To B or Not to B? That Is the Question, for Global Mother-to-Child HIV-1 Transmission Prevention Programs

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Despite significant global progress in preventing mother-to-child transmission (PMTCT) of human immunodeficiency virus 1 (HIV-1) over the past 10 years, an estimated 390,000 children became infected through MTCT in 2010 [1]. Providing antiretroviral drugs (ARVs) to pregnant women living with HIV infection is a key intervention of programs for PMTCT. The proportion of pregnant women living with HIV who received any ARVs for PMTCT in low- and middle-income countries in 2010 is increasing, and was estimated to be 59% [1]. Achieving a 90% reduction in new pediatric HIV infections by 2015, an ambitious target set by UNAIDS [2], will require leadership, commitment, and strategic deployment of resources. Even when the most effective antiretroviral regimens are available for free through public programs, many women and infants are lost at different stages in the “PMTCT cascade” (eg, maternal HIV testing, maternal entry into HIV care, maternal disease staging, maternal initiation of and adherence to ARVs, infant prophylaxis, infant HIV testing, and infant engagement in HIV care) [3]. These programmatic losses significantly compromise the effectiveness of PMTCT programs. Many countries are currently debating challenging decisions regarding whether to allocate additional resources to potentially more effective but costly antiretroviral regimens, or to direct scarce resources to other urgent needs, such as improving health infrastructure or supporting myriad other health programs in need [4]. The thoughtful analysis by Ciaranello et al of the clinical impact, cost, and cost-effectiveness of various antiretroviral regimens for preventing MTCT and optimizing maternal and child health in resource-limited settings is therefore particularly timely and relevant [5].

Among HIV-infected pregnant women not eligible for antiretroviral therapy (ART) for their own health (ie, with CD4 cell counts of >350 cells/mm³ and no World Health Organization [WHO] stage 3 or 4 illness by current guidelines), WHO recommends 1 of 2 antiretroviral options: either zidovudine during pregnancy (with other maternal ARVs during labor and for 1 week postpartum, and prolonged infant nevirapine prophylaxis during breastfeeding; option “A”); or 3-drug ARVs to the mother during pregnancy and breastfeeding while infants receive 4–6 weeks of ARVs (option “B”) [6]. A further option (“B+”) consists of universal lifelong ART to all pregnant women, regardless of HIV disease stage [7]. Whether or not (or to what extent) 3-drug ARV prophylaxis reduces MTCT or enhances infant HIV-free survival compared with zidovudine-based strategies, in women with higher CD4 cell counts, is not entirely clear from existing data, and is the subject of the ongoing PROMISE trial (being conducted by the IMPAACT network) [8]. Similarly, the impact of continued (vs interrupted) postpartum ART on maternal health and survival among women not meeting current treatment criteria is unknown (although it is anticipated from studies in general HIV-infected populations that ART will reduce their morbidity and mortality); this is also under study in the PROMISE trial [9].

Ciaranello et al have modeled maternal and infant health and cost-effectiveness outcomes in a simulated cohort of HIV-
infected pregnant women (who breastfeed for 18 months), using baseline health parameters and cost data from Zimbabwe and clinical outcomes data from South African cohorts. The authors are to be commended for conducting a careful and rigorous review of the literature upon which to base their assumptions, pursuing multiple sensitivity analyses that are responsive to many real-world implementation challenges, and considering both shorter- and longer-term outcomes.

Ciarnello et al conclude that any of the antiretroviral interventions (including single-dose nevirapine) are more effective and less expensive than providing no MTCT prevention intervention; and that option A (zidovudine) confers clinical benefit to mothers and infants and is cost-saving compared with single-dose nevirapine. These results confirm those of prior studies [10] and support the 2010 WHO recommendations, and many PMTCT programs use antiretroviral strategies that are consistent with these findings [1].

Importantly, the models of Ciarnello et al predict that option B will improve both maternal and infant health outcomes compared with option A, and will become cost-saving within 4 years postpartum. These findings add to a limited number of published analyses of cost-effectiveness of option B vs other PMTCT interventions [4, 11, 12] and are likely to be of significant current interest and relevance to many ministries of health. The projected cost saving is a key finding for programs that are considering whether to move from zidovudine-based to triple-ARV-based PMTCT regimens among women with higher CD4 cell count. The conclusion that option B will improve maternal and infant health outcomes and save money held true in sensitivity analyses of several real-world scenarios reflecting suboptimal PMTCT and pediatric ART uptake and maternal postnatal loss to follow-up. Certain programmatic factors also support the use of option B (rather than option A). First, option B simplifies and expedites the process of ARV initiation in pregnancy compared with option A, as it is not necessary to complete HIV disease staging and CD4 cell count measurement prior to initiating ART with option B (since all women will receive the same 3-drug antiretroviral regimens, usually efavirenz-tenofovir-emtricitabine). CD4 cell testing and disease staging pose significant (often insurmountable) obstacles to timely antiretroviral initiation during pregnancy in many resource-limited settings, given widespread health and laboratory infrastructure limitations and late presentation for antenatal care. Second, option B further enhances simplicity by allowing continuation of maternal ARVs during breastfeeding, removing the need for programs for infant formula or prolonged infant nevirapine prophylaxis (the latter programs require significant training of staff, counseling of patients, and supply chain management for additional products).

The authors also project that option B will increase maternal life expectancy, with an incremental cost-effectiveness ratio that is comparable with that of other HIV-related interventions ($1370/Year of Life Saved). Several additional programmatic and epidemiologic factors also favor option B+ over option B. First, rates of postpartum loss to follow-up among women not taking ART are likely even higher than those reported in the literature (with increasing time from delivery) [13]; this would likely further favor option B+ over option B, given the risk of adverse health outcomes among women who are not regularly screened for ART eligibility after stopping 3-drug ARVs postpartum. Second, the additional several years of ART (on average) that women will receive as part of option B+ (compared with waiting to initiate lifelong ART until CD4 cell count declines to <350 cells/mm$^3$) [14] is a small fraction of the projected approximately 30 years of ART that HIV-infected persons in resource-limited settings would receive over a lifetime [15]. In addition, if reduced heterosexual transmission [16, 17] that would likely be associated with continuous ART in postpartum women were incorporated into models, option B+ would likely become more cost-effective. Finally, there is also the potential for emergence of drug resistance with starting and stopping non-nucleoside reverse transcriptase inhibitor-based ART (potentially over multiple pregnancies and cycles in populations with high fertility rates), which favors option B+ over option B. Ironically, lifelong universal 3-drug ARV regimens in pregnancy (option B+) are likely to be particularly important and relevant in settings with the weakest health infrastructure, as this approach removes many of the programmatic bottlenecks related to screening and following up patients who are not yet receiving ART (presuming a public health approach to ART, with minimal laboratory screening and toxicity monitoring, task shifting, etc).

While the authors have been very careful to obtain comprehensive and accurate inputs and consider various scenarios in sensitivity analyses, it is helpful to consider several caveats. First, this analysis cannot in isolation inform ministries of health as to whether investment in more intensive PMTCT programs is the most urgent or cost-effective use of their funds, compared with investment in other endeavors. Second, cost is not the only consideration from a resource perspective: trained human resources and appropriate space are often limited even when funding is available. Furthermore, while modeling can be very informative, it is inherently limited by existing data and the assumptions made. Also, these findings may not be applicable to different populations (eg, women who formula-feed or who breastfeed for a different duration and populations with lower rates of—or later—presentation for antenatal care), and inputs and assumptions will undoubtedly change over time (an inherent risk of projecting over
a long period, although this is a useful and important feature of the models presented here). The presented models do not take adverse birth outcomes and potential toxicity or risks to infants of in utero 3-drug ARV exposure into account during the current pregnancy (nor with widespread first-trimester exposure to efavirenz among babies born to mothers who initiate efavirenz-based ART initiated as part of option B+ and who become pregnant again). Finally, as the authors say, it will be critical to assess actual uptake of, adherence to, and virologic suppression and retention in women continuing 3-drug ARVs as part of option B+ in real-world programs, as these factors can influence conclusions (as is also demonstrated by one of the sensitivity analyses presented by the authors); there is theoretical reason for concern that motivation to start and adhere to universal ART will be lower among persons with minimal clinical symptoms and high CD4 cell count, but this remains to be determined.

The timely findings presented by Ciaranello et al can help inform the ongoing debate regarding whether to adopt universal ART in pregnancy, and may add momentum to new recommendations for giving lifelong ART to all patients regardless of CD4 cell count [18]. Ideally, governments and donors will support implementation of the most effective and cost-effective interventions, in this case PMTCT options B or B+ (particularly option B, which is projected to be cost-saving as well as beneficial for maternal and infant health). At regional and facility levels, countries may need to support policies that encourage a mix of interventions based on variable existing and evolving local capacities, focusing on use of the simplest effective regimens and systems. However, implementation of options B or B+ should not occur at the expense of investing in the timely initiation of ART in more people living with advanced HIV disease and low CD4 cell count, nor at the expense of reaching far more HIV-infected women with any effective PMTCT services (in 2010, an estimated 40% of HIV-infected women received no antiretroviral intervention to prevent MTCT, and only 40% of HIV-infected women received an effective regimen [2]).

**Note**

**Potential conflicts of interest.** Both authors: No reported conflicts.

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**References**


