

Letter to the Editor

**Close to zero, but not zero: What is an acceptable HIV transmission risk through breastfeeding?**

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Dear Editors,

We read with great interest the results of the PROMISE study by Flynn et al. [1], which shows the association of maternal viral load and CD4 count with perinatal HIV-1 transmission. Only two infants acquired HIV-1, despite apparent undetectable or detectable but less than 40 copies/mL maternal viral load. These cases may well represent true episodes of transmission in the presence of undetectable viral replication and the authors discuss potential reasons including cell-free RNA of cell associated HIV-DNA in breast milk.

The PARTNER study [2] aimed at assessing whether the HIV transmission risk through condomless sex among serodifferent gay men in the context of virally suppressive ART was below an acceptable low level, defined as one infection per 500 couple years of follow up. By this, the second U of U = U (undetectable equals untransmittable) became a quantifiable statistically risk. This landmark study provided compelling evidence to support the U = U campaign for sexual transmission. Specifically the absence of any phylogenetically linked transmission in the PARTNER study turned into a crucially supportive argument. However, would a single case of sexual HIV-1 transmission from someone with an undetectable HIV-RNA disprove this conclusion?

We think that the PROMISE study results are consistent with those from the PARTNER study in statistically supporting that U = U for breastfeeding HIV-infected women and the risk of transmission to their infants. In the PARTNER study, the relevant exposure to risk of HIV transmission is the frequency of sexual acts without using a condom, which in the PROMISE

study corresponds to the frequency of breastfeeding episodes. Looking at it this way, both studies demonstrate vanishingly small risk per episode. In fact, PROMISE provides more information about how small the risk is, as one can see from the width of the confidence intervals below.

In the PARTNER study, zero transmissions were observed in 76,088 condomless sexual acts over 1,593 eligible couple-years of follow-up provided by 782 HIV serodiscordant couples. This gives an incidence rate of 0 with 95% interval (0.00, 4.85) per 100,000 condomless sexual acts. To calculate the incidence rate for mother-to-child HIV transmission through breast-feeding, one has to make assumptions about the frequency of feeds during the average 70 weeks of follow-up in the PROMISE trial. We think eight to 12 times per day is a reasonable assumption for the first few weeks with decreasing rates over time. We assumed the following mean frequencies for different ages: 0-12 weeks (W): 8-12 times, 12-24W: 6-8 times, 24-48W: 6 times, 48-70W: 4 times. This gives an average of 3,052 episodes of breast-feeding per child over 70 weeks and a total of about  $1,227 \times 3,052 = 3,744,804$  breast-feeding episodes that could have yielded two HIV infections at a HIV-RNA of less than 40 copies/mL in the PROMISE trial. This gives an estimated incidence rate of 0.053 HIV transmissions with 95% CI: (0.006, 0.193) per 100,000 breast-feeding episodes.

As much as successful antiretroviral therapy (ART) can enable people to avoid condom use to prevent HIV transmission, successful maternal ART that results in undetectable maternal HIV-1 plasma viral load can enable mothers to breast-feed. Like for the sexual transmission  $U = U [2]$ , pregnant women with HIV need access to testing, effective treatment, viral load monitoring to reach viral loads less than 50 copies/mL, and support to reach and maintain viral suppression. Optimally, they should have all this accessible before they become

pregnant. This will enable them to discuss and jointly decide with their HIV-physicians whether they can breastfeed their baby with acceptable evidence-based low level risk.

References:

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2. Rodger AJ, Cambiano V, Bruun T, et al. Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study. *Lancet*. 2019 Jun 15;393(10189):2428-2438.

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