Milk Mysteries: Why Are Women Who Exclusively Breast-Feed Less Likely to Transmit HIV during Breast-Feeding?

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(See the article by Lunney et al, on pages 762–769.)

At first it seemed counterintuitive. Why would human immunodeficiency virus (HIV)-infected women who exclusively breast-feed their infants be less likely to transmit HIV postnatally than women who breast-feed but also provide their infants other liquids and/or solids? Aren’t the exclusively breast-fed infants ingesting more HIV-containing human milk? Yet, following the original observation from Durban in South Africa [1], at least 3 other large epidemiologic studies, 2 of them set up specifically to examine this hypothesis, also observed significantly lower rates of postnatal HIV transmission among exclusively breast-fed infants, compared with predominantly or partially breast-fed infants [2–4]. Possible explanations for the mechanisms underlying this association have been discussed [5], but there are few data examining the pathways.

In this issue of the Journal, Lunney et al [6] take on the daunting task of testing one of the potential explanations for the HIV transmission–reducing effects of exclusive breast-feeding. They present data from the ZVITAMBO study undertaken in Zimbabwe which provided the first replication, and arguably the most powerful confirmation, of the association between exclusive breast-feeding and reduced risk of postnatal HIV transmission [3]. What made their nonexperimental study powerful was that during the course of the fieldwork, strengthened lactation counseling to support healthy breast-feeding was introduced for both HIV-infected and HIV-uninfected women. Following the improved counseling, uptake and duration of exclusive breast-feeding increased and postnatal HIV transmission decreased [7, 8]. This “natural experiment” nested within their cohort is probably the closest to a randomized design possible to address this hypothesis.

Exclusive breast-feeding is recommended for the general population primarily because human milk can satisfy all of an infants’ nutritional and fluid needs through the first 6 months of life [9]. The addition of supplements is, at best, unnecessary. At worst, these unnecessary supplements are harmful and have been associated with increased infant morbidity and mortality in HIV-uninfected populations [10]. Exclusive breast-feeding is also usually associated with on-demand feeding where suckling frequency and duration is largely determined by the infant.

If undisrupted, milk production becomes closely matched to infant need [11]. Lunney and colleagues hypothesize that the unnecessary supplements provided by mixed breast-feeding mothers are one such disruption and upend the physiological balance between milk production and removal. They hypothesize that irregular and/or infrequent suckling from the infant leads to milk stasis, to breast engorgement, to mastitis, to high quantities of HIV in breast milk, and finally to increased risk of postnatal HIV transmission. A logical and plausible pathway, especially in light of data demonstrating associations between exclusive breast-feeding and reduced likelihood of breast problems, including mastitis, among uninfected women [12].

To test the hypothesis about the pathway, the authors compared HIV RNA quantity and a marker of sub-clinical mastitis—the ratio of sodium to potassium (Na/K)—in breast milk collected at 6 weeks and at 3 and 6 months between HIV-infected women who reported giving their infant only breast milk or who reported giving their infant, in addition to breast milk, solids, and/or nonhuman milk at least once during the first 3 months of life. Surprisingly, they found no association between either breast milk HIV RNA quantity or Na/K ratio and feeding group. An upshot of these null findings is...
that it helps put to rest lingering concerns that the association between exclusive breast-feeding and reduced HIV transmission may be simply attributable to sicker women tending not to breast-feed exclusively [13]. In this study, exclusivity of breast-feeding persisted as a strong predictor of postnatal HIV transmission even after control for these markers of breast milk infectivity as well as after control of maternal plasma viral load and CD4 count. But the authors’ hypothesis about why exclusive breast-feeding reduces HIV transmission appears to be incorrect.

Or is it? Given the multifactorial processes driving postnatal HIV transmission, epidemiologic studies are blunt instruments to answer questions of pathogenesis. Infant feeding practices are variable over time, and dichotomous categories gloss over this variability. It is unclear whether the frequency and regularity of suckling was sufficiently different between the 2 feeding groups to initiate the hypothesized cascade resulting in transmission. There is uncertainty too in the temporal dynamics of these processes. It would have been interesting to examine associations soon after disruptions to exclusive breast-feeding or in the same mother before and after changes in her feeding practices occurred. Age of the child also complicates interpretation. In the first days and weeks while lactation is established, concentrations of sodium and many of the immunomodulatory components of milk are high and potassium is low. Interpretation of the meaning of an elevated Na/K ratio depends on the age of the child [14]. Lunney and colleagues also present some contradictory findings, namely that “breast problems” ascertained by maternal report or clinical exam were associated with feeding practice but “mastitis” defined by Na/K ratio was not. Intermittent viral shedding over time and between breasts [14] also complicates interpretation, and the low levels of viral shedding in breast milk at the borderline of detection of the assays available make it difficult to detect subtle associations. Given these limitations, the data presented cannot definitively rule out the hypothesis that changes in breast health account for the protective effects of exclusive breast-feeding. Nevertheless, these carefully conducted analyses do challenge us to refine and expand ideas about the mechanisms underlying this protection.

The puzzle of exclusive breast-feeding is part of a bigger puzzle about why postnatal HIV transmission through breast-feeding is so inefficient. Infants ingest many liters of virus-containing breast milk over many months, yet most do not become infected [15]. Other intriguing results shed new light on why this might be. Specifically, Lunney et al [6] present data demonstrating that the association between Na/K ratio in breast milk and postnatal HIV transmission is modified by maternal plasma viral load. When the quantity of HIV RNA in plasma from women is high, Na/K ratio is associated with an increased risk of postnatal HIV transmission. When levels of circulating HIV RNA in plasma from women are low, Na/K ratio shows a trend towards less postnatal HIV transmission. Because sodium is a marker of mammary permeability, as well as of mastitis, either nonpathological or pathological processes may be implicated in recruiting immune factors into breast milk that serve to prevent transmission in circumstances when viral exposures are sufficiently low. Our group, as well as others, have observed associations between immunomodulatory components of breast milk and reduced postnatal HIV transmission, but usually only after the adjustment for breast milk viral load [16, 17].

Even in an era of antiretroviral therapy, where providing treatment for mothers with low CD4 counts and infant prophylaxis if mothers have high CD4 counts can substantially reduce transmission [18, 19], studying the mechanisms underlying HIV transmission remains important. It remains important because these studies are central to the fundamental scientific challenge posed by HIV regarding why so many individuals (infants and adults) are exposed to the virus but do not acquire infection themselves. Breast milk may provide one of the keys to unlock these secrets.

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References

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