J Pediatr (Rio J). 2015;91(6):509–511

Jornal de Pediatria
www.jped.com.br

EDITORIAL

The road to eliminate mother-to-child HIV transmission☆,☆☆

O caminho para eliminação da transmissão vertical do HIV

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The World Health Organization's Global Health Observatory estimates that 78 million people have been infected with the human immunodeficiency virus (HIV) during the course of the epidemic, and that 39 million men, women, and children have died.[1] Nearly 1 in 20 adults in sub-Saharan Africa are currently living with the infection. HIV represents one of the world's most serious health problems.

The WHO global health sector strategy on HIV/acquired immunodeficiency syndrome (AIDS) has identified four strategic directions to guide countries' HIV response to achieve the United Nations' Millennium Development Goal of halting the spread of HIV/AIDS. A core element of strategic direction one was the elimination of new HIV infections in children.[2]

It is encouraging that the number of new HIV infections in children is decreasing in most parts of the world. In 2011, there were approximately 330,000 new childhood infections, and while this is a reduction of 43% since 2003, it remains unacceptably high.[3] Unfortunately, increased childhood infection rates were observed in Angola, Congo, Equatorial Guinea, and Guinea-Bissau.

While a small proportion of childhood infections result from blood transfusions, sexual abuse, or unsafe injecting practices, the main cause is mother-to-child transmission (MTCT),[3,4] which may happen in-utero, peripartum, or through breastfeeding.

Sixteen million women were living with HIV at the end of 2013[5] and many are of reproductive age. A total of 1,600,000 pregnancies are complicated by HIV infection worldwide, and MTCT rates, in the absence of therapeutic intervention, are estimated to be as high as 31%.[6] Conditions resulting in placental inflammation, age at first sexual intercourse, and genital ulcer disease are associated with higher rates of MTCT.

Substantial improvements in the rates of MTCT have been achieved since the first case of HIV MTCT was identified in 1983. Routine HIV screening in pregnancy has been recommended since the late 1990s; clinical trials of antiretrovirals have demonstrated safe, efficacious regimens during pregnancy, and funds have been directly allocated for research in MTCT.

Treatment of pregnant women with combination antiretroviral therapy (cART) has lead to a dramatic impact on MTCT.[7] cART was shown to reduce MTCT by almost 20-fold. It is estimated that between 2009 and 2011, cART provided in pregnancy prevented 409,000 childhood HIV infections.[3] In response to the weight of evidence for prevention of MTCT, the WHO Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection recommends that all pregnant and breastfeeding women with HIV should be commenced on antiretroviral therapy and those meeting eligibility criteria should receive lifelong treatment.[8]

It is believed that elimination of MTCT can be achieved through effective antiretroviral coverage, education, and appropriate supportive care. However, antiretroviral

☆ Please cite this article as: Redmond AM, McNamara JF. The road to eliminate mother-to-child HIV transmission. J Pediatr (Rio J). 2015;91:509–11.
☆☆ See paper by da Rosa et al. in pages 523–8.
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http://dx.doi.org/10.1016/j.jped.2015.08.004

coverage of pregnant women with HIV remains poor, with only 30% of eligible pregnant women receiving antiretroviral therapy (ART), as opposed to 54% for all eligible adults.[3] The majority of HIV-infected infants are born to mothers who are unaware of their HIV status,[4] highlighting the importance of screening programmes during pregnancy.

As a developing country, Brazil bears a heavy burden of the HIV epidemic, and has made significant progress in halting the spread of the infection. Brazil has a stable prevalence of HIV estimated at 1%, with approximately 718,000 people living with the virus. The prevalence of HIV infection in key populations in Brazil is estimated at 5.9% among drug users, 10.5% among men who have sex with men, and 4.9% among female commercial sex workers.[9]

In 2012, 8622 cases of AIDS were reported in women through the SINAN information system for notifiable diseases. Exposure in these women was determined as 96.6% heterosexual, 2.5% intravenous drug use, 0.8% MTCT, and 0.1% via transfusion. In the ten years between 2003 and 2012, the age of patients with AIDS has shifted to younger individuals, with highest rates observed in patients aged 30–49 years of age. There has been an increasing trend in detection rates among people aged 15–24 years,[9] increasing the proportion of women at reproductive age with HIV.

The Brazilian population is well-informed regarding the transmission of HIV: large-scale surveys show a 97% agreement to the statement that condom use is the best way to avoid HIV infection. Unfortunately, this does not translate as well as would be hoped to action, with only 55% prevalence of condom use with a casual partner in the previous 12 months in people aged 15–65 years.[9]

There has been an overall decrease in the detection rate of AIDS amongst children under 5 years (35.8%) over the ten years preceding 2012. This reduction was not observed uniformly across Brazil, and increases in notifications of AIDS in children were seen in the North and Northeast regions.[9]

MTCT remains the major route of acquisition of HIV for children under 5 years of age in Brazil. Identification of HIV in pregnancy is improving in Brazil, with an estimated screening coverage of 80% in a recent study in women presenting for pre-natal testing.[10] However, it is estimated that HIV testing only reaches 58.3% of the expected cases of HIV-positive pregnant women.[9] HIV in pregnancy was estimated at 0.38% prevalence in Brazil, with 50.7% of those infected with HIV aged between 20 and 29 years.

The article by da Rosa et al.,[11] in this issue of Jornal de Pediatria, presents a retrospective evaluation of rates of and factors associated with MTCT of HIV-1 at a large hospital in Southern Brazil over a 14-year period, between 1998 and 2011. The authors extracted data from the laboratory database and medical records for this purpose, and split the time into two sections for comparison. They reported that there had been a change in the prevalence of viral subtype C and in clinical management of HIV over time, although the exact parameters of these changes were not presented.

During that period, there were 353 live births to HIV-infected women. There was a reduction in the rate of MTCT of HIV from 11.8% to 3.2% over the two periods. The difference was highly significant, both statistically and clinically, dramatically altering the lives of the children protected from HIV infection. The authors found that the rates of low maternal viral load (<1000 copies/mL), high maternal $CD4^+$ T cell count (>500 $\times$ 10^9 cells/mL), and use of ART that was deemed complete (maternal ART during pregnancy and at delivery and zidovudine post exposure prophylaxis for the neonate) increased from the first to the second time period. It was also observed that management of labour changed over the two periods, with membrane rupture times of greater than 4 h being the norm in the earlier period (79.4%), but not during the later period (27%). There was not a significant change in the route of delivery over this time, however it is likely that the change in management of labour reflects national health department policy.

The retrospective nature of the study prevents firm conclusions being drawn regarding the cause of the dramatic fall in MTCT. It is likely that the fall in MTCT seen over the time evaluated in this study is due to a combination of factors, but that it is dominated by the increase in the proportion of women with low HIV viral load, which in turn is due to higher rates of pregnant women receiving cART. Prevention of MTCT is one of the benefits of treatment as prevention, and, as the implementation of this policy becomes more widespread, both in Brazil and worldwide, we can expect to see prevention of disease and prevention of transmission both to children of HIV-infected mothers and to sexual partners of PLHIV.

A range of interventions are recommended to prevent MTCT as outlined in international guidelines.[12,13] The majority of these interventions are being applied in Brazil, with admirable timeliness, including identification of HIV infection in pregnant women by screening during antenatal care; engaging and retaining HIV-infected women in care; recommending and making available cART for these women; screening for and treating other sexually transmissible infections in women at risk; and providing post exposure prophylaxis for children of HIV-infected mothers.[9]

Evidence concerning the impact on MTCT of prolonged (>4 h) rupture of membranes was evaluated in a meta-analysis in 2001 by the International Perinatal HIV Group.[14] This identified an increase in the risk of MTCT of 2% for each hour of membrane rupture. In contrast, a smaller, more recent study of 707 women who received prenatal care including ART at a single centre in Miami, Cotter et al. found no cases of perinatal transmission in women with plasma viral loads of <1000 HIV copies/mL with membrane rupture for up to 25 h.[15] In this cohort, only viral load >10,000 copies/mL was an independent risk factor for MTCT. So what is the difference here? It would appear to be cART. The studies included in the meta-analysis were predominantly conducted prior to the availability of cART, while the patients in the Miami study were receiving cART. While da Rosa et al.[11] found that prolonged rupture of membranes was a risk factor for transmission, it is likely to be much less potent a factor than uncontrolled HIV viraemia. For women who have not achieved virological suppression at the time of delivery, it is likely that elective caesarean section or, failing that, avoidance of prolonged rupture of membranes is still indicated.

Despite the fall in MTCT observed in this study and elsewhere, the rate is still too high. We all need to work to reduce the transmission rate to zero. Some of the strategies needed to achieve this are known, as listed above, and require energetic implementation and support. Some,

such as the engagement and retention in care of individuals who use injectable drugs, are more challenging. It is encouraging to see the efforts and funding for this group being prioritized in Brazil.[9] Women who have HIV infection diagnosed during pregnancy are a key focal group, as there is less time between treatment initiation and delivery to achieve virological suppression to prevent MTCT. Also, treatment adherence is a key issue in HIV care for all patients, but, as identified in a recent review, less than three quarters of pregnant women have optimal treatment adherence.[16] Whether this reflects uncertainty about the safety of medications for the foetus or lack of engagement with care, this also represents a key area for attention to end HIV transmission.

The findings of this study, along with the results from the START study showing the clear individual health benefit of early treatment,[17] tell us that rather than calling for more research, it is now time to implement what we already know to achieve the goal of an HIV-free generation.

Conflicts of interest

The authors declare no conflicts of interest.

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