Mortality among HIV-Exposed Infants: The First and Final Frontier

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(See the article by Kuhn et al, on pages 437–44.)

Excessive childhood mortality in sub-Saharan Africa is a tragic and familiar story. In the 1970s, >20% of children in Africa died before reaching 5 years of age, a rate higher than that in any other region in the world. When the human immunodeficiency virus (HIV) epidemic hit in the 1980s and 1990s, infant mortality rates increased further in some of the worst-affected areas as mother-to-child transmission (MTCT) became an important component of the problem. After more than a decade of research, there are now several proven antiretroviral interventions available to reduce MTCT of HIV to low levels, even in the context of breast-feeding, and the most extensive of these interventions may achieve MTCT rates as low as 1% [1–8]. However, as we chip away at MTCT in research cohorts and start to apply new interventions in program situations, we must not lose sight of overall infant mortality. Forty-three percent of the worldwide mortality among those <5 years of age currently occurs in Africa [9].

Three factors have emerged from the HIV epidemic to worsen the ongoing childhood mortality epidemic. First, more than one-half of HIV-infected infants will die within the first 2 years of life without antiretroviral treatment [10]. Fortunately, we now have the means to both prevent and treat infant HIV infection where antiretroviral agents are available, and expanding antiretroviral prevention and treatment programs remains a public health care priority. Second, infant feeding options pose a difficult dilemma: longer breast-feeding may increase MTCT of HIV and subsequent HIV-associated mortality, but shorter breast-feeding (or no breast-feeding) may increase mortality from common childhood illnesses [11, 12]. Finally, HIV-exposed but uninfected infants, who represent 30% of all children born in some areas of southern Africa, have higher mortality rates than do infants born to HIV-uninfected mothers, even when feeding patterns are similar [10, 13–15].

In this issue of *Clinical Infectious Diseases*, Kuhn et al [16] provide important data regarding the duration of breast-feeding for HIV-exposed but uninfected infants in Zambia. This was a new analysis from the Zambia Exclusive Breast-Feeding Study, which previously demonstrated no benefit of early weaning for HIV-free survival [11]. In the current analysis, a cumulative mortality rate of 13.6% is reported among 749 HIV-uninfected infants who were followed up for 1–24 months. At each interval studied through 18 months of age, weaning from breast milk was associated with a significantly higher risk of infant mortality than was continued breast-feeding beyond 18 months. Although the absolute mortality risk decreased after the first year of life, the risk associated with weaning progressed over time from a 2.0-fold risk with weaning at 4–5 months to a 3.5-fold risk at 6–12 months and to a 4.2-fold risk at 12–18 months. Infants born to women with CD4+ cell counts <350 cells/μL had greater risk associated with weaning before 18 months of age, possibly because of lesser breast milk protection or other heightened risks that occur when women have lower CD4+ cell counts.

Several additional risk factors contributed to mortality among infants in the first 2 years of life. Maternal death, infant birth weight <2500 g, other children in the household <5 years of age, and food insecurity were also significant risks for mortality in multivariable models. These findings suggest that, although feeding method is an important consideration, other measured and unmeasured factors may also contribute to infant mortality. The authors do an admirable job of controlling for confounders, such as reverse causality, by iden-
tifying infants who may have been unable to breast-feed because of an existing illness; however, maternal confounders related to weaning decisions were less easily measured. Detailed diagnostic data were unavailable to evaluate specific pathogens associated with infant deaths, and we continue to have lingering questions about why these infants, like others across Africa, die before the age of 2 years. The extent to which these results can be generalized to other settings in Africa or elsewhere in the developing world is also unknown, because mortality rates and the underlying causes of death vary.

The authors call our attention to one of the most important and modifiable risk factors for infant mortality—early weaning from breast-feeding. Unfortunately, this particular risk factor may also lead to late MTCT of HIV, and balancing these risks is a difficult task that requires knowledge of the local infant mortality rate. As improved preventive MTCT measures (such as antiretroviral prophylaxis for infants or highly active antiretroviral therapy for mothers) become available, the MTCT-mortality balance may tip for most regions in Africa, and an increased period of breast-feeding is likely to save lives. However, many unknowns remain, including the mortality benefit achievable in different settings from extended breast-feeding, the efficacy and safety of extending preventive MTCT interventions beyond the period currently studied, and the cost of extended interventions.

A striking message from this study is that the infant mortality rate is far too high. In a setting where >13% of HIV-uninfected infants died between 1 and 24 months of age and an additional 4% died in the first month of life, addressing the MTCT problem alone is clearly insufficient. These findings are generally consistent with those of other large studies that have demonstrated that a high mortality rate is, in part, related to HIV exposure: the 2-year mortality rate was at least 3-fold higher in Zimbabwe and 2-fold higher in Uganda among HIV-uninfected infants born to HIV-infected mothers, compared with that among infants born to HIV-uninfected mothers [13, 14]. The vulnerability of these HIV-exposed uninfected infants has been recognized for many years [17], but its cause remains elusive. Early investigators hypothesized that HIV-infected women may not be able to care for their infants as well as uninfected women. However, the consistently higher mortality rates among HIV-exposed infants across locations and maternal CD4+ cell counts, as well as the presence of risk even where maternal highly active antiretroviral therapy is available [15], suggest an immunologic or nutritional explanation. Breast milk quality is an obvious starting point, but initial attempts to find interpretable differences between the breast milk of HIV-infected and uninfected women have been unrevealing [15]. Furthermore, the results of the current study and others [12] suggest that, even if the breast milk of HIV-infected women has some deficiencies, breast-feeding remains one of the cornerstones of mortality prevention.

Interventions that allow for longer periods of safe breast-feeding are an important first step, but additional measures to reduce infant mortality both before and after weaning are needed. These measures might include infrastructure investments to reduce environmental pathogens and improve medical care. Provision of safe water is a priority, although a recent study in Kenya did not demonstrate efficacy from a water vessel intervention among HIV-exposed infants at the time of weaning [18], suggesting that the loss of breast milk protection is as important as unsafe exposures at weaning. Educational campaigns or home visits to promote appropriate feeding practices and early medical intervention may be effective where limited access to medical care is a problem. At the individual level, nutritional and micronutrient support for women and infants may reduce infant mortality rates, as demonstrated by a recent study in Tanzania showing the benefit of maternal vitamin D replacement for infant survival [19]. Other interventions include prophylactic vaccinations, use of bed nets in areas where malaria is prevalent, and the provision of prophylactic sulfamethoxazole-trimethoprim to HIV-infected women in pregnancy and to infected infants [20, 21].

In the end, to fully address childhood mortality, we need more information about the specific causes of mortality at the local level and about the nature of the vulnerability of HIV-exposed but uninfected infants. The authors of the current study provide us with valuable information about the high mortality risk among these infants in Zambia and demonstrate that weaning before 18 months of age is an important and potentially modifiable risk factor. From a public health standpoint, these findings fit well with recent advances in the prevention of MTCT during breast-feeding. However, MTCT prevention studies of longer duration are needed, and antiretroviral access still needs to expand globally. As these interventions scale up, this study reminds us that MTCT and mortality are inextricably bound and must be addressed as a whole.

Acknowledgments


References

4. Shapiro RL, Hughes M, Ogwu A, et al. A randomized trial comparing highly active antiretroviral therapy regimens for virologic effi-


