Early Infant Diagnosis of HIV

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Globally, the number of children younger than 15 years living with HIV infection has increased from 1.6 million in 2001 to 2.5 million in 2009. In 2009 alone, globally, 370,000 children under the age of 15 years were newly infected, i.e. approximately 1,000 a day; and 260,000 children died, the majority being under the age of five years. However, the number of newly infected children has been declining since 2003 due to increasing access to prevention of parent-to-child transmission (PPTCT) services. In India, it is estimated that currently about 115,000 children are living with HIV, and approximately 40,000 children below 15 years are provided with anti-retroviral therapy (ART) by the national program. However, most of the children receiving ART are older than 5 years of age. Unfortunately, children under 18 months are not getting diagnosed earlier, and are missing out on care, support and treatment [1].

Data from studies in resource-limited settings confirm that, for infants who acquire HIV before or around delivery, disease progression occurs very rapidly in the first few months of life, often leading to death. While 35% children do not see their first birthday, 53% do not celebrate their second birthday [2]. Because HIV-related mortality peaks at around 2-3 months of age, the window of opportunity to identify and link infants living with HIV to ART is very narrow. The risk of disease progression is inversely correlated with the age of the child, with the youngest children at greatest risk of rapid disease progression. Progression to moderate or severe immune suppression is also frequent in infected infants; by 12 months of age, approximately 50% of children develop moderate immune suppression, and 20% develop severe immune suppression. In the HIV Pediatric Prognostic Markers Collaborative Study meta-analysis [3], the one-year risk of AIDS or death was substantially higher in younger children than in older children at any given level of CD4 percentage, particularly for infants. In a recent study from South Africa [4], up to 80% of infected infants, who were well at 6 weeks, progressed to become eligible to start ART by 6-12 months of age.

Early initiation of ART on the other hand has been shown to improve survival of infected infants. Data from the South African CHER Trial (Children with HIV Early Antiretroviral Therapy) demonstrated that early HIV diagnosis and initiation of triple-drug ART before 12 weeks of age in asymptomatic perinatally infected children with normal CD4 percentage (CD4 percentage >25%), compared with delaying treatment until the child met clinical or immune criteria, resulted in a 75% reduction in early mortality and HIV progression. Most of the deaths in the children in the delayed treatment arm occurred in the first 6 months after study entry [5]. Because the risk of rapid progression is so high in young infants, and based on the data from the CHER study, initiation of ART has been suggested for all infants regardless of clinical status, CD4 percentage, or viral load. Before therapy is initiated, it is important to fully assess, discuss, and address issues associated with adherence with the HIV-infected infant's caregivers. However, given the high risk of disease progression and mortality in young HIV-infected infants, it is important to expedite this assessment in infants less than 12 months of age.

Early virological diagnosis of HIV infection in infants is the first step in securing their treatment and care. It also enables the identification of those who are HIV-exposed but uninfected, facilitates follow-up care and preventive measures that will help to ensure they remain uninfected, assists in the effective use of essential resources by targeting ART in children who need treatment, improves the psychosocial well-being of families and children, reduces potential stigma, discrimination and psychological distress for HIV-uninfected children, increases the chances of adoption for orphans, and facilitates life-planning for parents and/or children [6].

Despite the advances in understanding the disease in young children, among 104 countries reporting in 2012, only 35% of HIV-exposed infants underwent HIV virological testing within the first two months of life, and among those tested, up to 45% were lost to follow-up before the test result [7].

Early virologic diagnosis is possible using HIV DNA PCR, RNA PCR or ultrasensitive p24 (Up24) antigen [8]. National AIDS Control Organization (NACO) suggests to use the HIV DNA PCR in dried blood spot as a prime method for all the children, and if it is found positive, then to use this test in whole blood sample as a confirmatory test [1].

Updated WHO (2014) guidelines have emphasized on early virological testing at 4-6 weeks of age, or at the earliest opportunity thereafter. A confirmatory test on a new sample should be performed among those infants who test positive, but ART should not be delayed while awaiting results. Importantly, for infants who have negative virological testing results, the definitive diagnosis of HIV infection should be determined when HIV exposure (usually through breastfeeding) ends. Virological testing at 4-6 weeks of age will identify more than 95% of infants infected *in utero* and intrapartum. Some flexibility in implementing this recommendation may be required, based on current national or local postpartum and infant follow-up practices. However, testing beyond this time delays diagnosis and puts HIV-infected infants at risk for disease progression and death [9]. US guidelines recommend testing infants within one week of birth with first testing as early as 48 hours of life [8]. In India, the NACO recommendations for early infant diagnosis are: dried blood spot sample for HIV DNA PCR sent at 6 weeks of age, and if positive then a confirmatory test to be done on whole blood sample DNA PCR before starting ART at ART Center. The ART is initiated after infection is confirmed with positive test result on whole blood sample [1].

Early infant diagnosis of HIV infection at the primary care level in a resource-poor setting is challenging. Many children in the HIV diagnosis and treatment programs are lost to follow-up at various stages. Diagnostic tools with higher positive predictive value and point-of-care capacity, and better infrastructures for administering ART are needed to improve the management of HIV-exposed and HIV-infected infants [10]. A recent study has demonstrated an association between turnaround time of the results and receipt of the result by the caregivers. Caregivers were less likely to receive results at turnaround times greater than 49 days compared to 28 days or fewer. Hence, earlier delivery of results is probably associated with better receipt of result and better adherence to the therapy [11].

In the current issue of *Indian Pediatrics*, Hanna, *et al.* [12] report their experience from Southern India. The median age at first sampling was 4 months. Of those who had positive result, only 13% were tested within 6 weeks of birth, 29% by 4 months, 52% by 6 months and 85% by 12 months. More importantly, there were huge delays and loss to follow-up between first and second testing. Second specimen for confirmatory test was received for only two-thirds of the 246 infants who tested positive by dried blood spot. Turn-around time for final confirmatory result was as much as 270 days (median 46 days). Percentage of HIV positive children, who could be started on ART and age at which treatment was started, was not assessed in present study, which could have made more meaningful statement. This study has highlighted huge gaps in diagnosis, confirmation and initiation of ART in HIV-exposed infants in the region, which should be fulfilled with improvement in existing programs with adherence to WHO guidelines and better patient linkage to minimize the loss to follow-up.

Similar experience has been reported from Malawi [10] where despite active tracing, only 87.3% (110/126) of the mothers of infants who initially tested positive were told their infants' test results and ART was initiated in only 58% of the infants with confirmed HIV infection. As early infant diagnostic services continue to scale-up, more programmatic attention and support is needed to retain HIV-exposed infants in care, and ensure that those testing positive initiate treatment in a timely manner. Namibia's experience demonstrates that it is feasible for a rural, low-income country to achieve high national coverage of infant testing and treatment [13]. Similarly, study from three regions of Tanzania has also demonstrated an increase in testing of HIV-exposed infants over three years [14]. Challenges like sample turnaround time and loss to follow up must be overcome before this can translate into the intended goal of early initiation of lifesaving ART for the infants.

Virological testing at birth (as an additional test to the virological testing at 4-6 weeks in the diagnostic algorithm) has been proposed as a mean of earlier case finding and a way to improve the retention in the cascade of care. This may be considered for newborns at high risk of HIV infection, such as those born to HIV-infected mothers who did not receive prenatal ART or who had HIV viral loads >1,000 copies/mL close to the time of delivery. However, only 30%-40% of HIV-infected infants can be identified by 48 hours of age. The diagnostic sensitivity of virologic testing increases rapidly by age 2 weeks; infants with negative virologic tests before 1 month of age need to be retested at 1-2 months of age. Birth testing might allow ART initiation before peak mortality occurs, but numerous other factors should be considered. Because many intrapartum infections are not detectable at birth, a second virological test at six weeks, or at a later time, would still be required to identify the substantial number of intrapartum infections.

Programs and policy-makers have promoted birth testing as a way of accelerating the testing cascade and starting more children on treatment in a timely manner. The report of a case of functional cure in an infant treated very early in life (at 30 hours of age) has stimulated further

interest in testing infants at birth [15]. However, the feasibility of testing at birth is likely to be restricted to settings with a high rate of institutional delivery, and treatment within hours of birth must still overcome barriers that include the turnaround time for testing, effective linkage to treatment and care, non-availability of appropriate neonatal dosing data for most ARV drugs (such as lopinavir/ritonavir or nevirapine given as treatment, as opposed to prophylaxis), and changes to programmatic and service delivery practices. For these reasons, birth testing may have little programmatic impact on the proportion of children who initiate timely ART and survive, unless it is coupled with improvements in the cascade of care and further health system strengthening. Focus should be more on reducing the turnaround time and retention in care.

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