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Bystander Effects:

Children Who Escape Infection But Not Harm

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Few would disagree about the urgency of ensuring that pregnant HIV-infected women with advanced disease have access to highly active antiretroviral therapy (HAART). Not only is HAART a life-saving intervention for this critical societal stratum (young women and mothers), but it clearly reduces pre- and perinatal HIV transmission and is likely to be effective to reduce postnatal transmission through breast-feeding. The findings from Chatterjee et al¹ in this issue suggest that further benefits may extend to exposed-uninfected infants, providing yet another reason for strengthening HIV care and treatment programs for pregnant women.

Within a large mostly breast-fed cohort in Tanzania recruited before the widespread availability of HAART, risk factors for mortality to 2 years of age among children who remained uninfected despite being born to HIV-infected mothers were investigated. The study found that uninfected children whose infected mothers had more advanced HIV disease (including low CD4 cell counts and high viral loads) were twice as likely to die compared with uninfected children whose infected mothers had less advanced disease.¹ These intriguing results are consistent with 2 previous studies: 1 based on a pooled analysis² and 1 that considered mortality between birth and 4 months.³ These results are also consistent with early work indicating that exposed but uninfected children had more episodes of acute and persistent diarrhea compared with unexposed controls.⁴

Any benefits of HAART to reduce women's mortality postpartum contributes alone to better child outcomes, because, for obvious social reasons, orphans have a poor prognosis regardless of their HIV status.^{5–7} HAART might also be expected to reduce the vulnerability of uninfected children born to immunosuppressed mothers if it improves women's capabilities to look after their children. Despite intuitive appeal, whether sicker mothers are less able to take care of their children is far from established. We have previously demonstrated that the association between low maternal CD4 cell counts and increased infant mortality in the first few months of life is independent of maternal mortality and morbidity and is independent of separation attributable to maternal hospital admissions.³ Although these powerful social factors may exacerbate the vulnerability of exposed-uninfected infants, other biologic vulnerabilities, such as nutritional or immunologic deficiencies, may also exist. The precise nature of these vulnerabilities is important, because HAART may correct some but not all.

HAART rapidly leads to improvements in CD4 cell count but reconstitution of B- and T-cell function lags behind.⁸ If started, on average, 3 months before delivery, it is unclear whether measurable improvements in maternal immunity to common pathogens that threaten infant health are achieved. It is well established that infants rely on passively acquired antibodies for protection during the neonatal period. From the third trimester, specific transport mechanisms ensure that maternal antibody crosses the placenta and enters fetal circulation. Preterm delivery precipitously interrupts this transfer, thereby contributing to preterm infants' increased vulnerability to infections. Breast-feeding provides additional protection not only by passive provision of immunoglobulin and other immune factors but by priming the infant's immune system.⁹ If low maternal CD4 cell counts are markers of deficits in mucosal immunity in breast milk, we might expect the association to be strongest among breast-fed infants. To date, there has been too little reported variability in infant feeding practices within the published studies to investigate this.

Exposed-uninfected children have been widely studied to characterize immune responses after HIV exposures that do not result in infection. Multiple immunologic changes have been observed in addition to HIV-specific T-cell responses, including changes in T-cell subsets, cytokine and chemokine production, and maturation factors among others.¹⁰ We might have expected exposed-uninfected infants to be less rather than more susceptible to other infections, given their successful prior encounters with HIV and attrition (into the infected group) of those with infection vulnerability genes. It is possible, however, that these concomitant responses, such as more vigorous activation, may not be beneficial against other pathogens and may compromise later developmentally appropriate responses.

An alternate explanation for the increased risk of uninfected children of women with low CD4 cell counts is increased exposure to other pathogens, given more symptomatic disease and increased shedding. It is therefore of considerable interest that recent data from South Africa observed that exposed-uninfected infants hospitalized with pneumonia were almost 6-fold more likely to fail antibiotic therapy than equally sick uninfected infants of uninfected mothers.¹¹ Because all children in this study were admitted with severe clinical pathologic conditions, which, in effect, condition on pathogen exposure, these findings suggest some form of immune compromise among exposed-uninfected children. These results also raise the concerning issue of household transmission of multidrug-resistant organisms, which may be more common among immunosuppressed HIV-infected adults among whom routine cotrimoxazole is recommended and who are likely to have had multiple prior treatments for various infections.

The number of these vulnerable exposed-uninfected infants is large and growing. This is because there is no consistent decline in HIV seroprevalence among pregnant women in most countries, and there has been considerable progress in expanding access to programs to prevent mother-to-child HIV transmission. As access to HAART expands, we might expect some spin-off benefits for exposed-uninfected infants too; however, it is too soon for complacency. Why exposed-uninfected infants of mothers with advanced disease are at increased risk for severe morbidity and death remains unclear. These mechanisms are relevant to whether HAART is or is not fully able to benefit this group of children. Current funding streams and research agendas rightly focus on improving HIV prevention and expanding access to treatment. Unfortunately, this focus overlooks other adverse biologic consequences that maternal HIV infection may have for child health. Children of HIV-infected mothers are not only at risk of HIV infection and orphanhood but may also be affected by HIV in ways we do not yet fully understand. It is important to understand these vulnerabilities better so that interventions can be developed to complement existing prevention and treatment programs to improve the health of children.

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