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EDITORIAL

Breastfeeding, Antiretroviral Therapy, HIV Transmission, and the HIV Reservoir

Recommendations on breastfeeding by persons living with HIV (PLWH) have shifted globally over time. Because the absolute risk for HIV transmission through breast milk in the absence of antiretroviral therapy (ART) is as high as 16% to 20%, recommendations for low-resource settings in the early 1990s initially emphasized replacement feeding if acceptable, feasible, affordable, sustainable, and safe—or if not, exclusive breastfeeding for a shortened period with rapid weaning. However, in such settings, infant morbidity and mortality due to infectious diseases are high, safe water to reconstitute formula is limited, and formula is often unaffordable; studies soon showed that HIV-exposed infants who did not breastfeed had an increased risk for death, illness, and malnutrition (1, 2). By 2010, guidance in low-resource settings shifted toward breastfeeding by PLWH, particularly if the breastfeeding individual was receiving ART (1, 2). After clinical trials demonstrated that both maternal ART and infant antiretroviral prophylaxis can significantly decrease postnatal transmission risk (3), in 2016 the World Health Organization (WHO) recommended that PLWH receiving ART in low-resource settings breastfeed their infant through 12 to 24 months of age (1).

In contrast, until recently in high-resource settings, it was recommended that breastfeeding be avoided in PLWH because there is residual risk for breastfeeding-associated transmission even in the context of ART, formula feeding is safe and affordable, and morbidity and mortality secondary to respiratory and gastrointestinal infections are low (4). The risk for possible HIV transmission through breast milk was believed to outweigh the benefits of breastfeeding in these settings, resulting in disparate recommendations in low- versus high-resource settings, despite recommendations for universal lifelong ART for pregnant PLWH in both settings.

Research published in 2011 to 2016 provided evidence sufficient to conclude that sexual transmission does not occur in PLWH who have reached and sustained an undetectable viral load, defined as a plasma HIV RNA level lower than 200 copies/mL (5). In addition, sexual transmission was near zero even with low-level plasma viremia (HIV RNA level <1000 copies/mL) (5). These data resulted in the global campaign "Undetectable Equals Untransmittable" (U=U), stating that individuals with sustained viral suppression can have condomless sexual intercourse without placing their sexual partner at risk for HIV acquisition. The U=U campaign raised the question of whether U=U also holds true for vertical and breast milk HIV transmission.

Research has demonstrated zero transmission of HIV in utero or intrapartum (vertical) from PLWH receiving ART who attain an undetectable viral load (defined as a plasma HIV RNA level <50 copies/mL) before pregnancy and continue ART with sustained viral suppression during pregnancy (6). Of note, in contrast to HIV sexual transmission, there was a small residual risk for vertical HIV transmission if the plasma HIV RNA level was 50 to 399 copies/mL near delivery. Thus, using the definition of undetectable as a plasma HIV RNA level less than 50 copies/mL, U=U may be considered applicable to vertical transmission if ART resulting in sustained viral suppression is started before and continued during pregnancy.

Studies have shown that breast milk transmission from PLWH receiving ART with undetectable plasma HIV RNA is extremely low, under 1% (3). However, the risk is not zero because breast milk transmission from PLWH with an undetectable viral load has been reported (3, 7). Investigators have shown that although ART can result in undetectable cell-free HIV RNA in breast milk, cell-associated HIV DNA may still be present despite undetectable maternal plasma viral loads (8), although its significance is unclear.

Research by Osegueda and colleagues (9) evaluated the HIV reservoir within breast milk cells in the context of long-term sustained viral suppression, and it provides some reassuring new data. The authors evaluated HIV RNA in breast milk fluid and cell-associated HIV DNA in the cellular compartment of breast milk weekly over the first 7 weeks of lactation from an HIV-positive elite controller with an undetectable viral load for 9 years without ART, a woman with HIV receiving dolutegravir-based ART with an undetectable (<50 copies/mL) viral load for more than 5 years, and a woman without HIV as control. No HIV RNA was detected in the breast milk of either woman with HIV. Very low levels of cellular HIV DNA (0.08 to 0.74 HIV DNA copies per million cells) were detected in the women with HIV; after analyzing 14 million cells from the elite controller, the researchers detected no HIV provirus by full-length individual proviral sequencing, and in 11 million cells from the woman receiving long-term dolutegravir, they detected only 4 defective HIV copies with large internal deletions. Thus, the few proviruses recovered were non–replication-competent with large defects.

These data are reassuring and support the revised recommendations on infant feeding by PLWH in high-resource settings (10). In January 2023, the U.S. Department of Health and Human Services endorsed shared decision making regarding breastfeeding

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between health care providers and lactating PLWH with undetectable HIV viral loads receiving ART, recognizing the growing number of PLWH who desire to breastfeed their infant and the often complex social and cultural settings of their lives. Although avoidance of breastfeeding is the only infant feeding option that eliminates the risk for postnatal infection, breast milk transmission risk in persons with sustained viral suppression receiving ART is extremely low (3). In the context of a family-centered, nonjudgmental, harm-reduction approach, the provider and patient consider the unique values and circumstances of the patient, family, and cultural context and help and support the pregnant PLWH in making the best decision for themselves and their infant.

As noted by Osegueda and colleagues, more research is needed on the HIV reservoir in the breast milk of PLWH with sustained viral suppression across the full months of breastfeeding, given the small number studied over a limited time period. Although some preliminary studies have reported on HIV transmission outcomes of breastfeeding in the setting of ART and viral suppression in high-resource settings, these include few patients, and more data are needed. In addition, there is a lack of data and conflicting provider opinions regarding whether provision of infant antiretroviral prophylaxis in addition to effective maternal ART during breastfeeding is necessary, and further studies are needed. Finally, in the era of long-acting ART and broadly neutralizing antibodies, the role of new agents should be evaluated for both treatment of the lactating PLWH and prophylaxis for the breastfeeding infant.

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