

## EDITORIAL



## Breast-Feeding, Antiretroviral Prophylaxis, and HIV

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More than 200,000 of the 500,000 new human immunodeficiency virus (HIV) infections that occur each year in children are the result of transmission of the virus through the mother's breast milk.<sup>1</sup> In resource-constrained environments, how do we continue to promote breast-feeding, an important intervention for child survival,<sup>2</sup> without exposing more infants to this risk? This fundamental question plagues mothers and caregivers, especially in sub-Saharan Africa, where such choices are made every day.

In resource-constrained settings, current policies with respect to breast-feeding by mothers who are infected with HIV are guided by observational evidence that exclusive breast-feeding for the first 4 to 6 months of life reduces the risk of transmission of HIV as compared with mixed breast-feeding<sup>3,4</sup> (i.e., feeding both breast milk and formula) and may have survival benefits at 18 to 24 months that are similar to those for exclusive formula feeding.<sup>5,6</sup> Although peripartum prophylaxis with a single dose or a short course of antiretroviral agents effectively reduces intrapartum HIV transmission,<sup>7</sup> its effect does not extend much beyond 4 to 6 weeks in breast-feeding populations.<sup>8,9</sup>

Two studies published in this issue of the *Journal* offer important insight into research and policy development aimed at preventing mother-to-child transmission of HIV in resource-constrained settings.<sup>10,11</sup> Both are randomized, controlled trials, conducted in low-resource African settings that have a high prevalence of infection with HIV, and both groups of researchers had to deal with the immense challenges of conducting high-quality research in difficult conditions. They examined two critical questions in these settings: does either abrupt cessation of exclusive breast-feeding

at 4 months or longer postnatal antiretroviral prophylaxis to stem transmission of HIV through breast milk influence rates of new infection with HIV and child survival? The findings offer clear direction for future research but less clear direction for policy.

Kuhn et al.<sup>10</sup> found no significant difference in HIV-free survival at 24 months between children whose mothers were randomly assigned to a 2-month counseling program that encouraged abrupt weaning at 4 months and those whose mothers were encouraged to continue breast-feeding for the duration of their own choice (a median of 16 months). Among children who were infected with HIV by 4 months of age, being assigned to abrupt weaning significantly increased their risk of death. The authors conclude that early, abrupt cessation of breast-feeding by HIV-infected women in a low-resource setting is unwarranted for children who are exposed to HIV but are uninfected and is harmful for infants who are known to be infected with HIV.

Although the study was intended to be a randomized trial, the reality of conducting a study as challenging as this in a real-world setting meant that compliance was poor. Only two thirds of the early-cessation group had adhered to their group assignment at 5 months (1 month after their assigned date for cessation of breast-feeding had passed), and by 12 months, a quarter of the women were still breast-feeding. This was the case despite intensive counseling, provision of free formula and complementary food for 3 months, and home visits. Furthermore, 8% of the women elected to terminate breast-feeding early (before 4 months). The high (6.2%) rate of HIV transmission between 4 and 24 months in this group (expected, 0%) may be testimony to the substantial

noncompliance. Similarly, many women in the standard-practice group also did not comply with the study requirements (one third stopping breast-feeding at less than a year). Thus, although intention-to-treat analyses showed no statistical difference in 24-month HIV-free survival or HIV transmission, per-protocol analysis might have reached different conclusions. Child mortality rates were exceedingly high (almost 25%) in both groups, again diluting any survival benefit that the slightly lower rate of HIV infection in the early-cessation group might have offered in other settings.

The availability of preliminary results of the study by Kuhn et al. in 2006 influenced the World Health Organization to change its recommendation that breast-feeding should preferably cease at 6 months to an alternative stance that “at 6 months, if replacement feeding is still not acceptable, feasible, affordable, sustainable and safe (AFASS), continuation of breastfeeding with additional complementary foods is recommended.”<sup>12</sup> In contrast, recently published observational cohort studies among populations in Africa have provided compelling evidence that late postnatal transmission of HIV through breast-feeding can be substantial, increasing the risk of HIV infection by a factor of about 7.5.<sup>13,14</sup> A recent nonrandomized, urban cohort study in Ivory Coast that offered short-course regimens of combinations of antiretroviral drugs to prevent mother-to-child transmission together with either exclusive formula-feeding or shortened breast-feeding found that both of these feeding options significantly reduced postnatal transmission of HIV at 18 months as compared with long-term breast-feeding, without increasing mortality.<sup>15</sup>

It is clear that the publication of Kuhn’s important work, cautioning against early cessation of breast-feeding, will not end the controversy about the best course of action for breast-feeding mothers when their infants reach 6 months of age. The findings of the study help set norms for future studies that will investigate ways to reduce postnatal transmission of HIV in resource-limited settings: none should be designed so that HIV-exposed infants are randomly assigned to infant-feeding interventions without knowledge of their HIV status.

In an effort to reduce the risk of transmission of HIV through breast milk but still maintain the benefits of breast-feeding, Kumwenda et al.<sup>11</sup> com-

pared the efficacy of three antiretroviral prophylaxis regimens for infants that were commenced at birth. An extended 14-week course of nevirapine, with or without added zidovudine, was 40 to 51% better in preventing HIV transmission at 9 months than a 1-week standard regimen (single-dose nevirapine combined with 1 week of daily zidovudine). Disappointingly, rates of HIV transmission more than doubled in both of the extended-prophylaxis groups in the period between 9 and 24 months, during which many of the mothers continued breast-feeding (e.g., breast-feeding rates of 14 to 19% at 15 months). In contrast to HIV-infection rates, mortality rates did not differ by treatment group. Although HIV-free survival was significantly better in both extended-prophylaxis groups at 9 months of age, this advantage was lost by 12 months in the group that received extended prophylaxis with nevirapine plus zidovudine and by 15 months in the group that received extended prophylaxis with nevirapine only. Continued breast-feeding beyond the period of antiretroviral prophylaxis clearly affected the durability of the extended regimens, making it difficult to recommend widespread implementation of the study strategies in populations that favor prolonged breast-feeding. It stands to reason that in settings where breast-feeding must be the practice for socioeconomic reasons, antiretroviral prophylaxis for infants for the duration of breast-feeding may be the logical approach; however, future studies are urgently needed to examine potential strategies such as shortening the breast-feeding period or prolonging antiretroviral prophylaxis for the infant. Furthermore, potential toxic effects of these antiretroviral regimens, including those to the developing infant, and a possible role of these regimens in the emergence of resistant HIV must be carefully assessed.

Indeed, current research is already examining the benefits of extending antiretroviral prophylaxis through the entire breast-feeding period. Similarly, efforts to tailor breast-feeding options to obtain optimal HIV-free survival continue. Ultimately, as the two studies reported here show, caregivers and mothers in low-resource settings will continue to select options that best suit their own cultural, economic, and psychological needs, and science will need to adapt and design strategies to meet their needs, rather than the other way around.

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