

## Pediatric HIV-AIDS: Challenges We Face Today

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### Introduction

HIV once considered a debilitating fatal illness is now a chronic treatable infection, mostly due to the advent of effective antiretroviral therapy (ART). But with the benefits of longevity, also comes the burden of morbidity, which can present not only due to the disease itself but also due the therapy which is being offered currently. This holds true more so for children, who are susceptible not only to the myriad manifestations of the disease and the adverse effects of ART, but also to the long term psychosocial consequences of the disease. Children are started on ART much earlier in life and are thus more prone to the adverse effects of ART as compared to adults.

Pediatric HIV primarily is a vertically transmitted infection (1). Most of the cases of newly diagnosed HIV infection in children are being reported from South East Asia and Africa while countries like the USA and western European countries report less than 1% of newly infected HIV positive children (2). This has been due to ineffective Prevention of Parent to Child Transmission (PPTCT) programs in the developing countries, especially in the setting of continued breast feeding. However, with newer PPTCT regimens for women who are breast feeding, the transmission rate from the mother to the child is expected to decrease from 35-40% to less than 5%.

Thus, the challenges which we face today in tackling pediatric HIV are prevention of vertical transmission of HIV, prevention of morbidities due to the disease and the therapy and also the emerging patterns of drug resistance in children.

### *Magnitude of pediatric HIV in India*

As per UNICEF, in 2007 approximately 2.1 million children under 15 years were living with HIV. An estimated

290,000 children under 15 died of AIDS-related causes. It is estimated that 70,000 children below the age of 15 years are living with HIV in India and 21,000 children are infected every year through parent-to-child transmission. India has a low HIV prevalence of 0.34 percent. Yet in terms of individuals infected, India is home to the third largest number of people living with HIV in the world. It is estimated that out of 27 million pregnancies every year, nearly 49,000 occur in HIV-positive mothers. In 2009, only 11489 of an estimated 49,000 pregnant women living with HIV received ART to prevent parent-to-child transmission. This is because of multiple factors including social customs, lack of family support and financial barriers, which constrain women from availing the institutional care necessary for administering treatment (3).

### *Prevention of parent-to-child transmission (PPTCT)*

One of the major achievements in Pediatric HIV research was the demonstration by the Pediatric AIDS Clinical Trials Group 076 (PACTG 076) clinical trial that administration of zidovudine to pregnant women and their infants could reduce risk of perinatal transmission by nearly 70% (4). Subsequent clinical trials and observational studies demonstrated that combination antiretroviral (ARV) prophylaxis (initially dual- and then triple-combination therapy) given to a mother antenatally was associated with further declines in transmission to less than 2% (5).

However, all these demonstrated reduction in transmission in mothers who were not breast feeding. Till 2006, PPTCT guidelines in India by the National AIDS Control Organization (NACO) recommended use of single dose Nevirapine (NVP) to the mother at the onset

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**Table 1. World Health Organization (WHO) Guidelines for Prevention of Mother to Child Transmission of HIV. (2010) (7)**

Option A	Option B
For pregnant women: <ul style="list-style-type: none"> <li>• Antepartum daily AZT</li> <li>• Single dose NVP at onset of labor</li> <li>• AZT + 3TC during labor and delivery</li> <li>• Twice daily AZT + 3TC for 7 days postpartum (to reduce risk of NVP resistance in the mother)</li> </ul>	For pregnant women: <p>Triple ARV drugs starting from as early as 14 weeks of gestation until one week after all exposure to breast milk has ended.</p> <p>Recommended regimens include:</p> <ul style="list-style-type: none"> <li>• AZT + 3TC + LPV/r</li> <li>• AZT + 3TC + ABC</li> <li>• AZT + 3TC + EFV</li> <li>• TDF + 3TC (or FTC) + EFV</li> </ul>
For infants If breast feeding: Single dose NVP at birth and then daily administration of NVP to the infant from birth until one week after all exposure to breast milk has ended.  If non-breast feeding: Single dose NVP at birth and then daily administration of NVP or AZT from birth until 4 to 6 weeks of age.  Type of delivery Vaginal	For infants Daily administration of AZT or NVP from birth until 4 to 6 weeks of age          Type of delivery Vaginal

*AZT = Zidovudine, 3TC = Lamivudine, LPVr = Lopinavir/ritonavir, ABC = Abacavir, EFV = Efavirenz, TDF = Tenofovir Note: Single dose NVP and AZT+3TC intra- and post-partum can be omitted if the mother receives more than 4 weeks of AZT during pregnancy.*

of labour as well as to the baby within 48 hours of birth. However this was still not effective in decreasing the transmission due to continued breast feeding, and this issue has remained untackled for a long time. However, with recent trials in breast feeding mothers have clearly shown that when antiretrovirals are taken throughout the duration of pregnancy and breastfeeding, the transmission is greatly reduced to 2 percent (6). But these regimens require strict adherence to the antiretrovirals (ARVs) as well as good monitoring and support to the mothers during therapy in order to avoid emergence of resistant strains and defaulting leading to increased transmission. This approach offers new hope to HIV infected mothers in developing nations who cannot safely feed their babies with replacement. The newborn infant thus benefits from the protective effects of breast feeding against infections like diarrhea and pneumonia without being subjected to a significantly increased HIV transmission risk. This led to the WHO recommendations in 2010 (7) as depicted in *Table 1*.

However, with difficulty in implementing the guidelines due to logistics and technical difficulty, WHO recommended a consolidated guideline in 2013 (7) to simplify implementation of PPTCT in developing countries and also to prevent drug resistance in the mother. These guidelines stated that for programmatic and operational reasons, particularly in generalized epidemics, all pregnant and breastfeeding women with HIV should initiate ART as lifelong treatment, regardless of CD4 count or clinical status. This new approach of lifelong ART for all pregnant and breastfeeding women with HIV, is referred to as "Option B+ . The new 2013 guidelines recommend that countries currently implementing Option A based on the 2010 guidelines should transition, with appropriate planning, to option B+. Option A is no longer recommended.

According to the 2013 WHO guidelines for the use of antiretroviral drugs, a once-daily 3 drug fixed-dose combination of tenofovir and lamivudine (or emtricitabine) and efavirenz is recommended as first-line ART in HIV

infected pregnant and breastfeeding women and should be continued lifelong either in all mothers or those requiring therapy for their own health. Infants of these mothers should receive six weeks of infant prophylaxis with daily Nevirapine (or twice-daily AZT). Infant prophylaxis should begin at birth or when HIV exposure is recognized postpartum (7).

#### ***Pediatric care and treatment:***

Treatment of pediatric HIV infection has evolved since antiretroviral therapy began in the late 1980s. Prior to the availability of antiretroviral drugs for children, care focused on prevention and management of HIV-related complications and provision of palliative care. Initial studies of monotherapy in children in the mid-1990s demonstrated significant clinical and immunologic benefit with treatment; further research demonstrated that combination therapy (initially dual-NRTI treatment in 1996/97) led to better clinical, immunologic, and virologic outcomes than monotherapy. Currently, highly active combination regimens including at least three drugs are recommended (8).

#### ***When to Start Antiretroviral Therapy***

Decisions regarding when to start therapy, what drugs to choose in antiretroviral-naïve children, and how to treat antiretroviral experienced children remain complex. The major shift in the 2013 WHO guidelines for antiretroviral therapy (ART) in children from previous recommendations is that it should be initiated in all children infected with HIV below five years of age, regardless of WHO clinical stage or CD4 cell count. Also recommended is that ART should be initiated in all HIV-infected children five years of age and older with CD4 cell count  $<500$  cells/mm<sup>3</sup>, regardless of WHO clinical stage. But again, these recommendations are conditional because of the lack of evidence, however, this approach is expected to provide a high coverage of pediatric ART (7). Also with approval of tenofovir (TDF) for use in children above 2 years of age by US FDA (9), the choice of first line NRTI backbone for ART regimen recommended by WHO in children less than 10 years would be Abacavir (ABC) + lamivudine (3TC) or Zidovudine (AZT) + 3TC and in those above 10 years would be TDF + 3TC (or emtricitabine (FTC) with an NNRTI. In children above 5 years, ART now being

recommended in those with CD4 count less than 500 cells/cumm as compared to previous guidelines of  $<350$  cells/cumm (7), more children will be eligible for ART earlier. However, currently no evidence from randomized controlled trials to suggest that a strategy of initiating ART when the CD4 count is above 350 cells/microL (versus deferring initiation to around 350 cells/microL) results in benefit to the HIV infected child or adolescent and data from observational studies are inconsistent (10).

#### ***ART Resistance***

ART aims to decrease viral load and improve clinical and immunological status of HIV infected patients. However, development of increasing drug resistance is proving to be a major obstacle in selection of appropriate therapy. Studies done on Indian population indicate that prevalence of HIV resistance mutations is around 9.6% in treatment naïve population (11) and up to 81-96% in treatment experienced patients with virologic failure (12,13). The pediatric population in particular is not only at a higher risk of developing resistance due to greater viral loads (14) and difficulty in adherence and accurate dosing, but resistance proves a greater challenge in children as they require longer therapy than adults. Newly diagnosed vertically infected children may be infected with resistant virus strains while being exposed to various antiretrovirals (ARVs) in utero or through breast milk. Also children till now were predominantly on Zidovudine (AZT) and stavudine (d4T) based regimens which can lead to thymidine analogue mutations (TAMs) which lead to multi NRTI resistance with reduced susceptibility to all NRTIs(15). With public sector PPTCT programs implementing single dose Nevirapine (NVP) to mother and child at the time of labour and birth respectively, transmission of HIV reduced to 12-13% at 6 weeks, however resistance to NNRTI became an issue in those children who became infected.

Poor adherence is another factor that adds to the resistance, as it can render a whole class of ARVs ineffective. ART is unforgiving of lapses in therapy with rates of adherence as high as 95% required to suppress viral replication maximally & to avoid regimen failures which lead to limited options in future therapy (16).

Children have to depend largely on their care givers for the success of their therapy. Often children live in

families where the adult care giver is ill & is subjected to significant stress physically, emotionally, socially & financially. The complexity of antiretroviral therapy with multiple medications, unpalatable formulations and strict dosing intervals, the need for depending on an adult care giver, the need for frequent clinical & laboratory monitoring for therapeutic responses as well as side effects & above all, the financial constraints in a resource poor setting, makes adherence ever more challenging in children(17,18).

A recent Cochrane review states that there is insufficient evidence from clinical trials in support of either early or CD4-guided initiation of ART in HIV-infected children aged 2 to 5 years (18). Thus, whether treatment with ART in all children below 5 years of age or to start based on clinical and immunological criteria needs to be clarified in further studies before this is implemented large scale in a programmatic manner.

### Conclusion

Today, pediatric HIV is on a path breaking journey. With newer recommendations for PPTCT regimens which are more effective, the vertical transmission of HIV and thus the magnitude of newly infected pediatric HIV should come down drastically, provided these are implemented effectively and expeditiously on a large scale. Again, with newer ART regimens in children being available, the older toxic drugs would be eventually phased out. However the challenge of emerging drug resistance in the paradigm of pediatric HIV remains, and which would assume greater importance as these children achieve greater longevity. Role of starting ART in these children earlier needs to be re-analyzed.

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