Turning the Tide on HIV in Women and Children: Preventing Breast-Milk HIV Transmission While Increasing Maternal Life Expectancy

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(See the Major Article by Hudgens et al, on pages 131–9.)

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In 2011, an estimated 330,000 new pediatric human immunodeficiency virus (HIV) infections still occurred in low- and middle-income countries, mostly as a consequence of mother-to-child transmission [1]. A large individual data pooled analysis of African prospective studies recently concluded that 26% of postnatal and 52% of perinatal HIV infections led to child death 1 year after acquisition of HIV in the absence of appropriate care and treatment [2]. This severe burden of pediatric HIV/AIDS and its negative impact on infant survival cannot be reversed as long as three-quarters of HIV-infections in children remain undiagnosed and thus untreated [3]. In this context, prevention of mother-to-child transmission of HIV is more than ever a pressing need, particularly in sub-Saharan Africa where the transmission rates are highest, with most African children breastfed for >6 months.

Reducing the risk of mother-to-child transmission requires in all instances the provision of antiretroviral drugs to the mother and/or her child [4]. The initiation or continuation of lifelong antiretroviral therapy (ART) is a universal standard among pregnant and breastfeeding women who are eligible for their own health, dramatically improving maternal survival while lowering very substantially the rates of both vertical and sexual HIV transmission by reducing the infectivity of all body secretions. Addressing the same issues among women with moderate to high CD4 cell counts was more subject to debate in the World Health Organization 2010 guidelines, which gave countries 2 equally rated options: providing antiretroviral prophylaxis primarily to either the breastfed child or to the breastfeeding mother. Each of these options bore advantages and disadvantages [5, 6].

The carefully conducted individual data pooled analysis of 5 large randomized clinical trials published in this issue of Clinical Infectious Diseases provides new insights on the efficacy of nevirapine prophylaxis in infants for preventing breast-milk transmission of HIV [7]. Daily nevirapine treatment of infants for 28 weeks reduced the risk of breast-milk HIV transmissions by 71%. However, to be fully effective, this antiretroviral-based intervention would need to be maintained throughout the entire breastfeeding exposure period, which was not done in the studies included in this pooled analysis. Moreover, this infant-only strategy should ideally involve drugs that are less likely than nevirapine to select resistant virus and compromise the future treatment needs of the few children contaminated despite this intervention. The French National Agency for Research on AIDS and Viral Hepatitis is currently sponsoring a randomized clinical trial (ANRS 12174) conducted in 4 African countries that is expected to yield more results on these 2 unresolved issues; in this trial, 2 alternatives to nevirapine are being assessed in syrup formulation (lopinavir boosted by ritonavir and lamivudine) and infant antiretroviral prophylaxis is provided as long as breastfeeding is continued [8]. This trial, along with results from operational studies addressing the feasibility and acceptability of long-term daily provision of antiretroviral drugs to breastfed infants born to HIV-infected mothers, are needed to clarify the benefits and risks of this infant-only approach to preventing...
mother-to-child HIV transmission. In any case, the question remains: Would this strategy be the best for both HIV-infected women and their children?

From a maternal point of view, we have learned from a noninterventional cohort in Zimbabwe that postpartum mortality was significantly increased among HIV-infected women with high CD4 cell counts (ie, not eligible for ART according to local standards), compared with HIV-uninfected women from the same population [9]. More recently, the Breastfeeding, Antiretrovirals, and Nutrition randomized clinical trial, part of this pooled analysis and conducted in Malawi among HIV-infected women with CD4 cell counts >250 cells/mL, yielded significant fewer maternal deaths among women receiving a triple-antiretroviral combination than among those not receiving such drugs [10]. A few weeks ago, an updated analysis of the Médecins Sans Frontières international African program concluded that mortality during ART remained higher in all other CD4 cell count strata than for adults (68% women) with a CD4 response >500 CD4 cells/mL [11]. One could therefore argue for the early initiation of triple-antiretroviral regimens among women with moderate to high CD4 cell counts to increase maternal life expectancy. From a public health perspective, because maternal ART keeps an infected mother alive, such treatment would have the indirect benefit of maximizing the chances of survival for her children, both HIV infected and uninfected [2]. Moreover, early treatment initiation in women would also reduce HIV transmission to HIV-uninfected male sexual partners [12]. From an operational point of view, offering the same triple-antiretroviral regimen to both eligible and ineligible women would make this programmatic approach universal and thus easier to implement. Given these many advantages, the World Health Organization has recently stated that providing antiretroviral combinations to all breastfeeding mothers had advantages over providing antiretroviral prophylaxis to their breastfed children.

If all pregnant and breastfeeding HIV-infected mothers were offered antiretroviral combinations, the questions of whether, how, and when to stop this intervention among women not eligible according to current guidelines are still unanswered. The Kesho Bora trial, a randomized clinical trial in multiple African countries, recently assessed the short-term risk for maternal health of stopping maternal triple-antiretroviral prophylaxis after cessation of breastfeeding among women with high CD4 cell count at initiation [14]. After having received a triple-antiretroviral combination for as long as 10 months (from 28 weeks gestation through 6 months postpartum), <5% of women with an initial CD4 cell count of 350–500 cells/mL progressed to death, stage 4 disease, or ≥1 CD4 cell count <200 cells/mL within 18 months of stopping prophylaxis. However, and probably more importantly, 25% of these women progressed to a CD4 cell count <350 cells/mL in the same time span, therefore becoming eligible for treatment initiation for their own health. This observation should be put in perspective with the fact that in sub-Saharan Africa the average total fertility rate is >5 children per woman [15]; that is, these women will soon become pregnant again and should therefore restart antiretroviral prophylaxis until their infant is no longer at risk of HIV contamination. Is this legitimate in this context to stop the triple-antiretroviral regimen started during the first pregnancy? It is indeed well known from studies in nonpregnant adults that intermittent ART, guided by CD4 cell counts, is associated with an increased risk of opportunistic disease or death [16, 17].

In sum, a new model for preventing mother-to-child transmission of HIV is now emerging, with initiation of lifelong ART in all HIV-positive pregnant and breastfeeding women, regardless of their CD4 cell counts [13]. United Nations agencies are now calling for the transformation of programs to prevent mother-to-child HIV transmission into newly formulated ART programs to meet global HIV targets [18]. This generalization of ART through the decentralization of services is already being implemented in Malawi [19], where it has already led to a 6-fold increase in the number of pregnant and breastfeeding HIV-infected women starting ART [20]. It is no longer time to argue against or for this approach, but it is now critical to carefully document the programmatic experience with this strategy in terms of feasibility, acceptability and infant and maternal safety. This new biomedical approach of the mother-child pair will be fully successful only if community-based interventions make HIV testing and counseling of pregnant women universal, thus reducing stigma and favoring the overall family care approach to HIV infection.

**Note**

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

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