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Antiretroviral drugs for preventing mother-to-child transmission of HIV in sub-Saharan Africa: Balancing efficacy and infant toxicity

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Abstract

Objective—Antiretroviral drugs (ARVs) can prevent HIV mother-to-child transmission (PMTCT), but *in utero* ARV exposure may be associated with neurologic symptoms due to mitochondrial toxicity (MT). We sought to identify the currently recommended PMTCT regimen that optimally balances risks of pediatric HIV infection and neurologic MT.

Design—Published MTCT and MT data were used in a decision analytic model of MTCT among women in sub-Saharan Africa.

Methods—We investigated the HIV and MT risks associated with no ARV prophylaxis and five recommended regimens ranging from single-dose nevirapine to 3-drug ART. Sensitivity analyses varied all parameters, including infant feeding strategy and the disability of MT relative to HIV.

Results—Provision of no ARVs is the least effective and least toxic strategy, with 18-month HIV risk of 30.4% and MT risk of 0.2% (breastfed infants). With increasing drug number and duration, HIV risk decreases markedly (to 4.9% with 3-drug ART), but MT risk also increases (to 2.2%, also with 3-drug ART). Despite increased toxicity, 3-drug ART minimizes total adverse pediatric outcomes (HIV plus MT), unless the highest published risks are true for both HIV and MT, or the disability from MT exceeds 6.4 times that of HIV infection.

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Conclusions—The risk of pediatric MT from effective PMTCT regimens is at least an order of magnitude lower than the risk of HIV infection associated with less effective regimens. Concern regarding MT should not currently limit the use of 3-drug ART for PMTCT where it is available.

Keywords

HIV/AIDS; PMTCT; mitochondrial toxicity; pediatric HIV; antiretroviral therapy; sub-Saharan Africa; decision analysis

Introduction

The use of antiretroviral drugs (ARVs) to prevent mother-to-child transmission of HIV infection (PMTCT) is one of the most successful achievements in HIV prevention. Following the Pediatric AIDS Clinical Trial Group (PACTG) Study 076 in 1994[1], zidovudine (ZDV) monotherapy was widely used for PMTCT, where available [2]. Subsequent trials have investigated antepartum, intrapartum, and postpartum regimens combining ZDV, lamivudine (3TC), nevirapine (NVP), and protease inhibitors (PIs) [3-16]. MTCT rates have been reduced from more than 25% [1,17] to less than 2% [4,8,18] when potent 3-drug antiretroviral therapy (ART) is available and breastfeeding is avoided, and recently reported interventions have reduced transmission to breastfed infants from over 40% (at 24 months of age) [3,17] to 1-7% (at 6-18 months) [19-26].

Most regimens have demonstrated favorable safety profiles for both mothers and infants during the duration of trial follow-up [3,8,10,16,27]. In 1999, however, French perinatologists reported 8 cases of severe cognitive and neurological dysfunction among HIV-negative children after *in utero* ARV exposure [28]. These neurologic symptoms, including hypotonia, seizures, encephalopathy, and neuropathy, were similar to both congenital mitochondrial dysfunction in children and ARV-induced mitochondrial toxicity (MT) in HIV-infected children and adults [28]. Since this first report, other studies of the effects of *in utero* ARV exposure on mitochondrial function in HIV-negative children have differed in methodologies and conclusions [29-41].

Clinicians and policy makers currently recommend PMTCT regimens in the absence of complete data about both the prevalence and severity of mitochondrial toxicity. Although more intensive ARV regimens substantially reduce MTCT among women with low CD4 counts, the magnitude of MTCT reduction with 3-drug ART compared to shorter-course ARV regimens among women with CD4 >200/ μ L is less well known [11,22,26]. It is also unknown whether exposure to more ARVs for longer durations, or to specific drugs during particular periods of fetal development, causes higher MT risk. Because MT related to nucleoside reverse transcriptase inhibitors (NRTIs) may be rare and remains controversial, the challenge of identifying the optimal ARV regimen to balance efficacy (reduction in MTCT) with toxicity (pediatric neurologic MT) is well-suited for assessment by decision analysis [42]. We used existing data in a decision analytic model to quantify the effects of recommended PMTCT regimens on HIV transmission and neurologic MT at 18 months of age for infants in sub-Saharan Africa and to determine the MT risk that would warrant a change in current PMTCT recommendations.

Methods

We designed a decision analytic model of pregnant, HIV-infected, ART-naïve women in sub-Saharan Africa not meeting 2006 World Health Organization (WHO) criteria for initiation of ART for their own HIV infection (CD4 > 200/ μ L and no history of AIDS) [43]. Using published MTCT and neurologic MT risks, we examined the pediatric outcomes at 18 months of age

associated with no ARV prophylaxis and with five different recommended PMTCT strategies (Table 1) [43,44].

Modeled PMTCT Strategies

For women in resource-limited settings not meeting criteria for ART themselves, WHO recommends four increasingly intensive PMTCT regimens, depending on resource availability [43]. Table 1 outlines the antenatal, intrapartum, and postnatal components of these regimens. We evaluated all WHO-recommended strategies, as well as no ARVs (for the purpose of comparison) and PI-based 3-drug ART, as recommended in the US [44] (Table 1).

The base case analysis was performed for breastfeeding mothers without access to elective cesarean section. The effects of formula feeding and of the availability and effectiveness of elective cesarean section on reduction in MTCT were evaluated in sensitivity analyses. Model structure is shown in Figure 1. Additional details are provided in the Technical Appendix.

Outcomes/Case definitions

Neurologic MT was defined according to the Enquête Périnatale Française (EPF) clinical case definition, excluding any requirement for radiographic, biochemical, or histological findings [32] (Technical Appendix). Intrauterine, intrapartum, and postpartum HIV infections were defined according to the timing of first positive infant virologic test (HIV-1 DNA, RNA, or culture), as typically defined for PMTCT trials [7,12,26]. The standard trial definition of intrapartum infection (first positive virologic test between 3 days and 4-8 weeks of age) reflects the limited sensitivity of these assays in the early weeks of life due to delayed viremia [45], but necessitates the inclusion of early postpartum transmission due to breastfeeding in the “intrapartum” category.

Model Parameters

HIV transmission risk—In the base case analysis, risks of HIV transmission for each ARV regimen were derived from publications or presentations meeting the following inclusion criteria: clinical trial of a modeled regimen, conducted in Africa, ≥ 12 months follow-up, and reporting probabilities of HIV infection at each time point among infants who were HIV-negative at the prior time point (or data that permitted these calculations). Clinical trial-based data were used to inform all analyses. With one exception [23] (Technical Appendix), observational reports were excluded, because higher rates of loss to follow-up might bias results. Studies meeting most, but not all, inclusion criteria were included in ranges examined in sensitivity analyses (Technical Appendix Table 1).

For each HIV transmission time point and ARV strategy, the base case transmission risk was derived from the most widely accepted or cited estimate (based on expert opinion), aiming for the midpoint of the range of reported transmission risks (Table 2). PMTCT data were used to calculate the probability of infection during the intrauterine, intrapartum/early postpartum, and late postpartum periods among children who were uninfected at the previous time point.

MTCT risks were assigned to either breastfed or formula-fed strategies according to the predominant feeding practice in each trial. For each breastfed strategy, the median duration of breastfeeding was assumed to be equal to that of the trial population (range for base case analysis, 9 - >20 months) [3,17,27,46-49]. We simulated extended breastfeeding in order to 1) generate 18-month results applicable to African populations in which this practice is common, and 2) conservatively estimate the benefits of peripartum ARVs, the protective effects of which are likely to fade with prolonged breastfeeding [27].

Neurologic MT risk—Because an independent risk of fetal mitochondrial dysfunction has been postulated to result from maternal HIV viremia [39,50], the base case analysis derived the risk of mitochondrial dysfunction among HIV-exposed but ARV-unexposed children from the upper confidence limit reported in the EPF cohort: 0 of 1748 ARV-unexposed children, 95% CI (0, 0.17%) [32,51]. Sensitivity analyses evaluated MT risks ranging from the general population risk (0.01%) [52,53] to 2.9%, as reported among ARV-exposed children in PACTG 219/219C (2.9%, 95% CI (0.6%-8.4%)) [39] (Table 2).

The risks of MT among HIV- and ARV-exposed children were derived from two studies of living, uninfected children incorporating routine neuropsychiatric assessment [32,39]. The base case analysis made use of the MT risks associated with exposure to ZDV (1.88%) and ZDV/3TC (2.04%) at any time during pregnancy in the PACTG 219/219C report [39] (Table 2). Sensitivity analyses incorporated the range of risks reported in these two studies: the overall MT risk was 0.26% [32]- 1.8% [39]; when stratified by time of earliest exposure to specific NRTIs, MT risks in the PACTG 219/219C cohort ranged from 0.4% (first exposure to 3TC in 2nd trimester) to 6.9% (first exposure to 3TC in 3rd trimester) [39].

Assumptions

When data to inform HIV transmission and neurologic MT risks were incomplete for any PMTCT strategy, we assumed differences in transmission or toxicity risks compared to the most similar strategy, based on individual components of each regimen (Table 2; Technical Appendix). In the base case analysis, because MTCT risks among women with CD4 > 200/μL were rarely available [22], we relied on transmission risks from all women participating in the included PMTCT trials (participants reported with CD4 < 200/μL: range 5-24%, mean 12.9%). We then used the lowest published transmission risks to create a “best case” scenario for HIV risk which may better reflect MTCT from women with less advanced disease. Adherence to ARV and feeding strategies was assumed to be equal to that in the trials (Table 2).

Sensitivity analyses

Sensitivity analyses were performed on all model parameters and assumptions, feeding strategy, the availability of elective cesarean section, and all uncertain input parameters (Table 2; Technical Appendix). In order to determine the prevalence of MT which would change current practice, we varied the risks of neurologic MT associated with each ARV strategy, with individual components of each strategy, and with maternal HIV viremia over published and clinically plausible ranges (Table 2). The highest and lowest published risks of HIV transmission and MT were used to create “best case” and “worst case” scenarios for each outcome. The disability of MT relative to pediatric HIV infection was also evaluated in sensitivity analyses.

Results

Base case analysis

Among breastfeeding women, provision of no ARVs is the least effective and least toxic PMTCT strategy (HIV transmission risk of 30.4% and MT risk of 0.2%, at 18 months of age). With increasing number and duration of ARVs, the 18-month HIV transmission risk declines markedly (to 4.9% with 3-drug ART). When antepartum NRTIs are used, MT risks rise from 0.2% (no ARVs; sdNVP) to 2.0% (both scZDV regimens) and 2.2% (3-drug ART). Despite this increased toxicity, 3-drug ART minimizes total adverse events, defined as the sum of HIV infections and MT cases (Table 3, Section I).

Using population-level estimates, treating 10,000 breastfeeding mothers with the scZDV/sdNVP/CBV regimen (the next most effective and next least toxic regimen) compared to 3-drug ART would prevent 15 cases of MT, but would allow 507 additional HIV infections. To substantially reduce MT compared to 3-drug ART (0.2% vs. 2.2%), one would choose the sdNVP/CBV regimen; this choice would prevent 202 cases of MT in the same population, but 1303 additional HIV infections would occur.

Sensitivity analyses

Formula feeding—When formula-fed infants are evaluated using other base case parameters, 3-drug ART remains the strategy that minimizes total adverse events (Table 3, Section I).

Worst- and best-case scenarios—We used the highest published risks of HIV transmission and MT associated with each PMTCT regimen to create a “worst-case” (highest toxicity and lowest efficacy) scenario. In contrast to the base case, if the “worst-case” risks are simultaneously true for both MT and HIV, then both scZDV regimens minimize total adverse outcomes compared to 3-drug ART in breast- and formula-fed infants (Table 3, Section II). When the “worst-case” estimates are used only for MT risk (Table 3, Section III), the order of strategies is identical to that in the base case for breastfed infants, but both scZDV regimens are superior to 3-drug ART in formula-fed infants. When the “worst-case” estimates are used only for HIV risk, the order of the strategies is unchanged from the base case, regardless of feeding strategy (Technical Appendix).

When “best case” HIV risks, which may better reflect MTCT risks from mothers with CD4 > 200/μL, are combined with base case MT risks, the order of strategies is also unchanged from the base case (Table 3, Section IV). However, when “best case” HIV risks and “worst case” MT risks are simultaneously examined (Table 3, Section V), the less intensive regimens (scZDV/sdNVP/CBV in breastfed infants, and all ARV regimens in formula-fed infants) minimize total adverse outcomes, compared to 3-drug ART (Technical Appendix).

Relative disability of MT and HIV—We varied the degree of disability associated with neurologic MT as a function of the disability associated with pediatric HIV (Figure 2) and compared the total adverse pediatric outcomes (HIV and MT) associated with each strategy. Using the base case input parameters, we first compared 3-drug ART to the most effective regimen that excludes an NRTI, conferring a substantial decrease in toxicity (sdNVP/CBV). In breastfed infants, the morbidity of MT would have to exceed 6.4 times the morbidity of pediatric HIV infection to recommend the sdNVP/CBV regimen over 3-drug ART (open arrow). We then compared 3-drug ART to the next most effective and next least toxic regimen (scZDV/sdNVP/CBV). Here, the threshold is higher, because the number of excess cases of HIV that occur when the scZDV/sdNVP/CBV regimen is substituted for 3-drug ART greatly exceeds the number of MT cases prevented: the morbidity of MT would need to exceed 32.1 times that of HIV in breastfed infants in order to recommend the scZDV/sdNVP/CBV regimen over 3-drug ART (closed arrow).

Discussion

The efficacy of ARVs in the prevention of MTCT of HIV is widely accepted[54]. Two studies report an association between *in utero* ARV exposure and infant neurologic dysfunction possibly related to MT [32,39], but the true prevalence and severity of this postulated MT remain controversial [55,56]. Motivated by the possibility that the association between ARV exposure and MT is causal [39], we conducted an exploratory analysis in order to determine

the prevalence and severity of MT at which current ARV recommendations for PMTCT would merit change [43,44].

This decision analytic model assesses the 18-month risks for pediatric HIV transmission and neurologic MT, following the administration of six different PMTCT regimens to pregnant, HIV-infected women in sub-Saharan Africa. Model results reflect the published efficacy of ARVs for PMTCT; base case estimates of HIV transmission at 18 months in breastfed infants range from 4.9% with 3-drug ART to 30.4% with no ARVs. These results calibrate with results from observational studies [57,58] and with syntheses of PMTCT trials in sub-Saharan Africa [3,18,59,60], including 40-50% (relative) [59,61] and 14-15% (absolute) [59,62,63] increases in MTCT risk due to breastfeeding. Because MT has primarily been attributed to *in utero* NRTI exposure, the three least effective PMTCT regimens, all of which exclude antepartum NRTIs, demonstrate low toxicity risks. Overall, 3-drug ART initiated in the first trimester results in many fewer pediatric HIV infections, slightly more cases of pediatric neurologic MT, and substantially fewer total adverse pediatric outcomes (HIV infections and MT cases) than the less toxic but less effective regimens.

Published studies of ARV-associated MT have differed in methodology and MT case definition, which may explain inconsistent findings [2,5,29-38,40,64-69]. In addition, most studies have not controlled for maternal substance abuse and socioeconomic factors [68], high maternal viral load [50], and maternal disease stage [39], all of which have been hypothesized to cause infant mitochondrial dysfunction and adverse neurologic outcomes [39,50,68]. We therefore chose data from the only two studies using routine neuropsychiatric evaluations of living, HIV-uninfected children [32,39]. Brogly *et al.* demonstrated a significantly higher risk of MT when NRTIs (ZDV, 3TC, or both) were initiated in the third trimester than in the first trimester [39]. They postulate a period of neurodevelopment late in gestation in which the fetal brain is uniquely sensitive to NRTI-induced MT [70-72]. The authors were unable to control for high maternal RNA at delivery (likely a result of late ARV initiation) and maternal drug use (a potential cause of late ARV initiation, although not associated with MT in this study). Because these factors may have led to the overestimation of MT risk from 3rd-trimester NRTI initiation, our base case analysis conservatively relied on the MT risk associated with *any* ZDV, 3TC, or ZDV/3TC exposure, regardless of timing (1.88% - 2.04%).

Our results demonstrate that at MT prevalences *lower* than the base case risks (as in the EPF, range 0.26-0.87%) [32], 3-drug ART would still minimize total adverse outcomes. More importantly, these results remain true at MT prevalences *higher* than the base case scenario. Our “worst-case” MT scenario used data from subgroups with 3rd-trimester initiation of ZDV, 3TC, or ZDV/3TC in PACTG 219/219C; results suggest that even if these “worst-case” MT estimates were correct, a change in recommended ARVs for PMTCT would be warranted only if the very highest or lowest published HIV risks associated with each regimen were also true. HIV transmission risks at 18 months in the “best-case” and “worst-case” scenarios are well outside commonly reported ranges [1,8,18,23,26,59,73].

Currently reported prevalences of MT are therefore unlikely to change PMTCT recommendations. However, little is known about the morbidity and mortality of ARV-associated neurologic MT [32,39,40,55], and prognostic information must be extrapolated from reports of congenital mitochondrial dysfunction [52,53,74,75]. As new data specific to ARV-associated MT emerge [4,32,39,40,55,76], a primary factor in the choice of PMTCT regimen will be the relative disability of MT compared to that of pediatric HIV infection. Pediatric HIV disease substantially reduces life expectancy in sub-Saharan Africa, even when therapy is available [77-80], and may itself be associated with significant neurodevelopmental delay [81]. If pediatric HIV infection consistently causes greater morbidity and mortality than MT, then the balance of risk and benefit will always favor more effective regimens for PMTCT.

If, however, MT is markedly more disabling than pediatric HIV (for example, if effective therapies for pediatric HIV become widely available), then policy makers may choose PMTCT strategies that permit more cases of HIV infection in order to avoid MT in uninfected children. The combined outcome of HIV infections plus MT cases allowed us to estimate that, at base-case MT risks, neurologic MT will need to be at least 6.4 times more disabling than HIV infection in order to prompt a change in current PMTCT recommendations.

Of note, this model did not examine maternal outcomes. Emerging data suggest a benefit to ART initiation at $CD4 > 200/\mu L$, as reflected in recent changes to US treatment guidelines [82]. Therefore, women included in our model are likely to benefit from 3-drug ART during pregnancy, and the effects on maternal health of withdrawing ART after use for PMTCT remain unknown [44,83,84]. Maternal drug-resistant HIV resulting from single- or dual-drug PMTCT regimens may also result in reduced efficacy of ART when it is eventually initiated [85]. These maternal effects may tip the balance of risk and benefit in favor of 3-drug ART when both maternal and pediatric outcomes are considered. Additionally, the model did not incorporate the costs of each PMTCT regimen or of clinical care for HIV- or MT-affected children after birth. In settings with severely constrained health care resources, concerns for costs may outweigh concerns for toxicity in the selection of ARV regimens for PMTCT.

This analysis required several simplifying assumptions. First, data are limited on late postpartum transmission rates by actual infant feeding practices [7,17,58]. Second, the model did not account for the neurodevelopmental effects of maternal age, preterm delivery, or stage of maternal HIV disease, which may affect pediatric neurologic outcomes [86]. Finally, women with $CD4 < 200/\mu L$ merit 3-drug ART for their own HIV infections as well as for PMTCT [43], and therefore were intentionally excluded from the model. Because MTCT data were not limited to women with high CD4 counts, the base case analysis likely overestimates transmission risks for women not requiring ART themselves [19,87].

The “best-case” scenario, in which the lowest published HIV transmission risks were attributed to each regimen, may more closely approximate true MTCT risks from women with less advanced disease. The results of the “best case” HIV scenario were unchanged from the base case, except when the highest published MT risks for 3-drug ART were simultaneously considered. For breastfed infants in this “best-case HIV/worst-case MT” scenario, scZDV/sdNVP/CBV was superior to 3-drug ART, due primarily to the high MT risk assigned to 3rd-trimester 3TC exposure. For formula-fed infants, all ARV regimens were superior to 3-drug ART, due to very low HIV risks assigned to less intensive regimens. The small differences in total adverse outcomes between strategies suggest that further studies are required to investigate 1) whether scZDV regimens are effective among women with $CD4 > 200/\mu L$, and 2) whether MT risks with 3-drug ART approach those observed in select subgroups of PACTG 219/219C [39]. If such data emerge and are simultaneously true, short-course regimens may be appropriate alternatives to 3-drug ART in women with high CD4 counts, especially when formula-feeding is feasible.

In resource-limited settings, concerns for toxicity, as well as for cost, may influence the selection of less effective ARV regimens for PMTCT than are recommended in developed nations [43]. Currently available data suggest that total pediatric adverse outcomes (HIV infections and cases of neurologic mitochondrial toxicity) are minimized by the use of PI-based 3-drug ART for PMTCT. Less effective ARV regimens would only be substantially superior to 3-drug ART if the very highest or lowest published risks of HIV, as well as the highest published risks of MT, associated with each strategy were simultaneously true, or if ARV-related mitochondrial toxicity were markedly more disabling than pediatric HIV infection. Access to diagnosis, prenatal care, and ARVs for HIV-infected women in resource-limited settings remain crucial to reducing the more than 500,000 perinatal infections that occur

worldwide each year, and every effort should be made to provide 3-drug ART to women who require therapy for their own health [54]. For women with less advanced HIV disease, nucleoside-sparing PMTCT regimens, or regimens that avoid combination nucleosides, may warrant further investigation. In the meantime, currently reported risks of mitochondrial toxicity should not lead providers or patients to avoid the use of 3-drug ART during pregnancy for PMTCT, and efforts should be expanded to increase the availability of 3-drug ART for PMTCT in resource-limited settings.

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Figure 1.

Women who did not meet WHO criteria for initiation of ART for their own HIV infections were considered eligible for each ARV and feeding strategy. During the period from 10 weeks of gestation through 18 months postpartum, each of the depicted events occurred based on probabilities derived from the published literature: intrauterine (IU) demise or HIV infection, intrapartum or early postpartum (IP) HIV infection, postpartum (PP) HIV infection, or neurologic mitochondrial toxicity (MT), resulting in the outcomes depicted at the end of each path.

Figure 2.

Effect of varying the relative disability of pediatric neurologic MT compared to pediatric HIV infection on total adverse pediatric outcomes (HIV plus MT): base case analysis. On the horizontal axis is the relative disability of MT compared to HIV infection (MT ranging from 0 – 35 times more disabling than HIV). On the vertical axis is the probability of total pediatric morbidity (HIV plus MT). Thresholds are highlighted at which the sdNVP/CBV regimen (open arrow) and the scZDV/sdNVP/CBV regimen (closed arrow) minimize total morbidity compared to 3-drug ART.

Table 1

PMTCT strategies examined in a decision model for sub-Saharan Africa

Strategy	Prenatal	Intrapartum	Postpartum (to mother)	Neonatal
No ARVs	None	None	None	None
sdNVP	None	sdNVP	None	sdNVP
sdNVP/CBV	None	sdNVP + ZDV/3TC	ZDV/3TC × 7d	sdNVP
scZDV/sdNVP	ZDV from 28w	sdNVP	None	ZDV × 7d + sdNVP
scZDV/sdNVP/CBV	ZDV from 28w	sdNVP + ZDV/3TC	ZDV/3TC × 7d	ZDV × 7d + sdNVP
PI-based 3-drug ART	ZDV/3TC/PI from 8-12w	ZDV/3TC/PI	None	ZDV × 6 w

Abbreviations: **PMTCT**: prevention of mother-to-child transmission of HIV; **ARVs**: antiretroviral drugs; **sdNVP**: single-dose nevirapine; **ZDV**: zidovudine; **3TC**: lamivudine; **CBV**: “Combivir tail” (7 days of maternal ZDV/3TC), **sc**: short-course (from 28 weeks of gestation); **PI**: protease inhibitor; **28w**: 28 weeks of gestational age; **8-12w**: between 8 and 12 weeks of gestational age; **7d**: 7 days; **6w**: 6 weeks.

Table 2
Selected input parameters for a decision model of PMTCT strategies in sub-Saharan Africa

Parameter	Base case value for each regimen (range for sensitivity analysis, breastfed infants) ^a				
	No ARV's	sdNVP	sdNVP/CBV	scZDV/sdNVP	3-drug ART
Probability of intrauterine demise				0.0049 [1] (0 – 1.64%) [7,8,11,14,15,17,88]	
Probability of intrauterine HIV infection	0.07 [7,15,17,19,46,89] (0.031-0.095) [1,6,14,49, 90-93]	0.07 [7,15,17,19,46,89] (0.031-0.095) [1,6,14,49, 90-93]	0.07 [7,15,17,19,46,89] (0.031-0.095) [1,6,14,49,90-93]	0.038 [26] (0.01-0.0389) [3,8,11]	0.0143 [25] (0.004-0.024) [4,12, 22-24,26]
Probability of intrapartum/ early postpartum HIV infection	0.139 [17] (0.0903-0.1903) [1,3,5,14, 46-48,90]	0.046 [15] (0.0392 - 0.120) [7,19-22, 49,93]	0.0376 (0.0376-0.0564) [6,95] ^b	0.0234 (0.0059 - 0.037) [11,26] (0.003 – 0.037) [6] ^b	0.0154 [22] (0.009-0.0177) [24-26,73, 94]
Probability of postpartum HIV infection	0.0133 [47] (0.0718 – 0.1823) [3,5,17, 46,48]	0.089 [49] (0.0442-0.0947) [15,27,61] [19,89]	0.085 (0.0249 – 0.0947) [95] ^b	0.045 [26] (0.045-0.0737) [26,61] (0.03375 – 0.0737) [26,95] ^b	0.0208 [22] (0.009-0.0737) [15,24-26, 61,73,90,94]
Background probability of pediatric neurologic MT related to maternal HIV			0.0017 [32] (0.0001-0.0289) [39,52,53]		
Additional MT above background	0 ^b	0 ^b	0 (0 - 0.00006) ^b	0.0188 [39] (0 - 0.0290) [39,40]	0.0204 [39] (0 - 0.0676) [39,40]
Reduction in background risk of MT due to reduction in maternal viremia	0 ^b	0 ^b	0% ^b	0% ^b (0-50%) ^b	0% ^b (0-75%) ^b

^aParallel table provided in technical appendix lists base case values and ranges for sensitivity analysis for formula-fed infants

^bParallel table provided in technical appendix provides details of all assumptions used in model

Abbreviations: **ARV**: antiretroviral drugs; **ART**: antiretroviral therapy; **sNVP**: single-dose nevirapine; **MT**: mitochondrial toxicity; **ZDV**: zidovudine; **3TC**: lamivudine, **CBV**: “Combivir” tail (ZDV/3TC)

Model results: prevalence of pediatric HIV infection and neurologic mitochondrial toxicity at 18 months of age associated with each ARV strategy, under base case and “worst-case” scenarios*

Table 3

I. Primary results (base case estimates) for HIV and neurologic MT risk						
	<u>Breastfed Infants (%)</u>		Total^b	<u>Formula-fed infants (%)</u>		Total^b
	HIV	MT		HIV	MT	
No ARVs	30.4	0.2	30.6	17.4	0.2	17.5
sdNVP	19.1	0.2	19.2	10.4	0.2	10.5
sdNVP/CBV	18.0	0.2	18.1	9.8	0.2	10.0
scZDV/sdNVP	10.5	2.0	12.5	4.3	2.0	6.4
scZDV/sdNVP/CBV	10.0	2.0	12.1	4.3	2.0	6.4
3-drug ART	4.9	2.2	7.1	2.3	2.2	4.5
II. “Worst-case” results (highest published estimates) for both HIV and neurologic MT risk^a						
	<u>Breastfed Infants (%)</u>		Total^b	<u>Formula-fed infants (%)</u>		Total^b
	HIV	MT		HIV	MT	
No ARVs	39.9	2.9	42.8	29.9	2.9	32.8
sdNVP	27.8	2.9	30.7	14.5	2.9	17.4
sdNVP/CBV	23.7	2.9	26.6	12.9	2.9	15.8
scZDV/sdNVP	14.2	5.8	20.0	5.9	5.8	11.7
scZDV/sdNVP/CBV	13.5	5.8	19.3	5.8	5.8	11.6
3-drug ART	11.1	9.6	20.7	4.0	9.6	13.6
III. “Worst-case results” (highest published estimates) for neurologic MT risk; base case estimates for HIV^a						
	<u>Breastfed Infants (%)</u>		Total^b	<u>Formula-fed infants (%)</u>		Total^b
	HIV	MT		HIV	MT	
No ARVs	30.4	2.9	33.3	17.4	2.9	20.3
sdNVP	19.1	2.9	22.0	10.4	2.9	13.2
sdNVP/CBV	18.0	2.9	20.9	9.8	2.9	12.7
scZDV/sdNVP	10.5	5.8	16.2	4.3	5.8	10.1
scZDV/sdNVP/CBV	10.0	5.8	15.8	4.3	5.8	10.1
3-drug ART	4.9	9.6	14.5	2.3	9.6	11.9
IV. “Best-case results” (lowest published estimates) for HIV risk; base case estimates for neurologic MT						

I. Primary results (base case estimates) for HIV and neurologic MT risk						
	Breastfed Infants (%)			Formula-fed infants (%)		
	HIV	MT	Total ^b	HIV	MT	Total ^b
<u>Breastfed Infants (%)</u>						
	HIV	MT	Total ^b	HIV	MT	Total ^b
No ARVs	18.1	0.2	18.3	9.7	0.2	9.8
sdNVP	11.0	0.2	11.1	6.0	0.2	6.1
sdNVP/CBV	9.8	0.2	10.0	4.9	0.2	5.1
scZDV/sdNVP	6.0	2.0	8.0	1.6	2.0	3.6
scZDV/sdNVP/CBV	4.6	2.0	6.7	1.4	2.0	3.5
3-drug ART	1.3	2.2	3.5	0.9	2.2	3.1
V. “Best-case results” (lowest published estimates) for HIV risk and “worst-case results” (highest published estimates) for neurologic MT risk						
	Breastfed Infants (%)			Formula-fed infants (%)		
	HIV	MT	Total ^b	HIV	MT	Total ^b
<u>Breastfed Infants (%)</u>						
	HIV	MT	Total ^b	HIV	MT	Total ^b
No ARVs	18.1	2.9	21.0	9.7	2.9	12.6
sdNVP	11.0	2.9	13.9	6.0	2.9	8.9
sdNVP/CBV	9.8	2.9	12.7	4.9	2.9	7.8
scZDV/sdNVP	6.0	5.8	11.8	1.6	5.8	7.4
scZDV/sdNVP/CBV	4.6	5.8	10.4	1.4	5.8	7.2
3-drug ART	1.3	9.6	10.9	0.9	9.6	10.5

* Strategies that minimize overall adverse events (HIV and MT) are shown in boldface type.

^a Results of analysis using highest published rates for HIV only are provided in technical appendix.

^b Totals may not appear to equal exact sums, due to rounding of HIV and MT risks.

Abbreviations: **ARV**: antiretroviral drugs; **ART**: antiretroviral therapy; **sdNVP**: single-dose nevirapine; **scZDV**: short-course zidovudine; **3TC**: lamivudine, **CBV**: "Combivir" tablet (ZDV/3TC)