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What is needed to eliminate new pediatric HIV infections: The contribution of model-based analyses

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Abstract

Purpose of Review—Computer simulation models can identify key clinical, operational, and economic interventions that will be needed to achieve the elimination of new pediatric HIV infections. In this review, we summarize recent findings from model-based analyses of strategies for prevention of mother-to-child HIV transmission (MTCT).

Recent Findings—In order to achieve elimination of MTCT (eMTCT), model-based studies suggest that scale-up of services will be needed in several domains: uptake of services and retention in care (the PMTCT “cascade”), interventions to prevent HIV infections in women and reduce unintended pregnancies (the “four-pronged approach”), efforts to support medication adherence through long periods of pregnancy and breastfeeding, and strategies to make breastfeeding safer and/or shorter. Models also project the economic resources that will be needed to achieve these goals in the most efficient ways to allocate limited resources for eMTCT. Results suggest that currently recommended PMTCT regimens (WHO Option A, Option B, and Option B +) will be cost-effective in most settings.

Summary—Model-based results can guide future implementation science, by highlighting areas in which additional data are needed to make informed decisions and by outlining critical interventions that will be necessary in order to eliminate new pediatric HIV infections.

Keywords

pediatric HIV; modeling; elimination; PMTCT; cost-effectiveness

Introduction

In 2009, UNAIDS called for the elimination of new pediatric HIV infections by 2015 [1-3]. Elimination was defined as reducing the total number of new infant infections worldwide by 90%, or decreasing the risk of mother-to-child HIV transmission (MTCT) to <5%. Shortly after, the WHO released its 2010 guidelines for prevention of MTCT (PMTCT), again emphasizing the goal of eliminating pediatric HIV, and the Presidents Emergency Plan for AIDS Relief (PEPFAR) put forth its “Blueprint for an AIDS-free Generation” [4,5].

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The feasibility of eliminating MTCT (eMTCT) is supported by a growing body of data, which demonstrate MTCT rates as low as 1-5%, even in breastfeeding infants [6-11]. However, these excellent results are reported from select populations: women and children on antiretrovirals (ARVs) and enrolled in clinical trials or followed closely in research studies. The true number of infant HIV infections in a population, however, will also include infants born to women with unknown HIV status, thus receiving no ARVs for PMTCT, and infants who are lost to follow-up prior to early infant HIV diagnostic testing (EID), perhaps related to illness or death. Such infants are at greatest risk for HIV infection [12].

Computer simulation models can help clinicians and policymakers understand the rates of MTCT that are anticipated at the population level when all mothers and infants are considered, and therefore provide useful information about what will be necessary to truly achieve eMTCT targets. In addition, computer models can add value to traditional research methodologies, such as clinical trials and cohort studies, by integrating available data from multiple sources, projecting long-term clinical and economic outcomes beyond study periods, and identifying influential parameters for which additional data are need. In this review, we outline the role of model-based analyses in understanding the feasibility of eMTCT. We focus first on the clinical and operational aspects needed for PMTCT programs to reach “elimination” goals, and next on the cost-effectiveness and budgetary requirements of these efforts.

Clinical and operational requirements necessary to eliminate new pediatric HIV infections

Model-based analyses have highlighted the importance to eMTCT of: 1) uptake and retention throughout a “cascade” of PMTCT-related care, 2) medication adherence, 3) breastfeeding duration, and 4) the potential harms and benefits of more intensive PMTCT regimens.

The “PMTCT cascade of care” and the “four prongs” of maternal-child health

Effective PMTCT requires pregnant women and their infants to access healthcare services at many steps in a “PMTCT cascade of care,” which includes presentation to antenatal care, HIV and CD4 testing and result return, availability and patient acceptance of ARVs, and retention in care and medication adherence throughout pregnancy and breastfeeding [12,13]. Barker and colleagues were the first to use model-based analyses to demonstrate the multiplicative effect of drop-out at each step in this cascade [12-14]. For example, programs achieving 90% uptake at each of 8 steps in the cascade are in fact providing full services to only $(0.9)^8$, or 43%, of patients truly in need of care [13,15]. Furthermore, such high levels of uptake for individual steps in the cascade, while reported in some programs, are likely not the norm [15]. Two recent meta-analyses summarize reported uptake levels at various points in the PMTCT cascade, and highlight the high levels of drop-out seen over the course of care [16,17]. Worldwide, only 57% of mothers and 42% of infants are estimated to receive complete PMTCT services through pregnancy and the immediate post-partum period [18,19].

Model-based analyses can project the uptake of PMTCT services needed to reach eMTCT goals. Mahy *et al* projected that eMTCT targets cannot be met unless more than 90% of pregnant, HIV-infected women complete the PMTCT cascade (Figure 1) [14]. Other recent model-based analyses, despite different model structure and data inputs, have generated very similar results [12,13]. In addition, models emphasize the importance of the four-pronged approach to eMTCT outlined by UNAIDS and WHO: 1) prevention of HIV infection among women of reproductive age; 2) prevention of unintended pregnancies among HIV-infected

women; 3) PMTCT for women living with HIV; and 4) care for women and children living with HIV [2]. Although only Prong 3 is included in the traditional PMTCT cascade, addressing Prongs 1 and 2 will also be necessary to achieve eMTCT (Figure 1) [14].

Medication adherence

A recent meta-analysis reported “adequate” adherence (defined as taking >80% of doses) in only 64% of women receiving three-drug ARV regimens for PMTCT, with markedly lower adherence during the postnatal (53%) compared with antenatal (76%) periods [20]. Model-based analyses highlight that eMTCT will require much greater adherence than these reported levels during both pregnancy and breastfeeding. For example, our own group simulated a cohort of HIV-infected, pregnant women in Zimbabwe, incorporating a range of drug regimens (single-dose nevirapine, Option A, and Option B) and uptake levels (80%-100%; Figure 2) [13]. Results highlight that at most feasible uptake levels (80-95%), the eMTCT target of <5% is likely to be achieved only if infants experience the lowest published MTCT risks for each regimen. These lowest published risks are derived from clinical trials, such as the Mma Bana study in Botswana, where participants demonstrated outstanding adherence [6]. No studies to date have examined long-term adherence to Options A, B, or B+ outside of clinical trial settings. Over many months of pregnancy and breastfeeding, the ability of mothers to administer daily NVP to their infants, or to take ARVs themselves, will be a critical determinant of the feasibility of achieving eMTCT goals.

Duration of breastfeeding

Limiting the duration of breastfeeding is another important way in which new pediatric HIV infections might be reduced (Figure 1) [13,14]. However, the negative impacts of shorter breastfeeding durations must also be considered, including increased infant mortality from pneumonia, diarrhea, or malnutrition associated with weaning, especially in low-income countries with high early childhood mortality [21-23]. Models can explicitly examine the tradeoffs between breastfeeding-associated HIV transmission risks and replacement feeding-associated mortality risks, and have informed WHO guidelines for both PMTCT regimens and infant feeding [13,24]. Recently, Bingawaho *et al* found that in Rwanda, for example, the fewest new infant infections occurred with Option B and replacement feeding, yet the more comprehensive outcome of infant HIV-free survival was maximized instead with Option B and 12 months of breastfeeding [25].

Potential harms associated with PMTCT regimens

Recent data have suggested that Options A, B, or B+ may be associated with important adverse outcomes, including drug resistance, congenital anomalies, preterm delivery, and impaired growth [26-32]. Models can help clinicians and policymakers understand the importance of these reported risks, by explicitly examining the tradeoffs between adverse effects and the tremendous benefits of PMTCT. For example, Townsend *et al* used a computer model with European cohort data to examine the tradeoffs between PMTCT and preterm birth [33]. They found that for every 100 HIV infections prevented by offering triple therapy in place of zidovudine alone, an estimated 63 additional preterm deliveries would occur.

Models may be particularly useful when these risk estimates are highly uncertain: “what-if” or “threshold” analyses place currently available data in context. If the risk of adverse events projected to be necessary to change PMTCT recommendations is substantially higher than current data suggest, clinicians can be reassured that benefits likely outweigh risks. However, if this threshold value is close to reported adverse event risks, then additional research is warranted in order to better characterize true degree of risk. For example, we

modeled the balance between PMTCT and neurologic impairment from ARV-associated mitochondrial toxicity, finding that the risk of neurologic impairment would need to be 3-fold higher than suggested by large cohort studies to recommend against triple-drug regimens [34]. Next, model-based analysts must evaluate the relative morbidity, mortality, and costs of each outcome (preterm delivery, neurologic impairment, and HIV infection), to determine more explicitly whether the benefits outweigh the risks [33]. Our model estimated that neurologic mitochondrial toxicity would need to be 6.4 times more disabling than infant HIV infection to prompt a change in PMTCT guidelines [34]. More comprehensive simulation models of pediatric HIV infection, currently in development, will be better able to project the relative disability of these key clinical outcomes [35-37].

Additional benefits of Option B+

Although the PMTCT benefits of Options B and B+ are equivalent for any single pregnancy/breastfeeding period, Option B+ may confer additional important benefits. For example, MTCT in subsequent pregnancies is likely lower when women are on ART at conception [38]. Initiation of ART at high CD4 counts can prevent TB infection in mothers (and thus in infants) and reduce transmission from women to HIV-uninfected male partners [39]. The use of tenofovir/emtricitabine-containing regimens can also treat maternal hepatitis B infection, and continuation after weaning can prevent hepatitis B flares [40]. Furthermore, in men and nonpostpartum women, continuation of ART after weaning may prevent both AIDS-related and non-AIDS-related events; data specific to postpartum women are anticipated shortly [41-43]. At least three models have partially incorporated these potential benefits beyond PMTCT in the index pregnancy, and additional modeling work is anticipated as new clinical data emerge [43-46].

Economic investments necessary to eliminate new pediatric HIV infections

Model-based cost-effectiveness studies can guide program planners to efficiently allocate limited PMTCT resources. Through budget impact analyses, models can also aid program planning by forecasting the likely costs associated with alternative PMTCT strategies.

Cost-effectiveness analyses

Cost-effectiveness is a formal methodology to assess value for money. We calculate two discrete outcomes: 1) healthcare costs, in dollars or other currency, and 2) health benefits, in life-years saved (LYS), quality-adjusted life-years (QALYs), or disability-adjusted life-years (DALYs) [47-49]. Healthcare costs and benefits can be observed over short time horizons in clinical studies, or, more commonly, projected over varying horizons using model-based analyses. Comparing two alternative strategies, we calculate an incremental cost-effectiveness ratio (ICER) as the difference in costs divided by the difference in health benefits. In PMTCT analyses, many authors report ICERs denominated in \$/infection averted. Such ICERs cannot readily be compared to those of other HIV-related interventions, however, and do not incorporate important long-term costs and benefits. As a result, the conventional units of cost-effectiveness analysis -- \$/LYS, \$/QALY, or \$/DALY -- are preferred [48]. To determine if an intervention is cost-effective compared to its alternative, we evaluate its ICER against a threshold indicating a society's willingness to pay for one year of healthy life. Many analysts use gross domestic product (GDP)-based thresholds suggested by the WHO: an intervention with an ICER $<1 \times$ a country's *per-capita* GDP/QALY is considered "very cost-effective," and $<3 \times$ GDP/QALY "cost-effective" [50]. Because of substantial concerns about between-country equity with these GDP-based thresholds, other analysts choose instead to compare to reported ICERs of currently-implemented interventions, for example, first-line ART for adults in sub-Saharan Africa (500-\$5,000/YLS) [51,52].

Since 1994, at least 26 studies have examined the cost-effectiveness of PMTCT programs [25,44,46,53-59]. The earliest studies found that single-dose nevirapine (sdNVP) and antenatal zidovudine monotherapy were either cost-saving or very cost-effective, compared to no intervention, in a range of resource-limited settings [53]. Recently, 9 studies have evaluated Options A, B, or B+, with wide variations in the costs and outcomes considered, as well as the choice of comparator strategies (Table 1) [25,44,46,54-59].

The greatest number of recent reports have examined Option B, and found it to be either cost-saving or very cost-effective when compared to no PMTCT, sdNVP, or dual antenatal ARV prophylaxis [25,44,46,54,55,57-59]. Two studies have directly compared Option A to Option B, with conflicting findings. Auld *et al*, using PEPFAR data and considering pediatric outcomes, found Option B to be more expensive but equally effective [56]. Our own analysis for Zimbabwe found that Option B led to greater life-years gained for both mothers and infants, and was also less expensive [44]. These findings likely result from different assumptions about the efficacy of each regimen, as well as the inclusion or exclusion of maternal outcomes. A third study by Fasawe *et al* in Malawi examined maternal and infant outcomes for Options A and B separately; recalculations combining their maternal and pediatric results suggest that Option B is more effective, and very cost-effective, compared to Option A (~\$210/YLS) [46].

In addition, three studies have examined Options B and B+ [44,46,58]. Our work in Zimbabwe suggests that Option B+ is cost-effective, when directly compared to Option B, with an ICER of \$1,370/YLS [44]. Recalculations using maternal and pediatric results from Fasawe *et al* produce an ICER of \$670/YLS for Option B+ compared to Option B, also cost-effective by GDP thresholds for Malawi [46]. Kuznik *et al* considered only pediatric outcomes; recalculations using their results suggest that Option B+ would also be cost-effective compared to Option B in Uganda (ICERs of \$220-450/DALY) [58].

Affordability and budget impact analyses

Although cost-effectiveness analyses provide useful information about the relative value of PMTCT strategies, they do not describe whether interventions are affordable given specific budget constraints. Budget impact analyses, which project total program costs over shorter time horizons (often 1, 2, or 5 years), may be of greater usefulness to program planners. Although few studies have directly reported on affordability or budget impact, short-term costs can often be derived from the intermediate results of the cost-effectiveness analyses in Table 1. For example, in Malawi, projected 18-month PMTCT program costs ranged from \$740-1,010 per pregnant woman, and pediatric HIV care costs ranged from \$520-560/year [25]. In Zimbabwe, the higher upfront costs of Option B compared to Option A were projected to be offset by savings in maternal ART costs and pediatric ART and care costs by 4 years after delivery [44].

Lifetime projections can also add important information for health policy decisions. Stover *et al* projected the total lifetime costs, including maternal and pediatric ARV and care costs, for Options A, B, and B+ in four countries: Kenya, South Africa, Zambia, and Vietnam (Stover J, unpublished personal communication; Figure 3). This analysis, unlike other studies, incorporated both subsequent pregnancies and transmission to uninfected male partners. Results suggest that in most settings, lifetime costs will increase slightly from Options A to B to B+. However, the cost differences are small, and when cost-savings from averted adult transmission are included, Option B saves money compared to Option A, and Option B+ increases cost-savings further. Between-country differences in this study highlight the importance of variations in total fertility rate, breastfeeding duration, and time interval between pregnancies.

Taken together, the cost-effectiveness and budgetary impact analyses reviewed above highlight that costs may be less of a concern than previously thought for programs considering Options A, B, and B+. The overall costs of these regimens are likely to be fairly similar, and the greater upfront medication costs of Options B and B+ may be offset within a few years by averting costly pediatric infections or through health benefits to mothers or their male partners. As a result, non-economic concerns about Options B and B+, including important questions about feasibility, patient/family acceptance and adherence, and equity in the face of limited ART availability, may be of greater importance to decision makers than the costs of each regimen.

Conclusions

Model-based analyses suggest that reaching eMTCT targets is feasible, but only with dedicated efforts to support medication adherence and retention in care for women and infants throughout the PMTCT cascade, as well as interventions targeting all four prongs of maternal-child health care and shorter/safer breastfeeding practices. Models can also help clinicians and policymakers weigh potential toxicities against a range of benefits for individual PMTCT regimens, and can guide future implementation science by highlighting areas in which additional data are needed to make informed decisions. In addition, model-based cost-effectiveness analysis and budgetary projections can estimate the resources needed for PMTCT and the health value gained through these interventions.

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Key Points

- Model-based results can guide future implementation science, by highlighting areas in which additional data are needed to make informed decisions and by outlining critical interventions that will be necessary in order to eliminate new pediatric HIV infections.
- Model-based studies suggest that scale-up of services will be needed in several domains in order to achieve elimination of MTCT: uptake of services and retention in care (the PMTCT “cascade”), interventions to prevent HIV infections in women and reduce unintended pregnancies (the “four-pronged approach”), efforts to support medication adherence through long periods of pregnancy and breastfeeding, and strategies to make breastfeeding safer and/or shorter.
- Recent cost-effectiveness studies have found that Option B is either cost-saving or very cost-effective when compared to no PMTCT, sdNVP, or dual antenatal ARV prophylaxis.
- Although few studies have directly compared currently recommended PMTCT regimens (WHO Option A, Option B, and Option B+), results suggest that all three strategies will be cost-effective in most settings.
- The overall short-term costs of Options A, B, and B+ are likely to be fairly similar, and the greater upfront medication costs of Options B and B+ will likely be offset within a few years by averting costly pediatric infections or through other benefits to mothers or their male partners.

Figure 1. New HIV infections through mother-to-child transmission, projected by Mahy *et al* for 25 countries, 200-2015. [14]

Mahy *et al* projected the number of new infant HIV infections in 25 high HIV-burden countries under four scenarios: 1) Coverage of PMTCT services in 2009; 2) Scale-up of PMTCT services to reach 90% of pregnant, HIV-infected women with WHO 2010-recommended regimens ("90% uptake"); 3) 90% uptake (Scenario 2), combined with 50% reduction in incidence of new HIV infections among women of child-bearing age and elimination of unmet family planning needs; and 4) Scenario 3, combined with reduction in breastfeeding duration to 12 months. Their results indicate that, compared to Scenario 1, Scenario 2 would lead to a 60% reduction in new infections and an 11% MTCT rate, Scenario 3 to a 73% reduction in new infections and also an 11% MTCT rate, and Scenario 4 to a 79% reduction in new infections and an 8% MTCT rate. These results underscore the importance not only of near-perfect uptake at each step of the PMTCT cascade (UNAIDS/WHO Prong 3), but also of UNAIDS/WHO Prong 1 (prevention of HIV among women) and Prong 2 (prevention of unintended pregnancy among HIV-infected women) [2]. **PMTCT:** prevention of mother-to-child HIV transmission; **ARV:** antiretroviral drugs

Figure 2. Combinations of parameters needed to achieve MTCT risks < 5%, adapted from Ciaranello *et al.*, 2012 [13]

The chart on the left depicts results for Option A, while the chart on the right shows results for Option B. Within each chart, three levels of PMTCT uptake (defined as the proportion of pregnant, HIV-infected women receiving ARVs for PMTCT by delivery) are depicted across the horizontal axis. Uptake levels include 80% uptake (a WHO target in 2010), 95% uptake (reported in neighboring Botswana), and 100% uptake (to reflect maximum biologic efficacy of each regimen). The three sets of bars for each level of uptake show the range of published MTCT risks for each drug regimen, ranging from the lowest published risks (light grey), through the average of published risks (the base-case parameters, dark grey), to the highest-published risks (black). It is likely that this range of published risk for any given regimen reflects the impact of adherence in the reporting studies. The vertical axis reflects the MTCT risk projected by the model using each set of parameters. The dashed black line on each chart indicates the “elimination” target of reducing mother-to-child transmission to <5% by 2015.

sdNVP: single-dose nevirapine; **BF**: breastfeeding; **avg**: average; **MTCT**: mother-to-child HIV transmission;.

Figure 3. Budget impact projections (lifetime horizon) for mothers and infants: Results from the Future Institute analysis of WHO-recommended PMTCT regimens in four countries

Results are shown from Stover *et al* (unpublished work; personal communication presented to the World Health Organization Maternal-Child Health Guidelines committee, December 12, 2012). Incorporating drug and clinical care costs for HIV-infected women and their infants, the Futures team projected total lifetime costs, including PMTCT program costs, for the three drug regimens shown. All analyses include the impact of the modeled PMTCT regimens on first and subsequent pregnancies.

OptA: Option A, **OptB:** Option B, **OptB':** Option B, including reduced transmission to HIV-uninfected male partners of pregnant women; **OptB+:** Option B+; **OptB+':** Option B+, including reduced transmission to HIV-uninfected male partners of pregnant women.

Table 1

Cost-effectiveness analyses of WHO 2010-recommended regimens for PMTCT

Study	Country	Outcomes considered	Costs included	Regimen and comparator	\$/infection averted	\$/YLS or \$/DALY
Orlando, 2010 [54]	Malawi	Pediatric	Drugs, laboratory, personnel, facilities (PMTCT period); pediatric HIV care and ART (lifelong)	Option B (vs. none)	Cost-saving (public perspective)	Cost-saving (public perspective)
Robberstad, 2010[55]	Tanzania	Pediatric	Drugs, laboratory, personnel, facilities (PMTCT period)	Option B (vs. none)	\$4,060	\$160/DALY
Auld, 2010 (unpublished) [56]	15 PEPFAR countries	Pediatric	PMTCT program costs; pediatric care and ART (lifelong)	Option A (vs. Option B)	Cost-saving	Cost-saving
Shah, 2011 [57]	Nigeria	Pediatric	Drugs, laboratory, personnel (PMTCT period); pediatric care and ART (lifelong)	Option B (vs. AZT/3TC)	\$3,200	\$110/DALY
Kuznik, 2012 [58]	Uganda	Pediatric	Drugs, laboratory, personnel (PMTCT period); pediatric care and ART (lifelong)	Option B (vs. AZT/3TC)		\$100/DALY
Kuznik, 2012 (recalculated)	As above	As above	As above	Option B+ (vs. AZT/3TC)		\$350/DALY
Schmidt, 2012 [59]	Dominican Republic	Pediatric	Drugs (PMTCT period);	Option B+ (vs. Option B)		\$220-450/DALY
				Option B (vs. sdNVP)	Cost-saving	

Study	Country	Outcomes considered	Costs included	Regimen and comparator	\$/infection averted	\$/YLS or \$/DALY
Ciaranello, 2013 [44]	Zimbabwe	Pediatric, maternal	Drugs, laboratory, HIV care and ART (PMTCT period; maternal and pediatric lifelong)	Option B (vs. no PMTCT, sdNVP, or Option A)	Cost-saving	
Binagwaho, 2013 [25]	Rwanda	Pediatric	Drugs, laboratory, personnel, facilities; infant formula (PMTCT period only)	Option B+ (vs. Option B)		\$1,370/YLS
				Option B (vs. AZT/3TC)	Cost-saving	
				Option B w/ RF (vs. Option B w/6m BF)	\$7,320	
				Option B w/ 6m BF (vs. Option B w/ 12 BF)	\$11,880 *	
Fasawe, 2013 [46]	Malawi	Pediatric, maternal	Drugs, laboratory (PMTCT period); HIV care and ART (pediatric lifelong; maternal for 10 years)	Option A (vs. SOC)		\$40/DALY (pediatric)
				Option B (vs. SOC)		\$310/YLS (maternal) \$70/DALY (pediatric)
				Option B+ (vs. SOC)		\$340/YLS (maternal) \$60/DALY (pediatric) \$460/YLS (maternal)
Fasawe, 2013 (recalculated)	As above	As above	As above	Option A (vs. SOC)	Cost-saving	
				Option B (vs. Option A)	\$210/YLS **	
				Option B+ (vs. Option B)	\$670/YLS **	

Abbreviations: YLS: years of life saved; DALY: disability-adjusted life-year averted; AZT: zidovudine; 3TC: lamivudine; sdNVP: single-dose nevirapine; RF: replacement feeding; BF: breastfeeding; m: months; SOC: standard of care (in Fasawe paper, reflected current practice in 2010, which was a combination of ART, AZT/3TC, and sdNVP depending on access to CD4 testing and ARVs).

* Result (ICER of \$11,880) is \$/infant alive and uninfected, rather than \$/infection averted

** Recalculated ICERs using model results from Fasawe *et al.* To incorporate outcomes for both mothers and infants, results are shown using a composite of YLS gained for mothers and DALYs averted for infants, written as YLS for simplicity in the table.