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**Analysis**

**Pre-exposure prophylaxis for infants exposed to HIV through breast feeding**

Philippe Van de Perre and colleagues say current strategies for preventing transmission of HIV infection from mother to child are inadequate and call for infants to be given pre-exposure prophylaxis.

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The AIDS 2016 conference, held in July in Durban, South Africa, lauded pre-exposure prophylaxis (PrEP) as the way forward for substantially reducing the rate of new HIV infections worldwide. PrEP is defined as the continuous or intermittent use of an antiretroviral drug or drug combination to prevent HIV infection in people exposed to the virus. The underlying pathophysiological rationale is that impregnating uninfected cells and tissues with an antiviral drug could prevent infection by both cell-free and cell-associated HIV (cell-to-cell transfer). PrEP’s tolerance and efficacy have been demonstrated in well designed clinical trials in men who have sex with men (MSM).

In the Ipergay trial, 86% of HIV infections were averted in highly exposed men. PrEP has also been evaluated in other highly exposed groups such as transgender women, injecting drug users, serodiscordant heterosexual couples, and commercial sex workers.

**HIV exposed children: lost in translation**

Uninfected pregnant or breastfeeding women in high incidence areas have also been suggested as a potential target population for PrEP, but infants exposed to HIV through breast feeding have not been mentioned. Numerous public declarations and petitions have produced a strong advocacy for extension of the PrEP principle to all high risk populations exposed to HIV, considering access to PrEP as part of human rights. Recently, the World Health Organization recommended offering PrEP to any population in which the expected incidence of HIV infection is above 3 per 100 person-years.

So why are breastfed infants born to HIV infected women, a population that often has an overall HIV acquisition rate above 3/100 person-years, not receiving this clearly beneficial preventive health measure?

**Current strategy not good enough**

Since June 2013, the WHO has recommended universal lifelong antiretroviral therapy (ART)—known as “option B+”—for all pregnant and breastfeeding women infected with HIV-1, with the objective of eliminating mother-to-child transmission (defined by WHO as an overall rate of transmission lower than 5%). The B+ strategy also recommends that their babies receive nevirapine for six weeks to mitigate the risks of transmission during delivery. But infants who are breast fed continue to be exposed to a substantial risk of infection beyond the six week prophylaxis period.

The B+ strategy has been rolled out in most programmes to prevent mother-to-child transmission worldwide without any additional protection for breastfed infants. Although these programmes have been shown to increase the number of pregnant and breastfeeding women who receive ART, their success in prevention of infection in infants is less clear. According to UNAIDS estimates, improvement in services to prevent mother-to-child HIV transmission since 2010 has reduced the annual number of new infections among children globally by 56%.

However, the few available programmatic data on long term residual HIV transmission rates suggest that this is mainly accounted for by reduced in utero and intrapartum HIV transmission rather than in postnatal transmission through breast feeding. Also, there is considerable variation across countries and continents, with many countries, mainly in Africa...
Reasons for continued transmission

Most of the residual transmission is attributable to exposure through breast feeding. A recent study assessed community viral load in Kenyan, Malawian, and South African households, including more than 11 000 women of child bearing age, of whom 3296 were pregnant or breast feeding. A total of 608 pregnant or breastfeeding women had HIV infection, with the proportion with plasma RNA above 1000 copies/ml varying from 27% in Malawi to 73% in Kenya. Some of the women who had detectable viral load were unaware of their infection because they had not been tested or had become infected after antenatal screening; others had not started ART or were not taking it as recommended.

In 2015, about 150 000 children were infected with HIV worldwide. The vertical transmission rate from mother-to-infant at six weeks was 5% but rose to 8.9% by the conclusion of breast feeding. In Africa, the reasons for this high residual burden of child infections are multiple. The main reason is operational, with challenges in all phases of the care cascade (test, treat, and retain in care), including consistent testing of HIV exposed infants, starting infants on treatment, and retaining infants in care.

Primary obstacles to linkage and retention include the distance and resources required to travel to a health facility, cultural or stigma related challenges, logistic hurdles that exist in antenatal care centres, and resources and efficacy of linkage to definitive HIV care. Observational studies in different African settings report less than optimal adherence, with only 50-70% viral suppression in women one year after starting ART. In Malawi, where the B+ strategy was rolled out in 2011, one fifth of women identified never started ART during the early phases of the programme. In the early phases of the Swaziland programme, postnatal retention in care for HIV infected women was only 37% overall and 50% for those who started ART during pregnancy.

A study in Malawi found that women who started ART to prevent transmission to their child were five times more likely to default than women who started treatment for their own health. Maternal discontinuation of ART while breast feeding considerably increases risk of HIV transmission to the infant because of viral rebound, as observed after interrupting maternal ART. Indeed, even if only one HIV infection was averred out of 100 exposed infants, the cost per averted infection would be minimal ($1500). The estimated cost of daily administration of lamivudine paediatric suspension in a breastfed infant is less than $15 (£12; €14) a year. Cost effectiveness studies of infants breastfed by mothers taking ART show that their antiretroviral drug plasma levels are largely below 5% of the therapeutic level. This suggests that infant PrEP could be combined with maternal ART without a risk of overdosing or cumulative adverse effects.

In the near future, injectable long acting antiretroviral drugs such as rilpivirine or cabotegravir may become available. This would enable PrEP to be started from birth with only a few additional administrations to cover the duration of breastfeeding.

Infant prophylaxis has been used before

Administration of a daily antiviral drug to an uninfected but exposed breastfed infant meets the definition of PrEP: the prophylaxis is administered before exposure (ideally from birth) to an uninfected infant whose exposure to HIV is intermittent (during breast feeding) and persistent. Ironically, infants born to HIV infected women were the first to participate in ARV prophylaxis trials. They have probably contributed the highest number of participants in such studies worldwide. Indeed, prophylaxis with oral zidovudine was integrated in the first prophylactic protocol (ACTG 076) reported in 1994. Thereafter, numerous trials have included infant PrEP to prevent mother-to-child transmission, in combination or even as a sole preventive regimen. The most recent of these, the ANRS 12174 trial, showed that infant prophylaxis with either lamivudine (3TC) or boosted lopinavir (LPV/r) daily throughout breastfeeding for up to 12 months among infants of HIV infected women who did not qualify for ART for their own health was well tolerated and reduced the risk of postnatal transmission at 1 year of age to 0.5% (per protocol) or 1.4% (intention to treat). Adherence to infant PrEP in the trial was particularly high (over 90%).

Pharmacological data suggest that plasma drug levels lower than the therapeutic threshold are sufficient to protect infants. In addition, pharmacokinetic studies in infants breastfed by mothers taking ART show that their antiretroviral drug plasma levels are largely below 5% of the therapeutic level. This suggests that infant PrEP could be combined with maternal ART without a risk of overdosing or cumulative adverse effects. In near future, injectable long acting antiretroviral drugs such as rilpivirine or cabotegravir may become available. This would enable PrEP to be started from birth with only a few additional administrations to cover the duration of breastfeeding.

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suppressive ART regimen. Given the evidence that infant PrEP is effective, there is a moral imperative to correct the policy inequity that exists between HIV exposed adults and children. Scaling up existing interventions and enhanced access to PrEP to those in need are the most cost effective ways to stem new HIV infections.22 Expanding global prevention guidelines to include infant PrEP for infants exposed to HIV by breast feeding could be a major breakthrough as a public health approach to eliminate mother-to-child transmission.

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Key messages

- WHO recommends pre-exposure prophylaxis for any group with an expected incidence of HIV infection above 3/100 person-years
- Current strategies to prevent mother-to-child transmission of HIV cover only the first six weeks
- Many infections of breastfed infants occur after this period
- Adding infant PrEP to maternal ART is cheap and does not expose infants to unsafe doses
- Routine infant PrEP has the potential to be a breakthrough in elimination of mother-to-child transmission