EDITORIAL

Shift From PMTCT Program to ART Program

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Mother-to-child transmission (MTCT) accounts for 90% of HIV infections in children under the age of 15 years [1]. Without any intervention, the infant born to an HIV-infected pregnant woman has 25-45% risk of HIV infection during pregnancy, delivery, and breastfeeding [2]. In the absence of breastfeeding, intrauterine (transplacental) infection and peripartum infection account for 25-40% and 60-75%, respectively, of vertical infection. Breastfeeding carries an 8-25% risk of vertical transmission in the developing countries [3,4].

In 2000, there was a global surge in the new cases of HIV infections, and the world was staring at an HIV epidemic [5]. The alarm bells were enough to arouse the United Nations and its member states, and they became a signatory to the Millennium Declaration in September 2000 wherein they resolved to take terse measures to combat HIV by 2015 (Millennium Development Goal-6). The United Nations General Assembly Special Session on HIV/AIDS, held in June 2001, set the goal of reducing the proportion of infants infected with HIV by 20% by 2005, and by 50% by 2010 [6]. Scaling up of Prevention of Mother-to-Child Transmission (PMTCT) of HIV services and increased access to anti-retroviral therapy were the major armamentaria to attain this goal. Over the next fifteen years, much was achieved due to sustained efforts of all member states, and HIV-infection rates and AIDS-related deaths decreased by 40% [5].

PMTCT of HIV has been at the helm of all research in HIV. Ever since the Pediatric AIDS Clinical Trials Group demonstrated that administration of zidovudine (AZT) to pregnant women and their infants could reduce risk of perinatal transmission by nearly 70% [7], several clinical trials have used single, dual, or triple Anti Retroviral Therapy (ART) with or without breastfeeding, with different modes of delivery to reduce the risk of transmission from mother to child. Clinical trials initially focused on shortened zidovudine-alone prophylaxis regimens and moved to evaluating whether combination ARV regimens, such as short-course zidovudine combined with lamivudine, might have improved efficacy over zidovudine alone. Studies also evaluated whether even simpler, less expensive, single-drug regimens, such as single-dose intrapartum/neonatal nevirapine (NVP), would be effective, and whether combining such regimens with other short-course regimens might result in improved efficacy. The HIVNET 012 regimen advocated administration of single dose oral nevirapine (200 mg) to the mother during labour and also to the neonate (2 mg/kg) soon after birth [8]. The mothers were advised to exclusively breastfeed their babies till 6 months unless replacement feeding was acceptable, feasible, affordable, sustainable and safe. This regimen resulted in lesser chances of infant deaths and lesser HIV transmission during labour, and was well accepted in resource-poor countries as it was quite economical and convenient. However, it totally neglected the maternal health, and was not shown to be useful in preventing risk of HIV transmission antenatally or during the breastfeeding period. The rates of vertical transmission using this regimen were reported upto 10% [9,10]. Avoidance of breastfeeding was not a feasible option in several developing countries. In conditions where the mothers chose to breastfeed, it was not clear whether this option was made due to compulsion or by choice. In addition, there was a problem of acquisition of viral resistance to non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs [11].

In 2010, the WHO laid down new PMTCT ARV guidance [12] wherein countries had the option to choose between two prophylaxis regimens for pregnant women living with HIV with CD4 greater than 350 cells/mm3: Option A and Option B. Under Option A, women received antenatal (AZT starting at 14th week of gestation) and intrapartum (single dose NVP at onset of labour with first dose of AZT/3TC) antiretroviral prophylaxis along with an antiretroviral postpartum tail regimen (AZT/3TC for 7 days postpartum) to reduce risk of drug resistance, while infants receive daily nevirapine starting from birth until 1 week after cessation of all breastfeeding; or, if not

breastfeeding or if mother is on treatment, through age 4-6 weeks. Under Option B, all pregnant and lactating women with HIV initially are offered triple ART – beginning in the antenatal period and continued throughout the duration of breastfeeding. At the end of breastfeeding, women who do not yet require ART for their own health would discontinue the prophylaxis and continue to monitor their CD4 count, eventually re-starting ART when the CD4 falls below 350 cells/mm^3. Infants would be offered daily NVP or AZT from birth through age 4-6 weeks regardless of infant feeding method.

In 2011, a systematic review published clearly advocated that triple ART for all expectant and breastfeeding mothers along with NVP prophylaxis to the baby for 6 weeks duration is the best approach to mitigate MTCT of HIV [13]. In 2013, a third more efficacious approach was recommended by WHO i.e., Option B+, in which all pregnant women living with HIV are offered life-long triple-drug ART, regardless of their CD4 count or clinical staging and all HIV-exposed infants are offered 4-6 weeks of NVP/AZT regardless of feeding method [14]. This new regimen was shown to be associated with less than 2% risk of HIV transmission by vertical route. The WHO emphasized that whereever possible Option B+ be adopted as it was shown to reduce HIV-related mortality and also ensure better maternal health. Based on the new guidelines from WHO (June 2013), the National AIDS Control Organization (NACO) decided to provide life-long ART (triple drug regimen) for all pregnant and breastfeeding women living with HIV, in which all pregnant women living with HIV receive a triple drug ART regimen regardless of CD4 count or WHO clinical stage, with effect from January 1, 2014 [15]. This would not only ensure better maternal health, but also prevent stopping and starting ARV drugs with repeat pregnancies, reduce vertical transmission in future pregnancies and avoid drug resistance. In addition, infants would be administered 6 weeks of daily oral nevirapine therapy.

The study by Seenivasan, *et al*. [16] published in the current issue of *Indian Pediatrics* shows a vertical transmission rate of 6.7% amongst breastfed groups despite use of ARV prophylactic regimen using single dose NVP for mother-infant pairs. There was no HIV transmission detected amongst neonates born to mothers receiving triple ART. This study comes at a time when there is sufficient evidence to prove the superiority of triple ART for pregnant and breastfeeding mothers over the regimens using shorter regimens using fewer ARVs. All the same, it does add weight to the current recommendations of NACO on lifelong use of triple ARV in all pregnant women living with HIV and ARV prophylaxis with NVP in infants. However, it remains to be seen whether triple/dual ARV will replace nevirapine monotherapy for ARV prophylaxis in neonates exposed to HIV in the times to come. Till then the PMTCT centers should work in close conjunction with the ART centers to monitor both mothers and infants receiving anti-retroviral therapy/prophylaxis.

We must accept that changing guidelines is not a piece of cake and the entire health system needs to be refurbished. More healthcare workers, drugs, costs, laboratory set-ups, and better monitoring will be needed to enforce the revised guidelines. Only time will tell if resource-poor countries will be able to cope with the increased demands of these new guidelines and show positive results.

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