Prevention on Parent to Child Transmission of HIV – What is New?

Mamatha M. Lala · Rashid H. Merchant

Abstract Prevention of Mother-To-Child Transmission (PMTCT) of HIV has been at the forefront of research in the field of HIV/AIDS since the PACTG 076 proved successful in 1994. This was followed by many trials with single, dual, or triple Anti Retroviral Therapy (ART), with or without breastfeeding, with different modes of delivery. These trials aimed and promised to find a relatively simple, low-cost intervention that could virtually eliminate the risk of HIV transmission from mother to child, cutting across all geographic boundaries. However, translation of the findings from most of these research studies into successful national PMTCT programs and health policies has not been optimal. In the west, parent to child transmission of HIV has been virtually eliminated due to universal coverage, screening, planned conception wherever possible, thorough evaluation and appropriate antenatal, intranatal and postnatal interventions. In contrast, in resource limited settings where the magnitude of the problem is the greatest accounting for more than 95 % of all vertical transmissions of HIV, there is a constant struggle dealing with the birth of an infected infant every minute. It is time to make optimal choices to prevent the transmission of HIV from an infected mother to her child and virtually eliminate this largely preventable scourge in children.

Keywords Perinatal and pediatric HIV · Prevention of parent to child transmission · HIV and pregnancy · Vertical transmission and Interventions · Intrauterine infections · HIV-2

Introduction

Although largely eliminated in the developed world and there being plenty of evidence to show it is largely preventable, vertical transmission of HIV continues to remain an elusive goal, as evidenced by the prevailing, albeit slowly changing Global and Indian situation.

Global Situation

In 2009, about 370 000 children contracted HIV, down from 500 000 in 2001 [1]. About 26 % of the estimated 125 million pregnant women in low and middle income countries received an HIV test in 2009, an increase from 21 % in 2008 and 7 % in 2005; over half of the 1.4 million pregnant women living with HIV globally received antiretroviral drugs (ARVs) to prevent transmission, up from 45 % (37–57 %) in 2008 and 15 % (12–18 %) in 2005 [2]. However, many received single-dose nevirapine (sd-NVP), which although reduces peripartum transmission, is much less effective than the combination and longer ARV prophylaxis regimens, is associated with the acquisition of viral resistance and does not cover the breastfeeding period. This is of particular concern as postnatal transmission of HIV through breast-feeding continues to be a major problem in sub-Saharan Africa and other resource-limited settings including India. Despite remarkable gains in coverage and uptake and strong momentum towards virtual elimination, AIDS is still one of the leading causes of death among women of reproductive age globally and one of the major causes of maternal mortality [3].
Mother To Child Transmission (MTCT) is by far the most significant route of transmission of HIV infection in children <15 y. Not all infected pregnancies lead to infected babies; with no intervention, rates vary from 15 to 30 % in developed countries to 30–45 % in developing countries, mainly because of feeding practices that comprise almost universally of prolonged breastfeeding.

Indian Situation

In India, among 2.39 million HIV positive individuals, 39 % are women, with 0.48 % antenatal seroprevalence. In 2009, despite scale up efforts, only 21 % of the estimated total annual pregnancies of 270 lakh were counseled and tested for HIV and only 3 % of ANC sites offered HIV-testing services; between 17 and 48 % received sd-NVP for PPTCT along with 27 % of HIV-exposed infants [4].

The fetus can get infected antenatally (maternal blood, transplacental hemorrhage, infection via umbilical cord, gastrointestinal mucosa while swallowing infected amniotic fluid), intranatally (contact with mother’s blood/secretions during labor/delivery) and postnatally (breast milk). Maternal, viral, obstetric, fetal and infant factors all affect transmission making it essentially multifactorial [5]. Maternal plasma viral load is considered to be the strongest predictor of transmission, which occurs across the entire range of viral load, including very low/undetectable levels [6]. Advanced stage of disease and immune depletion are associated with a higher risk of transmission. A recent study from Zambia found higher rates of MTCT in women eligible for treatment for their own health and also noted high rates of maternal death; it also found that initiating ART in pregnant women in need of treatment for their own health would prevent 92 % of maternal deaths and 88 % of perinatal and postnatal infections [7]. Yet in 2009, in low/middle-income countries, only about half of the pregnant women who tested positive were assessed for their treatment eligibility [2].

For PMTCT, the World Health Organization (WHO) promotes a comprehensive approach [8]:

- Primary prevention of HIV infection among women of childbearing age;
- Preventing unintended pregnancies among women living with HIV;
- Preventing HIV transmission from a woman living with HIV to her infant; and
- Providing appropriate treatment, care and support to mothers living with HIV and their children and families.

In 2010, WHO revised the guidelines for PMTCT based on two key approaches: (a) Lifelong Anti Retroviral Therapy (ART) for women in need of treatment for their own health (also safe and effective in PMTCT) and (b) ARV prophylaxis to women not in need of treatment during pregnancy, delivery and breastfeeding along with prophylaxis to mother/baby during breastfeeding, where breastfeeding is judged to be the safest option. These recommendations could reduce the risk to <5 % (or even lower) in breastfeeding populations from 35 % and to <2 % from 25 % in non-breastfeeding populations, ensuring increased maternal and child survival [2]. The WHO eligibility criteria for initiation of ART for all HIV infected

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<tr>
<th>Table 1 ARV-prophylaxis options recommended for HIV-infected pregnant women who do not need treatment for their own health</th>
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<tr>
<td>Maternal AZT + infant ARV prophylaxis (Option A)</td>
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<tr>
<td><strong>Mother</strong></td>
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<tr>
<td>Antepartum twice-daily AZT starting from as early as 14 wk of gestation and continued during pregnancy. At onset of labour, sd-NVP and initiation of twice daily AZT + 3TC for 7 d postpartum.</td>
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<td>(Note: If maternal AZT was provided for more than 4 wk antenatally, omission of the sd-NVP and AZT + 3TC tail can be considered; in this case, continue maternal AZT during labour and stop at delivery).</td>
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<td><strong>Infant</strong></td>
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<td>For breastfeeding infants</td>
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<td>Daily NVP from birth for a minimum of 4 to 6 wk, and until 1 wk after all exposure to breast milk has ended.</td>
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<td><em>Infants receiving replacement feeding only</em></td>
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<tr>
<td>Daily NVP or sd-NVP + twice-daily AZT from birth until 4 to 6 wk of age.</td>
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AZT Zidovudine; 3TC Lamivudine; NVP Nevirapine; EFV Efavirenz; TDF Tenofovir; FTC Eemtricitabine; XTC 3TC or FTC; LPV-rt Lopinavir/Ritonovir; ABC Abacavir

http://www.who.int/hiv/pub/mtct/rapid_advice_mtct.pdf
pregnant women includes CD4 cell count <350 cells/mm³ irrespective of clinical staging; and for all in clinical stage 3 or 4, irrespective of CD4 cell count; The criteria are the same as for non-pregnant women and stresses the need to start ART irrespective of gestational age and continue ART throughout pregnancy, delivery and thereafter, with their infants receiving daily NVP until 6 wk of age if breastfed and daily ZDV or NVP from birth until 6 wk of age if not breastfed [2]; The recommendation for all HIV infected pregnant women who are not in need of ART for their own health (Table 1) is a choice between one of two equally efficacious ARV prophylaxis options A and B, starting from 14 wk gestation or soon thereafter. Both options significantly reduce risk of MTCT, have advantages and disadvantages in terms of cost, feasibility, acceptability and safety for mothers and infants. The choice has to be made and supported at the country level [2]. As per the 2012 Executive summary of the WHO on Programmatic update on ‘Use of Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants’, a new third option ‘Option B+’ is being proposed which not only provides the same triple ARV drugs to all HIV infected pregnant women beginning in the antenatal clinic setting but also continues this therapy for their life; the important advantages of Option B+ include: further simplification of regimen and service delivery and harmonization with ART programs, protection against mother-to-child transmission in future pregnancies, a continuing prevention benefit against sexual transmission to serodiscordant partners, and avoiding stopping and starting of ARV drugs.

The PPTCT program in India currently is a combination of low-cost, short-term prophylactic drug treatment, safe delivery practices, counseling, support and safe infant feeding methods. Pregnant women not needing treatment for their own health receive prophylactic single dose NVP, regular antenatal monitoring and supervised delivery combined with a single dose NVP to the infant within 72 h delivery with breast feeding [4]. Plans are on to implement the option B of the WHO recommendations in a phased manner in the country.

Strategies for PMTCT

Primary Strategies

Primarily preventing HIV infection in adolescent girls and women of childbearing age through awareness/education on safe sexual practices, sexually transmitted infections and family planning measures constitute primary preventive strategies and go a long way in controlling the pediatric HIV epidemic. Conforming to prevention as India’s primary response, National AIDS Control Program-III (NACP-III) seeks to expand strategies to the sub-district/community level, through information, education, counseling, promoting condom usage, treatment/cure for Sexually Transmitted Infections (STIs), etc. [4].

Secondary Strategies

Secondary Strategies to reduce transmission from an already infected mother to her child can be broadly classified as antenatal, intranatal and postnatal strategies.

Antenatal Strategies

Wide coverage with universal screening of all pregnant women as early as possible remains the greatest challenge and the key to a successful antenatal prevention program. As per National HIV testing policy, two ELISA using different principles are required to diagnose HIV infection in clinical settings [4]. It is important to impart knowledge to even HIV-negative women to provide them with necessary information and support to remain uninfected. If initially negative, but thought to be at high risk, a repeat screening may be offered at 28 wk of pregnancy. When a patient presents in labor without a HIV report, a rapid test is appropriate to initiate prophylaxis, followed by confirmation later.

In addition to routine antenatal investigations and immunological monitoring, thorough evaluation for clinical staging/opportunistic infections including asymptomatic genital tract infections with treatment should be instituted. As per American guidelines, not only is viral load estimation a part of initial work up, but also ARV drug-resistance studies before initiating/modifying regimens in women with viral loads above threshold for resistance testing (>500–1000 copies/ml) [9].

All HIV-infected pregnant women should be administered ARVs during pregnancy, regardless of the CD4 or HIV RNA levels with regimen chosen based on need for treatment vs. only prophylaxis. Effectiveness, teratogenic potential and possible adverse outcomes for mother/fetus are important considerations. The known benefits and potential risks should be discussed and the importance of adherence should be emphasized at every visit. All children exposed should have long-term clinical follow-up especially for mitochondrial toxicities, although extremely rare and risk should be balanced against the clear benefit in reducing transmission [9].

One of the major achievements in HIV research was the PACTG 076 that reduced the risk of perinatal transmission by nearly 70 % [10]. This paved the way for many a trial with single drug, dual drug/triple drug, with/without breastfeeding, with/without allowing spontaneous normal delivery, in various permutations and combinations with varying results [11].

There are growing concerns regarding the administration of regimens that do not fully suppress HIV replication, promoting the development of drug resistance. This implies risk for newborn HIV acquisition (possibly with a resistant strain), also jeopardizes the efficacy of future PMTCT/treatment options to the mother herself and her infant if infected. Resistance can be detected after sd-NVP exposure within 6–8 wk in up to 36 % (19–76 %) mothers and 53 % (36–87 %)
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<td>Post-exposure infant prophylaxis South Africa [27]</td>
<td>Neonatal sdNVP vs. ZDV for 6 wk</td>
<td>No AP or IP ARV</td>
<td>sdNVP vs. ZDV for 6 wk</td>
<td>For formula-fed infants only, MTCT was 14.3% in sdNVP arm vs. 14.1% in ZDV arm at 6 wk (not significant, ( P=0.30 )). For breastfed infants only, MTCT was 12.2% in sdNVP arm and 19.6% in ZDV arm (( P=0.03 )).</td>
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<td>Breastfeeding and formula feeding Mashi Botswana [28, 29]</td>
<td>Initial: short-course ZDV with/without maternal and infant sdNVP and with/without breast feeding</td>
<td>1st randomization</td>
<td>2nd randomization</td>
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<td></td>
<td>Revised: short-course ZDV + infant sdNVP with/without maternal sdNVP and with/without breast feeding; women with CD4 cell counts &lt;200 cells/mm(^3) receive combination therapy</td>
<td>ZDV from 34 wk Oral IP: ZDV + either sdNVP vs. placebo</td>
<td>Breastfeeding + ZDV (infant) 6 mo + sdNVP, infant only vs. Formula feeding + ZDV (infant) 4 weeks + sdNVP; infant only</td>
<td>In breastfeeding + infant ZDV arm, MTCT at 1 mo was 8.4% in sdNVP arm and 4.1% in placebo arm (difference not statistically significant). ( \quad )</td>
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<td>SWEN Uganda, Ethiopia, India [30] Breastfeeding</td>
<td>sdNVP vs. NVP for 6 wk</td>
<td>No AP ARV Oral IP: sdNVP</td>
<td>Infant sdNVP vs. NVP for 6 wk</td>
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<td>PEPI-Malawi Trial Malawi [31] Breastfeeding</td>
<td>sdNVP + ZDV for 1 wk (control) vs. two extended infant regimens (NVP or NVP/ZDV) for 14 wk</td>
<td>No AP ARV Oral IP: sdNVP (if mother presents in time)</td>
<td>Infant sdNVP + ZDV for 1 wk (control) vs. control + NVP for 14 wk vs. control + NVP/ZDV for 14 wk</td>
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**Notes:**
- MTCT at 6 wk was 5.3% in sdNVP arm vs. 2.5% in extended NVP arm (risk ratio 0.54, \( P=0.009 \)).
- MTCT at 6 mo was 9.0% in sdNVP arm vs. 6.9% in extended NVP arm (risk ratio 0.80, \( P=0.16 \)).
- HIV-free survival significantly lower in extended NVP arm at both 6 wk and 6 mo of age.
- Postnatal infection in infants uninfected at birth:
  - MTCT at age 6 wk was 5.1% in control vs. 1.7% in extended NVP (67%).
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<td>MITRA Tanzania [32]</td>
<td>Infant 3TC for 6 mo (observational)</td>
<td>ZDV/3TC from 36 wk through labor</td>
<td>Maternal ZDV/3TC for 1 wk; infant 3TC for 6 mo</td>
<td>MTCT at age 6 mo was 4.9 % (postnatal MTCT between ages 6 wk and 6 mo was 1.2 %).</td>
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<td>Breastfeeding</td>
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<td>Kisumu Breastfeeding Study (KiBS) Kenya [33]</td>
<td>Maternal triple-drug prophylaxis (observational)</td>
<td>ZDV/3TC/NVP (NFV if CD4 cell count &gt;250 cells/mm³) from 34 wk through labor</td>
<td>Maternal ZDV/3TC/NVP (NFV if CD4 cell count &gt;200 cells/mm³) for 6 mo; infant sdNVP</td>
<td>MTCT at age 6 mo was 5.0 % (postnatal MTCT between ages 7 d and 6 mowas 2.6 %).</td>
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<tr>
<td>MITRA-PLUS Tanzania [34]</td>
<td>Maternal triple-drug prophylaxis (observational)</td>
<td>ZDV/3TC/NVP (NFV if CD4 cell count &gt;200 cells/mm³) from 34 wk through labor</td>
<td>Maternal ZDV/3TC/NVP (NFV if CD4 cell count &gt;250 cells/mm³) for 6 mo; infant sdNVP</td>
<td>MTCT at age 6 mo was 5.0 % (Postnatal MTCT between ages 6 wk and 6 mo was 0.9 %), not significantly different from 6 mo infant prophylaxis in MITRA.</td>
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<td>Kesho Bora Multi-African [35]</td>
<td>Antepartum ZDV/sdNVP with no postnatal prophylaxis vs. maternal triple-drug prophylaxis in women with CD4 cell counts of 200–500 cells/mm³</td>
<td>Arm 1: ZDV/3TC/LPV/r</td>
<td>Arm 1: Maternal ZDV/3TC/LPV/r for 6 mo; infant sdNVP + ZDV for 1 wk</td>
<td>MTCT at birth was 1.8 % with maternal triple-drug prophylaxis Arm 1 and 2.5 % with ZDV/sdNVP Arm 2, not significantly different. In women with CD4 cell counts 350–500 cells/mm³, MTCT at birth was 1.7 % in both arms.</td>
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<td>Breastfeeding primarily</td>
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<td>Mma Bana Botswana [36]</td>
<td>Maternal triple-drug prophylaxis (comparies 2 regimens) in women with CD4 cell counts &gt;200 cells/mm³</td>
<td>Arm 1: ZDV/3TC/ABC</td>
<td>Arm 1: Maternal ZDV/3TC/ABC for 6 mo; infant sdNVP + ZDV for 4 wks</td>
<td>MTCT at age 6 mo overall was 1.3 %; 2.1 % in ZDV/3TC/ABC Arm 1 and 0.4 % in ZDV/3TC/LPV/r Arm 2 (P=0.53).</td>
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<td>Breastfeeding</td>
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<td>BAN Malawi [37]</td>
<td>Postpartum maternal triple-drug prophylaxis vs. infant NVP in women with CD4 cell counts ≥250 cells/mm³</td>
<td>No AP drugs</td>
<td>Arm 1 (control): Maternal ZDV/3TC for 1 wk; infant sdNVP + ZDV/3TC for 1 wk</td>
<td>MTCT at age 28 wk was 5.7 % in control Arm 1; 2.9 % in maternal triple-drug prophylaxis Arm 2 (P=0.009 vs.</td>
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Table 2 (continued)

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<tr>
<td>HPTN 046 [38] South Africa, Tanzania, Uganda, Zimbabwe</td>
<td>Postpartum prophylaxis of breast milk transmission of HIV with 6 wk vs. 6 mo of infant NVP</td>
<td>IP regimens: Arm 1 (control): ZDV/3TC + sdNVP Arm 2: ZDV/3TC + sdNVP Arm 3: ZDV/3TC + sdNVP</td>
<td>Arm 2: Control as above, then maternal ZDV/3TC/LPV/r for 6 mo Arm 3: Control as above, then infant NVP for 6 mo</td>
<td>• No significant difference between maternal triple-drug prophylaxis Arm 2 and infant NVP Arm 3 ($P&lt;0.001$ vs. control).</td>
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<td>Breastfeeding</td>
<td>Infant prophylaxis with 6 wk ZDV vs. 6 wk infant ZDV plus three doses of NVP in first week of life vs. 6 wk infant ZDV plus 2 wk of 3TC/NFV</td>
<td>AP drugs allowed if required for maternal health</td>
<td>All infants received daily NVP from birth through age 6 wk.</td>
<td>• In infants uninfected at age 6 wk, the 6-mo infant HIV infection rate was 1.1 % (0.3–1.8 %) in the extended NVP Arm 1 and 2.4 % (1.3–3.6 %) in the placebo Arm 2 ($P=0.048$). • For mothers receiving triple-ARV drugs at the time of randomization, in infants uninfected at age 6 wk, the 6-mo infant HIV infection rate was 0.2 % and not statistically different between extended NVP Arm 1 (0.5 %) and placebo Arm 2 (0 %). • For mothers with CD4 cell counts &gt;350 cells/mm³ who were not receiving triple ARV drugs, in infants uninfected at age 6 wk, the 6-mo infant HIV infection rate was 0.7 % (0–1.5 %) in the extended NVP Arm 1 and 2.8 % (1.3–4.4 %) in the placebo Arm 2 ($P=0.014$). • Intrapartum HIV transmission among infants with negative HIV test at birth: 4.8 % (3.2–7.1 %) ZDV (Arm 1) vs. 2.2 % (1.2–3.9 %) in ZDV plus NVP (Arm 2) ($P=0.046$ compared with Arm 1) vs. 2.4 % (1.4–4.3 %) in ZDV plus 3TC/NFV (Arm 3) ($P=0.046$ compared with Arm 1). • Overall HIV transmission rates, including in utero infection: 11.0 % (8.7–14.0 %) ZDV (Arm 1) vs. 7.1 % (5.2–9.6 %) in ZDV plus NVP (Arm 2) ($P=0.035$ compared with Arm 1) vs. 7.4 % (5.4–9.9 %) in ZDV</td>
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<td>Formula feeding</td>
<td>Infant prophylaxis with 6 wk ZDV vs. 6 wk infant ZDV plus three doses of NVP in first week of life vs. 6 wk infant ZDV plus 2 wk of 3TC/NFV</td>
<td>No AP drugs if mother presented early enough, IV ZDV during labor through delivery</td>
<td>Arm 1 (control): Infant ZDV for 6 wk</td>
<td>Arm 2: Control as above plus NVP with first dose within 48 h of birth, second dose 48 h later, and third dose 96 h after the second dose</td>
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NICHD-HPTN 040/PACTG 1043 Argentina, Brazil, South Africa, U.S. [39] | Control: Infant ZDV for 6 wk | All infants received daily NVP from birth through age 6 wk. | Arm 2: Daily infant placebo from 6 wk through age 6 mo of age | • At infant randomization at age 6 wk, 29 % of mothers in each arm were receiving a triple-ARV regimen for treatment of HIV. • For mothers receiving triple-ARV drugs at the time of randomization, in infants uninfected at age 6 wk, the 6-mo infant HIV infection rate was 0.2 % and not statistically different between extended NVP Arm 1 (0.5 %) and placebo Arm 2 (0 %). |
infants as shown in a Meta analysis [12]; upto 60–89 % with more sensitive techniques [13]. This is of major concern, because the first line treatment regimen for women who require treatment in India and most resource-limited settings is a NVP based regimen. As most HIV infections in India are of subtype C, it is particularly concerning that subtype C has been found to be associated with high rates of NVP resistance (69 %) [14].

Resistance to Lamivudine (3TC) has been shown to develop rapidly (12–40 %) [15]. Also Zidovudine (ZDV) monotherapy in pregnancy may lead to drug-resistant virus as demonstrated in trials in upto 10 %, upto 17 % of women and 8 % of their infected children, even upto 25 % and is related with a higher rate of transmission [16–18]. This is of major concern, as ZDV is a main component of PMTCT/standard treatment regimen in many countries. The high genetic barrier to resistance of boosted Protease Inhibitors (PI) and their short terminal half-life makes them more attractive options than Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), with Lopinavir/ritonavir being preferred PI regimen in pregnant women. Although there could be a small increased risk of preterm birth, a meta-analysis found no increase in risk of preterm birth with any ARV drug/combination ARV regimens (including PI), as compared to no drugs [19]. Careful regular monitoring for pregnancy complications and potential toxicities is warranted.

In addition, other risk factors: malnutrition, anemia, micronutrient deficiencies, sexually transmitted infections, tobacco/drug/alcohol use, unsafe sexual practices should be looked into and appropriate interventions provided, thereby seeking to reduce transmission risk and improving overall outcome.

Intranatal Strategies

Maximum transmissions take place late in pregnancy/labor, hence obstetric practices should be modified by avoiding invasive procedures: repeated per vaginal examinations, artificial rupture of membranes, fetal scalp monitoring/blood sampling, episiotomies and instrumental deliveries.

As a policy any pregnant woman without a documented HIV status at labor should be screened with a rapid test unless she declines, so that preventive measures, although less effective, could be implemented at this stage too.

Elective Lower Segment Cesarian Section (ELSCS) before labor/rupture of membranes has been shown to be safe and effective, but risks/benefits must be carefully weighed. As shown by Lallamant & team, also by the authors’ own experience (unpublished data), a short-term ART for PMTCT would benefit equally well and allow spontaneous normal delivery, avoiding many unnecessary ELSCS, which still carries a significant risk in many low-income countries [20]. ELSCS is recommended at 38 wk gestation for women with unknown or >1,000 copies/ml viral load at term as per the American Guidelines [9] and for women with >50 copies/ml as per the British Guidelines [21].

There is scarcity of evidence to conclusively say that inexpensive modalities like cleaning/disinfection of the birth canal can reduce MTCT although incidence of neonatal sepsis is definitely cut down.

Postnatal Strategies

Worldwide, breastfeeding is a major route of MTCT where safe feeding alternatives are not easily available. The prevention of this transmission remains the focus of PMTCT research: short course ARVs at labor/delivery; maternal HAART during last trimester, labor, and for upto 6 mo postpartum with a goal of minimizing maternal viral load in plasma and breast milk; interventions directed at protecting the infant during exclusive breastfeeding followed by weaning; active or passive immune strategies that boost infant immune responses during the period of breast milk exposure, etc.
However, in developed countries avoidance of breastfeeding remains an important component of PMTCT. In India where breast-feeding is a norm and a large majority of infants continue to breastfeed till about 2 y of age, safe breast feeding practices pose an enormous challenge [22].

There has been a major paradigm shift in WHO guidelines as evidence allows new recommendations for more effective/safer postpartum interventions in areas where breastfeeding is judged to be the most appropriate choice of infant feeding (Table 1). Exclusive breastfeeding for the first 6 mo with introduction of appropriate complementary food thereafter with continuation for 12 mo and gradual weaning within 1 mo is recommended [2].

As criteria for successful replacement feeding like acceptability, feasibility, affordability, sustainability and safety are very difficult to fulfill in resource limited settings, several potential interventions are implicated to make breastfeeding safe [23]; Main strategies being - decreasing infectivity by lowering viral load in breast milk through ARV prophylaxis/chemical/flash heat treatment, addressing factors affecting viral transfer (mixed feeding, infant thrush, nipple cuts, mastitis); and improving infant's defenses against HIV through passive/active immunization. Studies evaluating safety/immunogenicity of HIV vaccines in infants have hypothesized that passive immunization with HIV immunoglobulin may decrease MTCT [24]. A Phase III randomized clinical trial compared sd NVP+HIV immunoglobulin to sd NVP alone for PMTCT and concluded that giving mother-infant pairs an infusion of peripartum HIV hyperimmunoglobulin+sd NVP was as safe, but no more effective than sd NVP alone [25]. Cochrane systematic review concluded that although complete avoidance of breastfeeding is efficacious, it has significant associated morbidity/mortality; if breastfed, exclusive breastfeeding during the first few months of life and extended ARVs to the infant (NVP alone, or NVP+ZDV) could reduce transmission [26].

The results of recent major studies for PMTCT since 2005 are summarized in Table 2.

**Pregnancy with HIV-2 Infection**

Endemic in Angola, Mozambique and some West African countries, HIV-2 is found in parts of India [40]. HIV-2 has longer asymptomatic phase, slower progression to AIDS and appears to be less readily transmitted both sexually and vertically, also differing from HIV-1 in its susceptibility to ART and to develop drug resistance. Several studies confirm that rates of MTCT are low with/without interventions (0–4 %) [41–44]. HIV-2 has variable sensitivity to PIs, with lopinavir, saquinavir, and darunavir having the most activity [45]; while NVP, EFV and Enfuvirtide have no activity.

WHO recommends maternal prophylaxis with ZDV alone to be considered with 6-wk ZDV for infants for PMTCT. For women eligible for treatment (based on the same eligibility criteria as for HIV-1), WHO recommends a triple NRTI regimen (ZDV+3TC+Abacavir); in view of the low risk of transmission, lack of clinical trial data and program experience with maternal triple ARV prophylaxis or extended infant prophylaxis and the lack of effectiveness of NNRTI drugs, the additional interventions recommended for women with HIV-1 infection are not recommended [2].

However American recommendations are two NRTIs+boosted PI for women who require treatment for their own health and also for PMTCT with stopping of all drugs post partum [9]. The British recommend that pregnant women with detectable HIV-2 should be managed using a HAART regimen to which the virus is sensitive; if the viral load is detectable or mother is symptomatic or has low CD4 cell count, an ELSCS could be planned at 38 wk gestation; HIV-2 also can be transmitted through breastfeeding and hence advisable to avoid, if feasible alternatives are in place [21].

Pregnant women who have co-infection with HIV 1 and 2 should be treated according to the guidelines for HIV-1 mono infected patients, making sure that the ARV regimen chosen is also appropriate for HIV-2.

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**Role of Funding Source** None.

**References**