*Editorial*

# Ongoing Challenges and Recent Advances in the Prevention of Mother-to-Child Transmission of HIV

Nowhere are the global inequities in healthcare more apparent than in the prevention of mother-to-child transmission (PMTCT) of HIV. Every day ~700 children <15 years of age are newly infected with HIV, most through perinatal infection, with >90% of these infections occurring in the developing world [1, 2]. Without access to antiretroviral therapy, one-third of these children will die by 1 year of age, and one-half will die by age 2. We have known for more than a decade that the combination of universal prenatal HIV testing, highly active antiretroviral therapy (HAART) for HIV-infected pregnant women, perinatal antiretroviral prophylaxis to the mother and baby, elective caesarian section for women with HIV viral loads >1000 copies/ml near the time of delivery and avoidance of breastfeeding can virtually eliminate perinatal HIV transmission [3]. Indeed, the use of these PMTCT interventions has reduced the rate of perinatal HIV transmission from 25–30% to <1% in the USA, with only 162 cases of perinatal HIV transmission reported in 2012 [3, 4].

Since we know how to prevent perinatal HIV transmission, why are so many children still newly infected with HIV every day? Here is where global inequities manifest, in that therapies that work in the developed world may be logistically impossible or have unintended consequences in the developing world. The most striking example is with breastfeeding, which is estimated to be responsible for one-third to one-half of perinatal HIV transmission events [3]. A clinical trial in Botswana on infants born to HIV-infected mothers between 2001 and 2003 demonstrated that although avoidance of breastfeeding reduced the risk of HIV transmission by 38%, the infants who were formula-fed had almost twice the mortality rate at 7 months than their breastfed counterparts, mostly from diarrhea and pneumonia [5]. The conclusion was that lack of a dependable clean water source to make formula made breastfeeding a safer option, despite the increased risk of HIV transmission. Consequently, the PMTCT guidelines published by the World Health Organization (WHO) recommend that national authorities in each country decide whether to support breastfeeding or to encourage avoidance of breastfeeding depending on the availability of safe alternative feeding strategies [6].

Likewise, elective caesarian section for women with HIV viral loads >1000 copies/ml near the time of delivery would be logistically impossible in many developing countries. Even ignoring the difficulty of finding enough trained doctors and equipped surgical suites to safely perform the caesarian sections, the limited availability of viral load testing hinders the utility of this recommendation. Although it is standard of care to monitor HIV viral load every 3–6 months in HIV-infected patients on antiretroviral therapy in developed countries, this is almost never done in developing countries because of the prohibitive cost. The HIV nucleic acid amplification tests needed to determine viral load are quite expensive, costing 10–90 U.S. dollars per test [7]. Indeed, although the most recent (and most ambitious) guidelines published by the WHO in 2013 on the use of antiretroviral therapy recommend viral load monitoring, they also include the caveat that if viral load testing is not available, monitoring of CD4 count and clinical symptoms can be used to diagnose treatment failure instead [6]. The economic barriers to viral load testing are particularly problematic when trying to diagnose HIV infection in infants, because the cheaper serologic tests used to diagnose HIV infection in older children and adults are not effective in children <12 months of age due to the presence of maternal antibodies.

Finally, recommending HAART for all HIV-infected pregnant women is logistically difficult in many resource-limited settings, although there has been a trend toward expansion of coverage for pregnant women in the WHO guidelines. The recent 2013 WHO guidelines are the first to recommend HAART for all HIV-infected pregnant women irrespective of CD4 count for at least the duration of mother-to-child transmission risk, whereas earlier guidelines in 2006 and 2010 only recommended HAART for HIV-infected pregnant women with more advanced disease (with zidovudine alone plus nevirapine and lamivudine around the time of delivery recommended for those women who did not qualify for HAART) [6, 8]. The recommended first-line HAART regimen in pregnant women is also different in resource-limited settings. Two nucleoside reverse transcriptase inhibitors are universally recommended in both the 2013 WHO and the United States Department of Health and Human Services guidelines (tenofovir or zidovudine combined with lamivudine or emtricitabine). However, the third agent differs between the WHO guidelines, which recommend either efavirenz or nevirapine, and the United States Department of Health and Human Services guidelines, which


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recommend boosted atazanavir or lopinavir, and efavirenz only after the first trimester (due to the risk of teratogenicity) and nevirapine only in women with CD4 counts <250 cells/mm$^3$ (due to the risk of hepatotoxicity) [6, 9]. Of note, however, the long-held belief that efavirenz use in the first trimester increases the risk of teratogenicity is primarily based on a study done in monkeys, and a recent meta-analysis of human studies found no increased risk compared with other antiretroviral medications [10].

On a positive note, enormous efforts have gone into finding logistically feasible PMTCT methods for resource-limited settings. Because breastfeeding is the safer option for infants in the absence of safe alternative infant feeding strategies, multiple studies have investigated how to decrease the risk of HIV transmission during breastfeeding. Some notable findings include the following: exclusive breastfeeding, as opposed to mixed feeding with both breastfeeding and formula or solids, can decrease the rate of HIV transmission by almost half [11]; continuation of maternal HAART through the breastfeeding period can also decrease the risk of HIV transmission by almost half [12] and extending nevirapine prophylaxis for exposed infants can also reduce transmission rates [13]. WHO guidelines have incorporated these new findings by recommending either avoidance of breastfeeding entirely or exclusive breastfeeding for the first 6 months, HAART for breastfeeding mothers until after the child is weaned and a longer period of nevirapine prophylaxis for exposed infants [6]. Likewise, technologies like dried blood spot testing have been developed to make tests such as an HIV viral load more logistically feasible [7]. Finally, in 2011, the United Nations declared the goal of eliminating new HIV infections among children by 2015, as an extension of the Sixth Millennium Development Goal from 2000, which has led to unprecedented financial resources supporting PMTCT [2].

These new PMTCT methods combined with the renewed political and financial commitments have shown encouraging results. In the past 12 years, there has been a 52% decline in new HIV infections in children, with 260 000 newly infected children in 2012 [2]. Coverage of PMTCT programmes reached 63% globally in 2012, with 900 000 HIV-infected pregnant women receiving antiretroviral therapy or prophylaxis. However, there is considerable variation in the PMTCT coverage among different countries, with some WHO-defined priority countries now providing antiretroviral medications to >90% of HIV-infected pregnant women, whereas a number of countries are yet to reach antiretroviral coverage for even 20% of HIV-infected pregnant women.

Similar to the HIV epidemic in general, efforts on PMTCT have illustrated both the worst and the best of human nature. On the one hand, it is disturbing that infants born to HIV-infected mothers in the developing world, who are inarguably among the most vulnerable and innocent members of our society, are still at risk of perinatal HIV infection despite our knowledge on how to prevent it. However, the recent commitment by political leaders to eliminate perinatal HIV transmission, the increased financial resources committed to PMTCT and the tireless efforts by researchers to find PMTCT methods that work in resource-limited settings all demonstrate why humanity is worth saving. The latter gives me hope that in my lifetime, perinatal HIV transmission in all parts of the world may become a thing of the past.

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