Eliminating HIV transmission through breast milk from women taking antiretroviral drugs

Ameena Goga and colleagues argue that frequent testing of maternal viral load is needed to eliminate HIV transmission through breast milk in low and middle income settings

Mothers taking antiretroviral drugs with low plasma viral loads may still transmit HIV to their breastfeeding children. Given the widely acknowledged benefits of breastfeeding, eliminating the risk of vertical transmission of HIV through breast milk must be a priority.

Transmission from mother to child via breast milk is influenced by maternal HIV viral load and occurs through cell-free and cell associated HIV-1.[1] In women living with HIV, breast milk contains quiescent CD4 cells with high capacity to produce HIV and activated CD4 cells with replicating HIV, despite the presence of suppressive antiretroviral treatment.[1] Additionally, transfer of maternal cells through breastfeeding induced microchimerism may establish permanent HIV reservoirs in breastfeeding infants.[2]

Nonetheless, breast milk has multiple immediate and long term advantages: it contains bacterial genes facilitating carbohydrate, amino acid, and energy metabolism[3]; contributes to almost 40% of the infant microbiome during the first 30 days of life[3]; modulates the human virome[4]; reduces the risks of communicable and non-communicable diseases in childhood and adulthood[5]; and is associated with better IQ, educational attainment, and income at age 30 years.[6] Consequently, there is an urgent need to eliminate transmission of HIV through breast milk.

Although HIV and infant feeding guidelines previously recommended avoiding breastfeeding or reducing duration,[7-9] by 2016 modelling showed that in a setting where the mortality risk associated with avoiding breastfeeding is high, then 24 months of breastfeeding and maternal triple antiretroviral treatment maximises child HIV-free survival.[10]

Maternal antiretroviral treatment or infant prophylaxis during breastfeeding reduces the risk of HIV transmission through breast milk.[11-14] Since 2016, all Global Plan priority countries (where 90% of the world's pregnant women with HIV live) recommend lifelong antiretroviral treatment for pregnant and lactating women with HIV.[15 16] Additionally, in 2016 the World Health Organization recommended that women taking antiretroviral drugs should breastfeed for at least 12 months and may continue breastfeeding for up to 24 months or longer (similar to the general population) while being fully supported for adherence to antiretroviral treatment.[17]

WHO guidelines for HIV plasma viral load monitoring are not specific to pregnancy and lactation: a plasma viral load test is recommended at six months and 12 months, and then every 12 months.[18] Breast milk HIV viral load may be a better predictor of breast milk transmission than plasma viral load[1]; however, routine monitoring of breast milk viral load is costly, not widely performed, and not practical.

We have previously highlighted the increasing contribution of breast milk transmission to overall mother-to-child transmission in low and middle income countries because of challenges with early initiation of antiretroviral treatment and postnatal treatment adherence.[19] We have also highlighted the contribution of maternal prevalent or incident HIV infections to the paediatric HIV case rate[16 19 20] and proposed that current strategies may fall short of eliminating breast milk transmission.[19] Complementary interventions such as broadly neutralising antibodies or vaccines are needed.[19] We have also emphasised the critical need to dismantle structural barriers[16] and strengthen routine cohort monitoring of women living with HIV and their children to determine long term outcomes.[21] Here we consider whether we can eliminate breast milk transmission of HIV in women taking antiretroviral drugs.

KEY MESSAGES

- Mothers taking antiretroviral drugs with low detectable plasma viral loads may still transmit HIV.
- This is a result of challenges with antiretroviral treatment adherence and retention in care, viral load rebound between the viral load test intervals, transmission from a breast milk cellular reservoir, or postpartum or peripartum viral rebound.
- Point-of-care technologies for viral load testing during pregnancy and breastfeeding must be scaled up and results acted on to reduce transmission through breast milk.
- The utility of additional complementary interventions such as long acting maternal antiretroviral drugs, extended prophylaxis, broadly neutralising antibodies, or vaccines in infants whose mothers are receiving antiretroviral treatment needs further investigation.

Risk of transmission through breast milk during treatment

The risk of transmitting HIV through breast milk is not zero if women with HIV are not consistently and completely suppressed at <50 copies/mL plasma viral load throughout breastfeeding (see supplementary table 1; bmj.com). A major concern is that HIV transmission via breast milk has been described in women with previously documented viral load suppression; these findings may be because viral load measurements are taken or reviewed infrequently during breastfeeding.[22-25]

In many countries it is assumed that a viral load of <1000 copies/mL is associated with a low risk of mother to child transmission; however, in a South African study, women with a viral load of <1000 copies/mL at delivery accounted for 43% of early mother to child transmission (median age 44 days, interquartile range (IQR) 42-49 days).[26] If we extrapolate from a meta-analysis that included women taking antiretroviral drugs (with detectable or undetectable HIV viral load) and assume a 20% maternal HIV prevalence, six month mother to child transmission among women taking antiretroviral drugs

translates into 220 new infections per 100 000 live births, almost four times higher than the mother to child transmission elimination target of ≤50 new infections per 100 000 live births.[27] In this context, 12 month mother to child transmission translates into 580 new paediatric HIV infections per 100 000 live births—more than 10 times the global target.[27 28] In a study in Malawi (October 2014 to May 2016), women taking antiretroviral drugs with low detectable viral load (defined as ≥40-1000 copies/mL) contributed an excess of 460 new infant HIV infections annually, which translates into 60 additional infections per 100 000 births annually.[29]

If breast milk mother-to-child transmission occurs despite maternal antiretroviral treatment, as a result of prolonged or intermittent maternal viraemia independent of health system and individual barriers to viral suppression, then the utility of additional or complementary interventions needs investigating. Potential interventions include long acting antiretrovirals or intermittently administered broadly neutralising antibodies or vaccines that could induce passive or active immunity without reliance on daily administration. Promisingly, in neonatal macaque models, combined administration of broadly neutralising antibodies PGT121 and VRC07-523 administered within 30 to 48 hours of oral simian HIV exposure mediated effective post-exposure prophylaxis in infant macaques.[30 31]

Risk factors for breast milk transmission

Both maternal breast milk viral load and plasma viral load are predictors of breast milk HIV transmission.[23] When single dose nevirapine for mother and baby was the main intervention to prevent transmission, maternal plasma viral load >50 000 copies/mL accounted for 37% (95% confidence interval 22% to 51%) of breast milk transmission between 6 weeks and 12 months.[32] Multivariable analyses of data gathered in Malawi between 2014 and 2016 showed that maternal viral load was the only important predictor of transmission.[29] Consequently, frequent maternal plasma viral load monitoring and management for all pregnant and breastfeeding women are critical to achieve and maintain plasma viral load below the detection threshold.

Maternal plasma viral load monitoring

Despite increasing access to lifelong antiretroviral treatment, the coverage of plasma viral load monitoring during breastfeeding ranges from 38% to 98% in Global Plan priority countries.[29 33] Non-pregnant adult guidelines recommend six monthly viral load monitoring, but this may result in only 31% viral load testing coverage during pregnancy[34]; reasons for this include late antenatal booking, limited number of antenatal visits, underuse of routine maternal viral load monitoring, stigma, and inoperability of machines to measure viral load.[35 36]

Since 2019, some low and middle income countries, such as South Africa, recommend viral load testing at antenatal care booking (or three months after antenatal antiretroviral treatment initiation or switching), at delivery, and then six monthly.[37] If viral load is ≥1000 copies/mL or 500-<999 copies/mL then counselling and repeat viral load testing are recommended 4-6 weeks or 8-10 weeks later, respectively. Infant antiretroviral prophylaxis is extended beyond six weeks or includes two drugs only if maternal viral load is ≥1000 copies/mL. However, mother-to-child transmission can occur when viral load is <1000 copies/mL.[37] Consequently, current recommendations would not eliminate the risk of breast milk transmission.

Regardless of setting or year, the prevalence of plasma viral load suppression among women with HIV taking antiretroviral drugs is suboptimal (see supplementary table 2; bmj.com). In rural Uganda, by 2015 five year retention in care was 90% among women starting antiretroviral treatment during pregnancy, decreasing to 67.5% if those not followed up were assumed to be out of care.[38] Among women with HIV retained in care, viral suppression (≤400 copies/mL) was 89.6% (95% confidence interval 83.2% to 94.2%), falling to 80.7% (73.4% to 86.7%) among participants enrolled in the study, and to 60.5% (53.6% to 67.3%), assuming that those not enrolled in the study were not suppressed.[38]

Scaling up viral load monitoring

Breastfeeding women are a priority population for repeated plasma viral load measurements. However, in many Global Plan priority countries viral load monitoring scale-up is limited because of logistical challenges relating to plasma specimen collection. This requires EDTA tubes, which are often unavailable, can break in transit, and require storage, a cold chain, timely centrifugation, and transportation to central laboratories.[39]

Some countries have used dried blood spot or plasma separation cards to scale up viral load testing; however, dried blood spot viral load testing cannot reliably measure viral loads <1000 copies/mL.[39] Furthermore, the median time between sample collection and availability of results can be as long as 72 days.[40 41] Investing in mobile health technologies for use by clinicians and patients may improve turnaround times and prompt action for high viral load measurements. Plasma separation cards have a slightly lower limit of detection (790.2 copies/mL (95% confidence interval 658.9 to1003.6 copies/mL)),[41] are cost neutral,[39] and are easier to use.

Point-of-care viral load testing is a promising technology as results are available about two hours after sample collection. An open label, non-inferiority, randomised controlled trial found that point-of-care viral load monitoring with task shifting significantly improved retention and viral suppression among HIV infected adults in South Africa.[42] However, some point-of-care technologies cannot detect viral loads of <50 copies/mL. A systematic review for the Cepheid GeneXpert reported a pooled sensitivity of 96.5% (95% confidence interval 95.1 to 97.5) and pooled specificity of 96.6% (92.9 to 98.4) for a treatment failure threshold of 1000 copies/mL; two publications on the Abbott m-PIMA device sensitivities of 95.4% (89.7 to 98.5) and 97.1% (94.2 to 98.8) and specificities of 96.0% (93.7 to 97.6) and 76.9% (69.8 to 83.1) for a treatment failure threshold of 1000 copies/mL.[43]

Since March 2021 WHO has recommended point-of-care viral load testing to monitor treatment in people living with HIV.[43] Consequently, scaling up point-of-care viral load testing urgently requires implementation and integration into routine care, including regulatory approval, training, monitoring, planning for supply chain, reagent forecasting, human resources, device maintenance, quality assurance, and factoring in an additional two hour wait by patients.[43 44] Moreover, technological innovations to detect viral loads of <50 copies/mL are needed.[45]

Other challenges

The prospect of viral load suppression exists only if mothers access antiretroviral treatment. Historically, Global Plan priority countries have fragile health systems. For example, in sub-Saharan Africa, 83% of women have at least one antenatal visit—mainly during the second or third

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trimester—but only 55% have at least four antenatal visits.[46] Additionally, a meta-analysis of 1703 antiretroviral treatment clinics in 35 countries (2010-14) showed that 37.5% had at least one antiretroviral treatment out of stock during a 12 month period.[47] Similarly, in South Africa, in 2015, 20% of 2370 facilities reported at least one antiretroviral or TB related medicine out of stock on the day of contact and 36% during the previous three months.[48] These challenges have increased during the covid-19 pandemic,[49] requiring emphasis on maintaining sexual and reproductive health services in high burden and fragile settings.[50] Modelling illustrates that a six month disruption in prevention of mother-to-child transmission services during the covid-19 lockdown for 50% of people could result in 2.7 times more infants born with HIV in one year.[51] Consequently, we need concerted efforts to monitor, achieve, and sustain undetectable viral loads throughout breastfeeding.

Conclusion

Antiretroviral treatment effectively reduces viral load (and mother-to-child transmission), but for a variety of reasons many women do not effectively achieve and maintain undetectable viral loads throughout pregnancy and breastfeeding. Current approaches to viral load monitoring are poorly implemented and the response to high viral load measurements is suboptimal; thus the risk of breast milk transmission by women taking antiretroviral drugs has not been eliminated. Studies reporting maternal plasma viral load and breast milk mother-to-child transmission, together or separately, are difficult to compare—viral load measurements occur at different time points and cut-offs for viral suppression and laboratory techniques differ. It is therefore important to rapidly scale-up other strategies such as frequent point-of-care viral load testing coupled with timely implementation of additional interventions to reduce breast milk mother-to-child transmission among women taking antiretroviral drugs. However, the optimal frequency of viral load monitoring during breastfeeding still needs investigation. Data show that viraemia occurs during breastfeeding, providing strong justification for investigating the utility of interventions such as long acting antiretrovirals, broadly neutralising antibodies, or vaccines despite maternal antiretroviral treatment to eliminate breast milk transmission.

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Supplementary tables summarising studies assessing risk of mother-to-child transmission and viral load in mothers taking antiretroviral drugs

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