programme has evolved substantially over the past decade to reach a greater proportion of its pregnant population, yet 3800 incident HIV infections occurred among children aged 0–14 years in 2021, representing 2·4% of all infections globally.[7–10] In

Downloaded for Anonymous User (n/a) at University of the Witwatersrand Johannesburg from ClinicalKey.com by Elsevier on September 06, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Research in context

Evidence before this study

We searched PubMed for articles published between Jan 1, 2013, when guidelines for prevention of mother-to-child transmission (PMTCT), or vertical transmission, included option B+ (lifelong antiretroviral therapy [ART] for pregnant and breastfeeding women with HIV), and Sept 1, 2022, without any language restrictions. We used the search terms "elimination/prevention", "PMTCT/vertical transmission", "HIV", "interventions", and/or "mathematical modeling/modeling", and/or "cost-effective". Evidence before this study included mathematical modelling studies, cohort studies, implementation research, reviews, meta-analyses, and cost-effectiveness analyses of vertical transmission interventions. Studies have found option B+ (lifelong ART), HIV testing during late antenatal care, and pre-exposure prophylaxis for pregnant and breastfeeding women to be cost-effective individually. Option B+ and at least one HIV test during antenatal care are standard PMTCT policy across sub-Saharan African countries. Other studies, including modelling studies, found interventions promoting initiation and retention in HIV care programmes to be effective at reducing vertical transmission of HIV. However, no other modelling studies looked at a diverse slate of vertical transmission interventions in combination and their potential to be cost-effective.

Added value of this study

The aim of this study was to develop a mathematical model to analyse various vertical transmission interventions individually and in combination, to determine the optimal cost-effective scenarios leading to a reduction in vertical transmission of HIV in Zambia. Through the analysis of 190 strategic combinations of vertical transmission interventions, we identified one cost-saving and eight cost-effective scenarios that would lead to annual reductions in vertical transmission. Maternal peer-support groups, HIV retesting during late antenatal care, infant prophylaxis, and regimen shift were the most beneficial interventions at preventing vertical transmission. In combination these interventions can cost-effectively prevent between 23% and 43% of vertical transmissions over 1 year. However, even under the most optimistic scenarios, elimination of vertical transmission, by the WHO definition (ie, ≤50 cases per 100 000 livebirths and a vertical transmission rate of <5% for breastfeeding populations), is still out of reach under the selected slate of interventions. This analysis provides important insight into the resource allocation of PMTCT programmes and identifies gaps to be filled by additional intervention research.

Implications of all the available evidence

Vertical transmission interventions that lead to increased initiation and retention in HIV care, resulting in viral suppression, such as HIV retesting or testing, peer-to-peer support groups, and lifelong ART, are essential to reducing vertical transmission. Moreover, the implementation of these interventions in combination would be cost-effective. Intervention effectiveness remains to be improved in low-income and middle-income settings and new interventions should be developed to achieve elimination of vertical transmission of HIV.

Zambia, 99% of pregnant women attended at least one antenatal care visit as of 2018, and 90% received an HIV test with a result in 2021, indicating high coverage of services.[9] Additionally, among pregnant and breastfeeding women with HIV, an estimated 81–98% were receiving ART in 2021.[10] Although many women are receiving their necessary HIV treatment and antenatal care, vertical transmission of HIV remains prevalent. To address this gap, the Zambia PMTCT programme looks to scale up early infant diagnosis and point-of-care viral load testing for pregnant and breastfeeding women on ART, and to increase adherence to the programme through maternal support groups and by minimising mother and infant pairs lost to follow-up.[11] Although some of these interventions are already present in Zambia, they can be expanded to reach greater proportions of pregnant and breastfeeding women, to move towards eliminating vertical transmission.

Therefore, we developed a Markov model calibrated to Zambia to determine whether further scale-up of existing interventions or implementation of new interventions, in addition to currently existing universal test-and-treat approaches to reduce HIV infections, could eliminate vertical transmission. We aimed to understand what set of interventions scaled to different levels would be most cost-effective. Although this model was calibrated to Zambia, it can be adapted to other countries to guide country-specific PMTCT responses.

Methods

Population

A population of women of childbearing age (aged 15–49 years) in Zambia (n=1 107 255) who were either pregnant, giving birth, or breastfeeding was modelled for 12 months, to estimate the relative incidence of vertically transmitted HIV infections, the effect of various vertical transmission interventions, and associated costs (a conceptual model framework displaying how the interventions were implemented is presented in figure 1). At the model start, the population was distributed among those who were pregnant, giving birth, and breastfeeding, within mutually exclusive HIV-related health states (HIV-negative, HIV infected but undiagnosed, diagnosed but not taking ART, taking or prescribed ART and not virally suppressed, and virally suppressed). The baseline population included in the model reflects the estimated number of pregnant women in Zambia from the 2018

Downloaded for Anonymous User (n/a) at University of the Witwatersrand Johannesburg from ClinicalKey.com by Elsevier on September 06, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

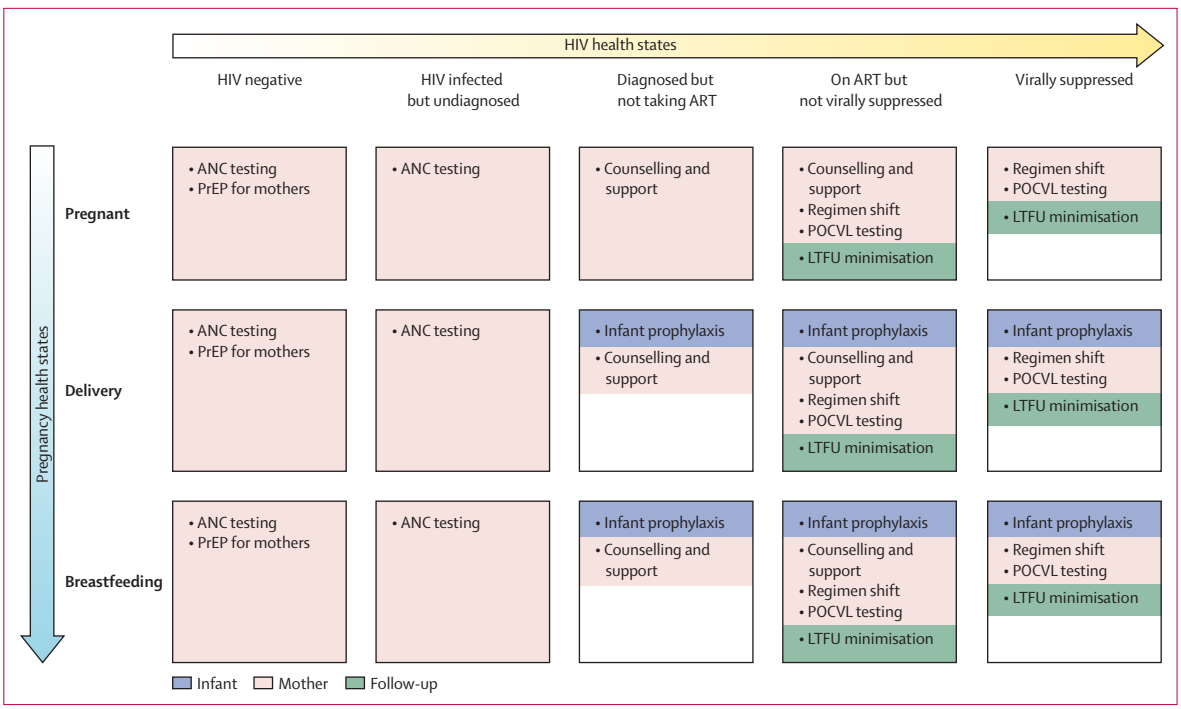

Figure 1: **Vertical transmission interventions included in the Markov model**
Interventions were assigned on the basis of HIV health state and pregnancy health state of the individual. The expected effect of each intervention differs by pregnancy health state and HIV health state. ANC=antenatal care. ART=antiretroviral therapy. LTFU=loss to follow-up. POCVL=point-of-care viral load. PrEP=pre-exposure prophylaxis.

Zambia Demographic and Health Survey. Together, the breastfeeding population plus those giving birth was estimated to be double the number of pregnant women in Zambia, given an average breastfeeding duration of 19 months in 2018 (appendix pp 1–2).[12] In Zambia, HIV prevalence among women of childbearing age (15–49 years) was 13·8% in 2018.[10] Distributions of the pregnant and breastfeeding population in respective health states are shown in the appendix (p 1). The modelled population was open: each month individuals could become pregnant, give birth, or begin breastfeeding, and they could also transition between HIV-related health states. Transition rates between population states can be found in the appendix (pp 2–3). This research uses a Markov compartmental model that was parameterised using publicly available data from the literature; given the nature of the study, formal ethical approval was not required.

Baseline model

The baseline Markov compartmental model (built in Microsoft Excel version 16.80) was implemented in 12 monthly timepoints and was parameterised to publicly available data from the Zambia Demographic and Health Survey, the Zambia Population-Based HIV Impact Assessment, UNAIDS, and published literature.[10–13] At each timepoint, transition rates created movement between compartments (ie, pregnancy health states), either from pregnancy to birth and breastfeeding, or between mutually exclusive HIV-related health states. The monthly rate of pregnancy was estimated from the crude birth rate in Zambia.[12] When individuals transitioned to the breastfeeding compartment, they remained through the end of the model to account for 19 months of breastfeeding. Movement between health states followed progression along the HIV-care continuum; however, regression in HIV health state was attributable to viral rebound or loss to follow-up.[14,15] Health state-dependent rates of vertical transmission were derived from the literature.[16–18] Vertically transmitted HIV infections and new incident infections among pregnant and breastfeeding women were calculated at each timepoint and summarised over 12 months.

See Online for appendix

Interventions

We conducted a literature review on PubMed to compile transmission interventions and effectiveness measures that could be feasibly incorporated into a model framework. The review was limited to articles published between Jan 1, 2013, and Sept 1, 2022. We used the search terms "elimination/prevention", "PMTCT/vertical transmission", "HIV", "interventions", and/or "mathematical modeling/modeling", and/or "cost-effective". No language restrictions were applied, as only articles in the English language were identified. The criteria for inclusion were quantitative evidence of

Downloaded for Anonymous User (n/a) at University of the Witwatersrand Johannesburg from ClinicalKey.com by Elsevier on September 06, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

	Description	Effect measure (range)	Model impact
Infant prophylaxis[19]	6-week course of nevirapine for infants exposed to HIV	50% (40–70)	Reduction in vertical transmission; implemented for 50% of population at baseline
Regimen shift[20]	ART regimen shift from efavirenz-based (TLE) to dolutegravir-based (TLD) regimens	64% (31–106)	Increased rate of transition to viral suppression; implemented for 80% of population at baseline
HIV retesting option one[21]	HIV retesting during late antenatal care, delivery, or 6 weeks postpartum*	19% (12–20)*	Reduction in vertical transmission
HIV retesting option two[21]	HIV retesting during late antenatal care, delivery, or 6 weeks postpartum, with an additional test at 14 weeks postpartum†	21% (13–21)†	Reduction in vertical transmission
HIV retesting option three[21]	HIV retesting during late antenatal care, delivery, or 6 weeks postpartum and additional retesting every 3 months during breastfeeding‡	22% (13–23)‡	Reduction in vertical transmission
PrEP[22,23]	PrEP provided to pregnant and breastfeeding women who are HIV-negative (assuming mixed adherence)	65% (26–83)	Reduction in risk of HIV infection among pregnant and breastfeeding women
Maternal peer-support groups[24]	Mothers in HIV care are enrolled in a mother-to-mother support group programme	87% (60–89)	Reduction in vertical transmission
Loss to follow-up tracing[25]	Immediate tracing of patient after missed clinic visit *vs* no tracing	29% (12–44)	Reduction in rate of loss to follow-up
POCVL testing[26]	Viral load testing at point-of-care *vs* standard laboratory viral load testing	10·3% (3·9–16·4)	Increased rate of viral suppression

POCVL=point-of-care viral load. PrEP=pre-exposure prophylaxis. TLD=tenofovir, lamivudine, and dolutegravir. TLE=tenofovir, lamivudine, and efavirenz. *Option one. †Option two. ‡Option three.

Table 1: **Key model input parameters: intervention effect measures**

	Cost (drugs, laboratory, staff, and overhead)	Timeframe
Infant prophylaxis[29]	$12·86	Per 6-week treatment
Antenatal HIV test[30]	$2·99	Per test
Pre-exposure prophylaxis[30]	$16·89	Per month
Antiretroviral therapy[31]		
TLD	$10·39	Per month
TLE	$10·67	Per month
Maternal peer-support groups[31]	$1·39	Per session
Loss to follow-up tracing[31]	$4·25	Per person traced
Point-of-care viral load[32,33]	$8·03	Additional cost per test above centralised viral load testing

All prices are in US dollars. TLD=tenofovir, lamivudine, and dolutegravir. TLE=tenofovir, lamivudine, and efavirenz.

Table 2: **Unit costs of interventions from the provider perspective**

reducing vertical transmission, or movement of pregnant and breastfeeding women living with HIV along the HIV-care continuum (ie, initiating ART or having viral suppression). Modelled interventions, relative measures of effect, and impact are presented in table 1. Interventions were as follows: infant prophylaxis for infants exposed to HIV; ART regimen shift from tenofovir, lamivudine, and efavirenz (TLE) to tenofovir, lamivudine, and dolutegravir (TLD), all taken orally once daily; three mutually exclusive HIV retesting schedule options; oral daily pre-exposure prophylaxis (PrEP) for any women who were pregnant and breastfeeding and HIV-negative (not considering risk or eligibility); HIV-positive mother-to-mother peer-support groups (hereafter referred to as maternal peer-support groups); tracing of those lost to follow-up; and point-of-care viral load testing. HIV retesting schedule options included an HIV retest in the late antenatal care period, at delivery or up to 6 weeks postpartum (option one), one additional test at 14 weeks postpartum (option two), or additional retesting every 3 months during breastfeeding (option three).

Interventions were presumed to decrease vertical transmission by promoting retention and thereby increasing transition rates along the HIV-care continuum, decreasing the rate of HIV incident infection, or reducing the overall rate of vertical transmission during pregnancy, delivery, and breastfeeding. Different combinations were analysed by implementing the use of interventions individually or simultaneously at various levels of scale-up. Interventions were implemented broadly within the population in need for a specified proportion of the population. Upon implementation, interventions were scaled up from respective baseline estimates to levels within their theoretical maximums—the maximum proportion of the population in need who could feasibly be reached under current programmes, determined from the literature.[19–26] The following theoretical maximums were included: 90% of all infants exposed to HIV receiving prophylaxis; 98% regimen shift from TLE to TLD regimens; 90% HIV retesting (option one); 85% retesting (option two); 80% retesting (option three); 80% maternal peer-support groups; 10% of any women who were pregnant and breastfeeding and HIV-negative receiving PrEP; 90% lost to follow-up tracing; and 60% point-of-care viral load testing. At baseline, only two interventions were implemented before scale-up, with 50% of infants exposed to HIV receiving prophylaxis and 80% of pregnant and breastfeeding women on ART receiving a TLD regimen.[11,27,28]

Costing

Costs were estimated from the provider perspective and sourced from previous costing studies in Zambia, then inflated to the 2022 US dollar (table 2).[30,32,34] The costing equations (appendix pp 5–6) considered the number of pregnant and breastfeeding women in each compartment, on which compartments the interventions

Downloaded for Anonymous User (n/a) at University of the Witwatersrand Johannesburg from ClinicalKey.com by Elsevier on September 06, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

exert effects, and the selected proportion of the population that receive the interventions. At baseline, the cost of ART for all pregnant and breastfeeding women receiving treatment, the cost of prophylaxis for infants exposed to HIV, and one assumed antenatal care HIV test during pregnancy were included.

Cost-effectiveness analysis

All interventions were analysed individually and in various combinations, comprising 190 distinct scenarios. The effectiveness measure for each scenario was the total number of maternal and infant infections averted. The additional cost for each scenario was calculated with respect to the baseline. A cost-effectiveness analysis was done with the incremental cost-effectiveness ratio (ICER) representing the cost for each additional HIV infection averted compared with the previous scenario on the cost-effectiveness frontier.

Sensitivity analysis

To capture relative uncertainty in estimated model parameters, a univariate sensitivity analysis was done on both baseline and intervention parameters. For the baseline HIV epidemiological parameters in Zambia, estimated ranges were considered from the literature that affected the total number of incident infant HIV infections over 12 months. For the interventions, ranges in effect measures were considered from the literature and were scaled to either 80% of the total population in need or 80% of the theoretical maximum when such was less than 80%. The intervention sensitivity analysis outcome was the total number of infant HIV infections averted over 12 months.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

In the baseline model, given current use of existing interventions, we expected 3994 infant infections and 5451 infections among pregnant and breastfeeding women in Zambia. Our modelled estimates were similar to those from UNAIDS, which in 2021 were 3800 incident infections among infants.[35] Given an HIV incidence among women of 5·38 per 1000 women aged 15–49 years, we expected 5776 incident infections within the modelled pregnant and breastfeeding population. These data estimates validated the parameterisation of the baseline model.

190 combinations of interventions were modelled and compared to baseline, with outcomes of interest being infant HIV infections averted, maternal HIV infections averted, and total cost of selected interventions. Interventions were first analysed individually and scaled up to their theoretical maximums. The three individual interventions giving the greatest proportional reduction in vertical transmission, when scaled to reach 80% of the population in need, were infant prophylaxis, maternal peer-support groups, and HIV retesting. Scaling up infant prophylaxis reduced vertical transmission by 4·5%, maternal peer-support groups reduced vertical transmission by 35·0%, and the three HIV retesting schedule options reduced vertical transmission by 6·3% (option one), 6·5% (option two), and 6·4% (option three). All other interventions, when scaled up to their respective

	Intervention	Additional infant infections averted	Additional maternal infections averted	Additional reduction in vertical transmission	Total cost	ICER (additional cost per infection averted)
Baseline	50% infant prophylaxis, 80% transitioned to TLD ART	0	0	0%	$21 025 879	NA
Scenario 1	84–98% of population transitioned to TLD ART	6–26	0	0·15–0·65%	$20 934 151–21 005 505	Cost-saving
Scenario 2	60% scale-up infant prophylaxis, 50% maternal support groups, 98% TLD ART	916	0	22·93%	$21 249 701	$244
Scenario 3	20% scale-up infant prophylaxis, 80% maternal support groups, 98% TLD ART	1424	0	35·65%	$21 396 749	$289
Scenario 4	80% scale-up infant prophylaxis, 80% maternal support groups, 98% TLD ART	1475	0	36·93%	$21 608 157	$4145
Scenario 5	80% scale-up infant prophylaxis, 80% maternal support groups, 50% lost to follow-up tracing, 98% TLD ART	1480	0	37·06%	$21 635 059	$5380
Scenario 6	80% scale-up infant prophylaxis, 80% maternal support groups, 80% HIV retesting option one, 80% lost to follow-up tracing, 98% TLD ART	1706	0	42·71%	$25 246 262	$15 979
Scenario 7	80% scale-up infant prophylaxis, 80% maternal support groups, 90% HIV retesting option one, 90% lost to follow-up tracing, 98% TLD ART	1734	0	43·42%	$25 701 026	$16 242
Scenario 8	80% scale-up infant prophylaxis, 90% HIV retesting option one, 80% maternal support groups, 10% pregnant and breastfeeding women on PrEP, 98% TLD ART	1746	354	43·72%	$47 465 344	$59 465
Scenario 9	80% scale-up infant prophylaxis, 85% HIV retesting option two, 80% maternal support groups, 10% pregnant and breastfeeding women on PrEP, 90% lost to follow-up minimisation, 60% POCVL testing, 98% TLD ART	1780	354	44·57%	$59 102 276	$342 263

Costs are in US dollars. Scenario percentages represent the proportion of the population receiving the intervention. ICERs were calculated by comparing scenarios to the previous strategy that was considered to be cost-effective. ART=antiretroviral therapy. ICER=incremental cost-effectiveness ratio. POCVL=point-of-care viral load. PrEP=pre-exposure prophylaxis. TLD=tenofovir, lamivudine, and dolutegravir.

Table 3: **Intervention combinations that were on the cost-effectiveness frontier**

Downloaded for Anonymous User (n/a) at University of the Witwatersrand Johannesburg from ClinicalKey.com by Elsevier on September 06, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

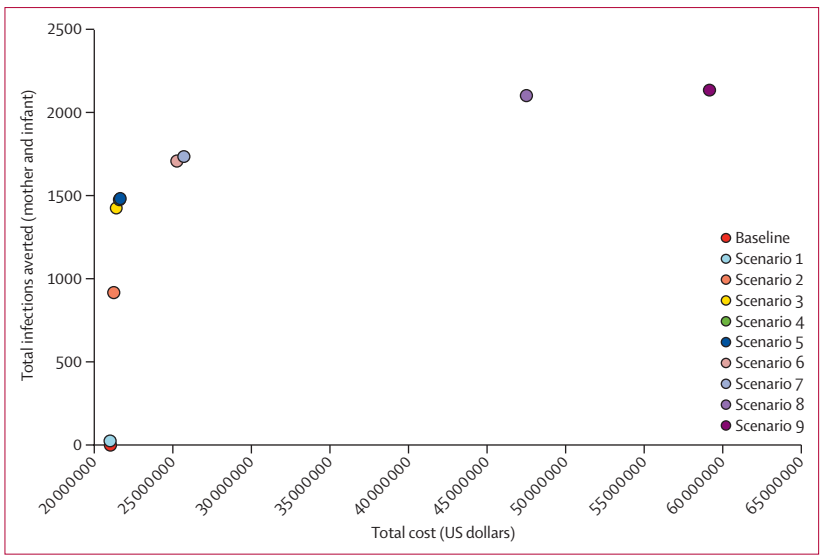

Figure 2: **Total infections averted among both mothers and infants by total cost (US dollars) among cost-effective interventions**
The scenario labels correspond with the scenario numbers distinguished in table 3.

theoretical maximums, reduced vertical transmission by about 1% or less (regimen shift [0·7%], loss to follow-up tracing [1·0%], PrEP [0·8%], and point-of-care viral load testing [1·2%]). PrEP was the only intervention that reduced incident infections among pregnant and breastfeeding women, with 354 infections averted (0·2% reduction) when administered to 10% of all HIV-negative pregnant and breastfeeding women, without risk-based targeting. When scaling PrEP beyond its theoretical maximum to 25% of pregnant and breastfeeding women and all other interventions at 100%, the maximum reduction in infant infections expected under the modelled conditions was 54·7%.

The cost-effectiveness analysis identified one cost-saving scenario and eight scenarios on the cost-effectiveness frontier (ie, considered to be cost-effective; table 3; figure 2). Regimen shift from TLE to TLD was cost saving, reflecting the decreased monthly cost of ART for TLD compared with TLE. All nine scenarios on the cost-effectiveness frontier included scaling up infant prophylaxis, transitioning 98% of pregnant and breastfeeding women to TLD, and use of maternal peer-support groups. The three most cost-effective scenarios (scenarios 7–9; table 3; figure 2) reduced infant infections by 43·4–44·6% (1734–1780 infections averted), with ICERs from US$16 242 to $342 263, and total PMTCT budget increases of 18·1–22·2%. There were two substantial increases in ICERs among the cost-effective scenarios. The first occurred between scenarios 3 and 4 (table 3; figure 2), when infant prophylaxis was substantially scaled (from 20% to 80%), resulting in high costs for low impact. The same was true for the second large increase in ICERs seen in scenarios 8 and 9 (table 3; figure 2), both of which incorporated PrEP, thereby significantly increasing total cost with minimal gains in averted infections among infants. The scenario with a 44·6% reduction in vertical transmission and the greatest ICER ($342 263) included all seven interventions.

When looking beyond 1 year and considering the lifetime costs of HIV-related care for infants infected with HIV, we can estimate the annual costs saved for the PMTCT programme. The top three most cost-effective scenarios prevented more than 43·4% of vertically transmitted infant infections during 1 year (1734–1780 infant infections), with the estimated annual cost of an infant infected with HIV being $521·15–624·29, and would save the PMTCT programme approximately $0·903–1·110 million.[34,36]

HIV epidemiological parameters and the rate of loss to follow-up were varied from their estimates in the source literature (figure 3A). The metrics with the greatest range in outcomes were the proportion of HIV infections diagnosed (2961–5285 infant infections) and ART coverage among pregnant and breastfeeding women in Zambia (3165–4823 mothers). Modifying these outcomes moderately affected the expected number of infant infections in the model, but considering that our output aligned with estimated data on infant infections, the selected parameter values at baseline indicated best estimates. The effectiveness of each intervention at preventing transmission was varied to determine which interventions had the greatest variability and effect on reducing vertical transmission; this analysis indicated that the interventions with the greatest reduction in vertical transmission also have the greatest variability (maternal peer-support groups, HIV retesting, and infant prophylaxis; figure 3B). However, even upon considering alternative estimates from the effect measure ranges, these interventions maintained the greatest reduction in vertical transmissions.

Discussion

Many countries with a substantial HIV burden, particularly low-income and middle-income countries in sub-Saharan Africa, have made progress in preventing vertical transmission, yet struggle to meet PMTCT targets. Current vertical transmission interventions can lead to substantial reductions in incident cases when used in the right combination, but have not yet given us the ability to reach elimination in low-income and middle-income settings. Elimination of vertical transmission under the WHO definition of less than 50 cases per 100 000 livebirths is out of reach under the modelled conditions and 1-year timeframe in this analysis. This conclusion is represented with a hypothetical, and likely infeasible scenario, in which all interventions are implemented for 100% of the population, except for PrEP at 25%, with a maximum reduction of 54·7% in infant infections, resulting in a final vertical transmission rate of 160 infant HIV

Downloaded for Anonymous User (n/a) at University of the Witwatersrand Johannesburg from ClinicalKey.com by Elsevier on September 06, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

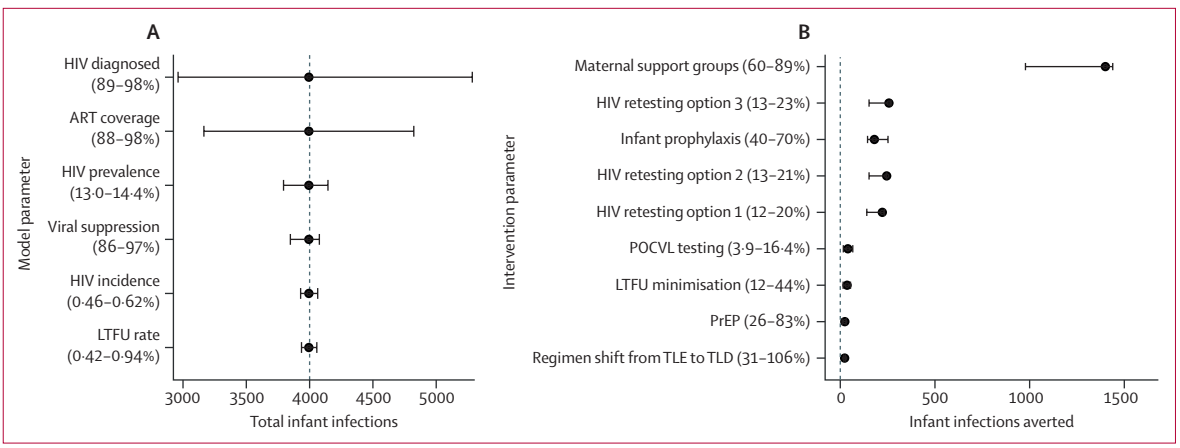

Figure 3: **Univariate sensitivity analysis of (A) baseline HIV epidemiological parameters in Zambia and the expected number of annual vertical transmissions and (B) intervention effectiveness measure parameters representing the expected number of infant HIV infections averted after 1 year**
The range for each parameter estimate is shown in parentheses. The dashed line in graph A represents model output under best estimates at 3994 infant infections. Effect measure ranges in parentheses correspond to those presented in table 3. ART=antiretroviral therapy. LTFU=loss to follow-up. POCVL=point-of-care viral load. PrEP=pre-exposure prophylaxis. TLD=tenofovir, lamivudine, and dolutegravir. TLE=tenofovir, lamivudine, and efavirenz.

infections per 100 000 livebirths. Because of the unrealistic costs of this scenario, it was not included in the cost-effectiveness analysis. Therefore, to eliminate vertical transmission, it is important to improve the effectiveness of these interventions and develop new, innovative interventions for PMTCT programmes.

Although the model results did not indicate achieving elimination of vertical transmission, between 35% and 44% of new infant infections can cost-effectively be reduced through scale-up of currently available interventions. The interventions with the greatest individual effect on incident vertical transmissions were infant prophylaxis and those that improved ART initiation and retention along the HIV-care continuum, which comprised increased maternal HIV retesting and maternal peer-support groups. Infant prophylaxis prevents the establishment of HIV infection among infants exposed to HIV and is particularly beneficial when HIV testing is done at or before delivery. HIV retesting diagnoses more incident and undetected infections, initiating pregnant and breastfeeding women into HIV care, and reducing the risk of vertical transmission. HIV retesting options one (ie, HIV retesting during late antenatal care, delivery, or 6 weeks postpartum) and two (ie, HIV retesting during late antenatal care, delivery, or 6 weeks postpartum, with an additional test at 14 weeks postpartum) both fell on the cost-effectiveness frontier (ie, were considered to be cost-effective), whereas option three (ie, HIV retesting during late antenatal care, delivery, or 6 weeks postpartum and additional retesting every 3 months during breastfeeding) was not found to be cost-effective, because it only marginally improved infections prevented at a greater cost with respect to HIV retesting option two. Maternal peer-support groups promote ART retention through the advice and guidance of mothers who are HIV positive, leading to higher rates of viral suppression, minimising the risk of vertical transmission.

The interventions found to be less effective at reducing overall vertical transmission over 1 year (regimen shift, loss to follow-up tracing, PrEP, and point-of-care viral load testing) led to reductions of 1% or less. This finding is largely because of the populations these interventions are targeted to, their respective coverage levels, and their relative effects. Regimen shift and point-of-care viral load testing are targeted to individuals who are already taking ART, but either have a low risk of transmission or are not virally suppressed, meaning there is a small number of women who could benefit from these interventions in terms of vertical transmission. Although PrEP prevents incident infections among women during pregnancy and breastfeeding, it is limited by a low level of coverage, mixed adherence (with oral PrEP), and it is more effective when targeted through risk (ie, risk-informed PrEP) in settings with greater than 2% prevalence of high viral load.[37] The effect of PrEP is also likely to improve with the introduction of long-acting products. Loss to follow-up tracing promotes retention in ART care and is an important component of HIV care programmes, but has a relatively low effect measure in this analysis, limiting its impact. However, these interventions, in combination, remain important to closing the existing gaps in eliminating vertical transmission and are key components of several scenarios on the cost-effectiveness frontier.

For a 2·9% increase in the budget of PMTCT programmes with an ICER of $5380, approximately 37% of infant infections were prevented with an 80% scale-up of infant prophylaxis (90% final coverage) and maternal peer-support groups (80% final coverage), immediate tracing of 50% of those lost to follow-up, and 98% TLD for those on ART. For a 22·2% increase in

Downloaded for Anonymous User (n/a) at University of the Witwatersrand Johannesburg from ClinicalKey.com by Elsevier on September 06, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

budget and an ICER of $16 242, up to 43% of infant infections were prevented. This scenario included TLD for 98% of those on ART, scaling infant prophylaxis and maternal support groups to 80%, targeting 90% of pregnant and breastfeeding women for HIV retesting in late antenatal care, delivery, or within 6 weeks postpartum, and tracing 90% of those lost to follow-up. The two final scenarios on the cost-effectiveness frontier that averted 44–45% of infections require at least a 126% budget increase for a 1% gain in outcomes. These increased costs are driven by PrEP and the high ICERs indicate poor efficiency, limiting the feasibility of this intervention as implemented (without risk targeting).

Our results indicated that increased funding for PMTCT programmes should largely be dedicated to scaling up the provision of infant prophylaxis and interventions that increase entry to and retention along the HIV-care continuum, particularly maternal support groups. Promotion of entry to and retention within the HIV-care continuum also requires increased maternal retesting to identify and initiate women who are HIV positive into care and then subsequently achieving and maintaining viral suppression through ART. Should funding needs be met in these other categories, strategic distribution of PrEP to at-risk populations of pregnant women as part of the PMTCT programme might then be beneficial. The emphasis on implementing and scaling up maternal retesting and support groups does not diminish the effectiveness of other interventions, but results indicated these interventions are the most cost-efficient under the modelled conditions. These results also provide evidence for potential donors to make decisions in which their funding could be targeted to maximise the reduction of incident vertical transmission HIV infections.

To the best of our knowledge, no other modelling study has modelled a country-wide population of pregnant and breastfeeding women to evaluate the effect of several vertical transmission interventions simultaneously and their potential for cost-effectiveness. Larsson and colleagues[38] modelled PMTCT programme services in Uganda, finding increased HIV testing during antenatal care combined with ART during pregnancy and breastfeeding could decrease childhood HIV infections by up to 60%. McCarthy and colleagues[39] developed a Markov model to estimate the effect of retention interventions from the Integrating and Scaling up PMTCT through Implementation Research initiative on the probabilities of vertical transmission of HIV. They found retention interventions, including a mother mentor programme, significantly reduced vertical transmission and an estimated approximately 3000 vertically transmitted infections could be averted across Nigeria, Malawi, and Zimbabwe. Further research by the Drug Resource Enhancement against AIDS and Malnutrition Program found that strategies such as peer-to-peer education and social support interventions increase retention among pregnant and breastfeeding women in HIV care.[40] Ngambi and colleagues[31] did a literature review of model-based cost-effectiveness studies on lifelong ART for pregnant and breastfeeding women (option B+). Most studies found beneficial outcomes for lifelong ART and maintained that option B+ is cost-effective. Beyond option B+, universal ART for the entire population (not limited to pregnant and breastfeeding women) is currently the standard policy in Zambia and was assumed for all initiated pregnant women in the model. The evidence from the literature supports our findings that increased diagnosis, and ART treatment coverage and retention, specifically through social programmes and maternal support, are imperative to closing the gaps in the elimination of vertical transmission.

Vertical transmission interventions not modelled included partner testing and involvement or other counselling-based retention alternatives. The model was limited by the availability of data. Intervention effectiveness was limited by results from the source literature; likewise, additional interventions did not have the available effectiveness data and therefore could not be included. Interventions were based on studies from other sub-Saharan African countries that were used as a proxy for Zambia (given the need for time-relevant data with quantitative effect measures), and might not fully reflect the effect within the Zambian population. We evaluated uncertainty through a sensitivity analysis; however, further studies are needed to better understand the effect of these interventions in Zambia. This model can also serve as an instrument for analysing vertical transmission interventions in other country contexts. Parameterising this model to other high-burden countries could serve as a useful tool to guide country-specific responses to prevent vertical transmission. Additionally, our modelled population was not stratified by risk, and interventions, such as PrEP, maternal retesting, and ART resistance, were implemented broadly, a notable limitation that might influence health outcomes and costs. In future modelling analyses, risk-based targeting of interventions could increase effectiveness.

Using the interventions modelled, it is possible to cost-effectively reduce vertical transmission by 23–43%. To optimise impact, high-impact interventions such as maternal HIV retesting and maternal support groups should be prioritised. With additional funding, other effective interventions can be scaled up to advance the goals of the Global Alliance to End Pediatric AIDS. Future work is needed to incorporate evidence on innovative interventions and HIV risk factors. This model can be used as a tool to improve PMTCT programmes in Zambia and other sub-Saharan African countries with strategic funding allocation. Additional research on intervention effectiveness is needed for future models to guide policy and decision making to eliminate vertical transmission of HIV.

Downloaded for Anonymous User (n/a) at University of the Witwatersrand Johannesburg from ClinicalKey.com by Elsevier on September 06, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Contributors

JMC, MAH, EC, JD, SD, KTLS, and BEN conceptualised the study. JMC, MAH, EC, and KTLS did the literature reviews and compiled data for model parameterisation. BEN collected cost data. JD, SD, and BEN oversaw data collection and parameterisation. JMC and KTLS developed the model structure. JMC and MAH did the data analysis. JMC, MAH, and BEN had full access to all data in the study. JD, SD, and BEN verified underlying data and assumptions. JD, SD, AW, SJ, CA, FM, PH, and HS critically evaluated the study. All authors contributed to reviewing and editing the manuscript for submission.

Declaration of interests

We declare no competing interests.

Data sharing

We acknowledge the importance of transparent and responsible data sharing to foster scientific collaboration and advance research. The data used for this study were gathered from publicly available literature and do not contain any information necessitating de-identification. The model built for this study is readily accessible in the appendix; therefore, data generated and analysed in this study are also indefinitely available upon publication. For additional information, interested parties can contact JMC (j.m.chevalier@amsterdamumc.nl) or MAH (m.hansen@amsterdamumc.nl).

References

1 UNICEF. HIV statistics global and regional trends UNICEF DATA. 2022. https://data.unicef.org/topic/hivaids/global-regional-trends/ (accessed Aug 31, 2022).

2 UNAIDS. AIDSinfo: global factsheets. 2021. https://aidsinfo.unaids.org/ (accessed Aug 31, 2022).

3 UNAIDS. In danger: UNAIDS global AIDS update. Geneva: Joint United Nations Programme on HIV/AIDS, 2022.

4 The Global Alliance to end AIDS in Children. Children & AIDS. https://www.childrenandaids.org/global-alliance (accessed Aug 31, 2022).

5 WHO. Updated recommendations on HIV prevention, infant diagnosis, antiretroviral initiation and monitoring. Geneva: World Health Organization, 2021.

6 Yah CS, Tambo E. Why is mother to child transmission (MTCT) of HIV a continual threat to new-borns in sub-Saharan Africa (SSA). *J Infect Public Health* 2019; **12:** 213–23.

7 Mwanza J, Kawonga M, Gray GE, Doherty T, Mutale W. Evolution of prevention of mother to child transmission of HIV policy in Zambia: application of the policy triangle to understand the roles of actors, process and power. *Glob Public Health* 2021; **10:** 1–15.

8 Population-Based HIV Impact Assessment. Zambia population-based HIV impact assessment. *J Int AIDS Soc* 2016; **2016:** 1–4.

9 UNAIDS. Country progress report: Zambia. 2020. https://www.unaids.org/sites/default/files/country/documents/ZMB_2020_countryreport.pdf (accessed Aug 31, 2022).

10 UNAIDS. AIDSinfo: epidemic and response: Zambia. 2021. https://aidsinfo.unaids.org (accessed Aug 31, 2022).

11 President's Emergency Plan For AIDS Relief. Zambia Country Operational Plan 2021 Strategic Direction Summary. PEPFAR. May 11, 2021. https://www.state.gov/wp-content/uploads/2021/09/Zambia_SDS_Final-Public_Aug-11-2021.pdf (accessed April 18, 2022).

12 Zambia Statistics Agency, Ministry of Health Zambia, ICF. Zambia demographic and health survey 2018. Lusaka, Zambia, and Rockville, MA, USA: Zambia Statistics Agency, Ministry of Health, and ICF, 2019.

13 Ministry of Health Zambia. Zambia population-based HIV impact assessment (ZAMPHIA) 2016: final report. Lusaka: Ministry of Health, 2019.

14 Meireles MV, Pascom A, Duarte EC, McFarland W. Comparative effectiveness of first-line antiretroviral therapy: results from a large real-world cohort after the implementation of dolutegravir. *AIDS* 2019; **33:** 1663–68.

15 Chi BH, Mutale W, Winston J, Phiri W, Price JT, Mwiche A. Infant HIV-free survival in the era of universal antiretroviral therapy for pregnant and breastfeeding women: a community based cohort study from rural Zambia. *Pediatr Infect Dis J* 2018; **37:** 1137–41.

16 Volmink J, Marais B. HIV: mother-to-child transmission. *BMJ Clin Evidence* 2008; **1:** 0909.

17 Dinh TH. Impact of timing of antiretroviral treatment and birth weight on mother-to-child human immunodeficiency virus transmission: findings from an 18-month prospective cohort of a nationally representative sample of mother-infant pairs during the transition from option A to option B+ in Zimbabwe. *Clin Infect Dis* 2017; **66:** 576–85.

18 Meyer L, Phillips TK, McIntyre JA, et al. HIV viraemia and mother-to-child transmission risk after antiretroviral therapy initiation in pregnancy in Cape Town, South Africa. *HIV Med* 2017; **18:** 80–88.

19 Hurst SA, Appelgren KE, Kourtis AP. Prevention of mother-to-child transmission of HIV type 1: the role of neonatal and infant prophylaxis. *Expert Rev Anti Infect Ther* 2015; **13:** 169–81.

20 Kintu K, Malaba TR, Nakibuka J, et al. Dolutegravir versus efavirenz in women starting HIV therapy in late pregnancy (DolPHIN-2): an open-label, randomised controlled trial. *Lancet HIV* 2020; **7:** e332–39.

21 Meisner J, Roberts DA, Rodriguez P, et al. Optimizing HIV retesting during pregnancy and postpartum in four countries: a cost-effectiveness analysis. *J Int AIDS Soc* 2021; **24:** e25686.

22 Sheth AN, Rolle CP, Gandhi M. HIV pre-exposure prophylaxis for women. *J Virus Erad* 2016; **2:** 149–55.

23 Hanscom B, Janes HE, Guarino PD, et al. Brief report: preventing HIV-1 infection in women using oral preexposure prophylaxis: a meta-analysis of current evidence. *J Acquir Immune Defic Syndr* 2016; **73:** 606–08.

24 Hunduma F, Gebrehanna E, Adugna Debela F. Determinants of mother-to-child transmission of HIV in public hospitals of West Shewa Zone, Central Ethiopia: case-control study. *HIV/AIDS* 2021; **13:** 435–43.

25 Estill J, Tweya H, Egger M, 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* 1999; **65:** e179–86.

26 Drain PK, Dorward J, Violette LR, et al. Point-of-care HIV viral load testing combined with task shifting to improve treatment outcomes (STREAM): findings from an open-label, non-inferiority, randomised controlled trial. *Lancet HIV* 2020; **7:** e229–37.

27 Kebaya LMN, Wamalwa D, Kariuki N, Admani B, Ayieko P, Nduati R. Efficacy of mobile phone use on adherence to nevirapine prophylaxis and retention in care among the HIV-exposed infants in prevention of mother to child transmission of HIV: a randomized controlled trial. *BMC Prediatrics* 2021; **21:** 186.

28 Kaiser JL, Fong RM, Ngoma T, McGlasson KL, Biemba G, Hamer DH. The effects of maternity waiting homes on the health workforce and maternal health service delivery in rural Zambia: a qualitative analysis. *Hum Resource Health* 2019; **17:** 93.

29 Nichols BE, Cele R, Jamieson L, et al. Community-based delivery of HIV treatment in Zambia: costs and outcomes. *AIDS* 2021; **35:** 299–306.

30 Hendrickson C, Long LC, van Rensburg C, et al. The early-stage comprehensive costs of routine PrEP implementation and scale-up in Zambia. *medRxiv* 2021; published online Jan 1. https://doi.org/10.1101/2021.12.18.21268023.

31 Ngambi PG, Kalungia AC, Law MR, et al. Evidence on the cost-effectiveness of lifelong antiretroviral therapy for prevention of mother-to-child transmission of HIV: implications for resource-limited countries in sub-Saharan Africa. *Expert Rev Pharmacoecon Outcomes Res* 2017; **17:** 459–67.

32 Girdwood SJ, Nichols BE, Moyo C, Crompton T, Chimhamhiwa D, Rosen S. Optimizing viral load testing access for the last mile: geospatial cost model for point of care instrument placement. *PLoS One* 2019; **14:** e0221586.

33 Nichols BE, Girdwood SJ, Crompton T, et al. Monitoring viral load for the last mile: what will it cost? *J Int AIDS Soc* 2019; **22:** e25337.

34 Frank SC, Cohn J, Dunning L, et al. Clinical impact and cost-effectiveness of incorporating point-of-care (POC) assays into early infant HIV diagnosis (EID) programs at 6 weeks of age in Zimbabwe: a modelling study. *Lancet HIV* 2019; **6:** e182–90.

35 UNAIDS. UNAIDS data 2021. https://www.unaids.org/en/resources/documents/2021/2021_unaids_data (accessed Aug 31, 2022).

Downloaded for Anonymous User (n/a) at University of the Witwatersrand Johannesburg from ClinicalKey.com by Elsevier on September 06, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

36 Desmonde S, Frank SC, Coovadia A, et al. Cost-effectiveness of preemptive switching to efavirenz-based antiretroviral therapy for children with human immunodeficiency virus. *Open Forum Infect Dis* 2019; **6:** ofz276.

37 Phillips AN, Bershteyn A, Revill P, et al. Cost-effectiveness of easy-access, risk-informed oral pre-exposure prophylaxis in HIV epidemics in sub-Saharan Africa: a modelling study. *Lancet HIV* 2022; **9:** e353–62.

38 Larsson EC, Ekström AM, Pariyo G, et al. Prevention of mother-to-child transmission of HIV in rural Uganda: modelling effectiveness and impact of scaling-up PMTCT services. *Glob Health Action* 2015; **8:** 26308.

39 McCarthy E, Joseph J, Foster G, et al. Modeling the impact of retention interventions on mother-to-child transmission of HIV: results from INSPIRE studies in Malawi, Nigeria, and Zimbabwe. *J Acquir Immune Defic Syndr* 2017; **75** (suppl 2)**:** S233–39.

40 Liotta G, Marazzi MC, Mothibi KE, et al. Elimination of mother-to-child transmission of HIV infection: the drug resource enhancement against AIDS and malnutrition model. *Int J Environ Res Public Health* 2015; **12:** 13224–39.

Downloaded for Anonymous User (n/a) at University of the Witwatersrand Johannesburg from ClinicalKey.com by Elsevier on September 06, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.