Update on successes and challenges regarding mother-to-child transmission of HIV

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Purpose of review

There is an unprecedented global commitment to reverse the pediatric HIV epidemic by making prevention of mother-to-child transmission (PMTCT) services accessible in all countries. This review outlines the successes made and the challenges that remain.

Recent findings

In resource-rich countries, mother-to-child transmission rates of HIV as low as 1% have been achieved. The efficacy of short-course antiretrovirals for PMTCT in Africa is estimated at 50%. Coinfections with herpes simplex virus type 2, other sexually transmitted infections resulting in genital ulcers, and endemic infectious diseases (e.g., malaria) may increase the risk of mother-to-child transmission of HIV. Vertical transmission of drug-resistant viruses has been reported; the prevalence and effect of transmitted resistant virus on treatment outcomes are under investigation. Obstacles facing PMTCT in resource-limited countries include the lack of healthcare infrastructure, limited manpower, and competing public health priorities with the limited healthcare budget.

Summary

Although the birth of an HIV-infected child in a resource-rich country is now a sentinel health event, in most resource-limited countries the birth of an HIV-infected child continues to be the status quo. Comprehensive PMTCT, including antiretroviral treatment for HIV-infected women and children, should be paramount in resource-limited countries.

Keywords

antiretroviral drugs, drug-resistant virus, HIV, prevention of mother-to-child transmission, resource-limited setting, resource-rich setting

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Introduction

Much progress has been made in containing the HIV epidemic, although it is unevenly applied among countries. The introduction of antiretroviral chemoprophylaxis to prevent mother-to-child transmission (MTCT) of HIV was an important milestone in pediatric HIV. In 2007, about 370 000 (330 000–410 000) children less than 15 years of age became infected with HIV, almost exclusively through MTCT [1]. The United Nations General Assembly made a commitment in 2001 to reduce MTCT of HIV by 20 and 50% by 2005 and 2010, respectively [2]. In this review, the successes at reaching these goals and the challenges that remain are discussed.

Basic principles of mother-to-child transmission of HIV

Without any intervention to prevent transmission, the rate of MTCT of HIV is estimated at 12–40% [3]. MTCT of HIV can occur before, during, and after birth. The relative contribution of each of these modes of perinatal transmission is not well defined [4]. Risk factors associated with MTCT are illustrated in Table 1. In resource-limited countries, breast-feeding contributes significantly to MTCT.

Prevention of mother-to-child transmission

Current interventions to prevent MTCT target the late intrauterine and intrapartum periods, when most transmission events occur. Administration of antiretroviral drugs to an HIV-infected mother and her infant, careful management of labor and delivery (with elective cesarean delivery for women with high HIV viral loads), and avoidance of breast-feeding have reduced the rate of MTCT to less than 2%.

The containment of the HIV epidemic is inextricably linked to the socioeconomic, cultural, and political milieu of a country. Therefore, the successes and challenges of

Table 1 Risk factors associated with mother-to-child transmission of HIV

Risk factor	Possible mechanism of infection MTCT
Maternal Health	
Advanced HIV disease	High viral load and low $CD4^+$ T cells
Primary HIV infection	High viral load, lack of immune response
No maternal ARV treatment	High viral load
Obstetric factors	
Vaginal delivery	Exposure to HIV-infected genital secretions
Episiotomies and vaginal tears	Exposure to HIV-infected blood
Instrumental deliveries	Exposure of breached infant skin to secretions containing HIV
Chorionic villus biopsy or amniocentesis	Increased risk of placental microtransfusion
Fetal electrode monitoring	Breach in infant skin and exposure to infected secretions
Prolonged rupture of fetal membranes	Prolonged exposure to HIV-infected secretions
Chorioamnionitis	Ascending infection
Low birth weight	Impaired fetal or placental membranes
Prematurity	Impaired fetal or placental membranes
Maternal coinfection	
Malaria (placental malaria)	Increased viral load, disruption in placental architecture
HSV-2	Increased plasma viral load, increased shedding of HIV in genital secretions, genital ulcers
Other STIs	Genital ulcerations and exposure to HIV-infected blood or genital secretions
Infant feeding	
Breast-feeding	Mastitis, cell-free and cell-associated virus
Mixed feeding	Contaminated formula or water used in preparing formula may cause gastroenteritis leading to microtrauma to infant's bowel and provides entry to HIV virus
Miscellaneous factors	
Infant–mother HLA concordance	HLA molecules on the surface of HIV-infected maternal cells are recognized as 'self' by cytotoxic T-lymphocytes or NK cells of the infant and are, therefore, less likely to be destroyed
Maternal HLA homozygosity	Increased viral load
Presence of CCR5 Δ32 mutation in T cells of exposed infants	Decreased susceptibility to HIV infection

ARV, antiretroviral; HLA, human leukocyte antigen; HSV-2, herpes simplex virus type 2; MTCT, mother-to-child transmission; NK, natural killer; STIs, sexually transmitted infections.

the prevention of MTCT (PMTCT) of HIV are discussed under two headings: resource-rich countries (high-income countries) and resource-limited countries (low and middle-income countries).

Prevention of mother-to-child transmission successes in resource-rich countries

In 1994, a landmark Pediatric AIDS Clinical Trials group study (PACTG 076) demonstrated a 67% reduction in perinatal HIV transmission with the administration of a combination of prenatal, intrapartum, and neonatal zidovudine [5]. The US Public Health Task Force adopted the study's finding and recommended that all pregnant women should be offered HIV testing, and those women who were identified as HIV-infected should be given the three-part zidovudine regimen (i.e., the PACTG 076 regimen). There is an increase in the acceptance and completion of rapid HIV testing in resource-rich countries [6•].

Perinatal transmission rates as low as 1% have been achieved as a result of the use of the PACTG 076 regimen (Table 2) [7], highly active antiretroviral therapy (HAART) regimens, and appropriate management of labor and delivery. Therefore, the birth of an infected child in a resource-rich country is now a sentinel health event signaling a chain of missed opportunities and barriers to available PMTCT programs [8]. The Centers for Disease Control and Prevention estimates that 100–200 infants with HIV infection are born in the United States annually. The rate of MTCT of HIV continues to decrease; in 2005, only about 67 HIV-infected infants were born in the United States [9].

Prevention of mother-to-child transmission challenges in resource-rich countries

There are ongoing issues that may reverse or threaten the gains achieved in PMTCT of HIV in resource-rich countries.

Late access to mother-to-child transmission prevention services

In a French study, it was observed that pregnant women who have emigrated from sub-Saharan African countries had delayed access to HIV testing and antenatal care as compared with French-born pregnant women [10••]. In the United States, racial/ethnic differences in the time to initiation of HAART have been observed among HIV-infected pregnant women; 42% of white women started therapy prior to pregnancy as compared with 29% of

Table 2 Randomized controlled trials of antiretroviral prophylaxis for reduction of mother-to-child transmission of HIV infection

Study, Year	Site	Breast-feeding allowed	Drugs tested	Intervention	Comments
PACTG 076, 1994	USA, France	No	ZDV	ZDV given from 14–34-week gestation, during intrapartum period, and postnatally to the newborn for 6 weeks	8.3% transmission, i.e., 68% reduction in transmission at 18 months
Bangkok trial, 1999	Bangkok	No	ZDV	ZDV from 36-week gestation and during intrapartum period	50% reduction in transmission at 6 months
PHPT, 2000	Thailand	No	ZDV	ZDV from 26-week gestation, during intrapartum period and postnatally for 6 weeks; or ZDV from 26-week gestation, during intrapartum, and postnatally for 3 days; or ZDV from 35-week gestation, during intrapartum period, and postnatally for 6 weeks; or ZDV from 35-week gestation, during intrapartum period, and postnatally for 3 days	Interim analysis transmission risk: long–long (from 26–6 weeks postnatal) was 4.1%; short–short (35 weeks to 3 days postnatal) was 10.5% (this arm later terminated); final analysis transmission risk: long–long, 6.5%; long–short, 4.7%; short–long, 8.6%
Ivory Coast Trial, 1999	Ivory Coast	Yes	ZDV	ZDV from 36-week gestation and during intrapartum	37% reduction at age of 3 months
DITRAME, 1999	Ivory Coast, Burkina Faso	Yes	ZDV	ZDV from 3–38-week gestation, during intrapartum, and postnatally	38% reduction at age of 6 months, and 30% reduction at age of 15 months
HIVNET 012, 1999	Uganda	Yes	NVP vs. ZDV	NVP single dose at labor onset, and NVP single dose to neonate at 48–72 h; or ZDV given orally every 3 h at onset of labor, and ZDV orally b.i.d. for 7 days to neonate	47% reduction in NVP-treated compared with ZDV-treated group
PACTG 316, 2002	USA, Europe, Brazil, and the Bahamas	No	Usual ARV and NVP	Usual ARV and placebo; or usual ARV and NVP during intrapartum and postnatal periods	Transmission rate among the usual ARV and placebo was 1.6% compared with 1.4% transmission of the NVP arm
PHPT, 2004	Thailand	No	ZDV and NVP	Standard ZDV and NVP during intrapartum period and postnatally; or standard ZDV and NVP during intrapartum period; or standard ZDV only	Transmission risk: standard ZDV and two doses of NVP was 1.9%; standard ZDV and one dose of NVP intrapartum was 2.8%; and standard ZDV alone was 6.3%
PETRA, 2002	Africa	Yes	ZDV and 3TC	ZDV and 3TC from 36-week gestation, during intrapartum period, and postnatally; or ZDV and 3TC during intrapartum period and postnatally; or ZDV and 3TC during intrapartum period	The greatest effect (transmission risk of 5.7%) was observed with the three-part regimen
SAINT, 2003	Africa	Yes	NVP vs. ZDV and 3TC	NVP during intrapartum period and postnatally to newborn at 48 h; or short-course ZDV and 3TC during intrapartum period and to the newborn postnatally for 7 days	Transmission in NVP arm was 12.3% compared with short-course ZDV and 3TC of 9.3%
NVAZ, 2003	Africa	Yes	NVP and ZDV	Single-dose NVP postnatally to newborn; or single-dose NVP and 1-week ZDV postnatally to the newborn	Transmission risk with the NVP-only arm was 20.9% compared with the combination arm 15.3%

3TC, lamivudine; DITRAME, Diminution de la Transmission Mere-Enfant; HIVNET, HIV Network for Prevention Trials; NVAZ, Nevirapine/AZT (Zidovudine) Trial; NVP, nevirapine; PACTG, Pediatric AIDS Clinical Trials group; PETRA, Perinatal Transmission Trial; PHPT, Perinatal HIV Prevention Trial; SAINT, South Africa Intrapartum Nevirapine Trials; ZDV, zidovudine. Adapted from [7].

Hispanic and 27% of black women [11]. Moreover, the number of teenagers who were perinatally infected, are nonadherent to their HAART regimens, and who access care very late in pregnancy is on the rise.

Nonadherence to HIV testing guidelines during pregnancy by providers

There are some providers who continue to offer routine HIV testing during pregnancy solely to women they consider at high risk, rather than to all pregnant women. There are cases of infected infants born to women who tested negative in early pregnancy but who seroconverted later in pregnancy, presumably as a result of recent acquisition of primary infection.

Herpes simplex virus type 2 coinfection and the risk of mother-to-child transmission of HIV

Genital ulcer diseases, including herpes simplex virus type 2 (HSV-2) and syphilis, facilitate sexual transmission and acquisition of HIV. HSV-2 coinfection with HIV results in increased genital shedding of HIV [12]. It is postulated that HSV-2 coinfection may increase the risk of MTCT of HIV. In a case–control study of HIV-infected women enrolled in an MTCT trial in Zimbabwe, HSV-2 infection was associated with increased intrapartum MTCT of HIV [adjusted odds ratio, 1.50; 95% confidence interval (CI), 1.09–2.08] [13••]. The administration of valaciclovir (which suppresses subclinical and clinical reactivation of HSV-2) to HIV-infected women reduced their genital and plasma HIV viral loads [14••]. Further research is needed to determine whether treatment of HSV-2 coinfection in HIV-infected pregnant women will result in further reduction of MTCT of HIV.

Effect of perinatal antiretroviral exposure on infants

There are limited data on the short-term and long-term toxicities associated with exposure of an infant to antiretroviral drugs *in utero* and during infancy. In a long-term study (4–6 years), no adverse events were observed with in-utero exposure to zidovudine; however, there were occasional episodes of transient and self-limiting anemia [15]. The Women And Infants Transmission Study (WITS) group recently reported small but significant differences in several hematologic parameters in the first 24 months of life between infants exposed and unexposed to perinatal antiretrovirals [16]. There is a need for continuous surveillance of infants exposed *in utero* to combination antiretroviral therapy for emergence of adverse events.

Drug-resistant HIV and its impact on mother-to-child transmission

In a recent study (PACTG P1030), about a quarter of a cohort of recently infected US-born infants were infected with drug-resistant HIV [17••]. Moreover, postnatal treatment of an infant to prevent MTCT may select for drug-resistant HIV acquired from the mother [18]. Resistant virus may be archived in the resting $CD4^+$ T cells of the infants within the first 6 months [17••]. Although not statistically significant, children with drug-resistant virus tended to have a poor treatment outcome. Moreover, poor virologic response to nevirapine-containing HAART regimens in the postpartum period has been observed in HIV-infected women exposed to intrapartum nevirapine [19].

Prevention of mother-to-child transmission successes in resource-limited countries

In resource-limited countries, a number of randomized trials have assessed the efficacy of short-course antiretrovirals (sc-ARVs) to reduce MTCT of HIV (Table 2) [7]. WHO recommends either the use of combination antiretroviral treatment (usually including nevirapine) for pregnant women in need of treatment for their own health or the administration of short-course zidovudine (sc-ZDV) followed by single-dose nevirapine (SDNVP) during labor or a 7-day postpartum short course of zidovudine and lamivudine if antiretroviral treatment is not yet indicated [20]. However, SDNVP administered to the mother at labor and to the infant within 48–72 h of life is the most popular regimen because of the ease of administration and low cost (Table 2).

Increased coverage of antiretroviral to HIV-positive pregnant women

Through the global initiative to scale up antiretroviral access in resource-limited countries, the proportion of HIV-positive pregnant women receiving antiretrovirals increased from 9% in 2004 to 33% in 2007 [1].

Efficacy of short-course antiretroviral regimens to prevent mother-to-child transmission

The efficacy of sc-ARV varies from country to country because of differences in PMTCT coverage, components, and available antiretroviral regimens (Table 2). In a meta-analysis of published clinical trials on PMTCT in Africa, the efficacy of sc-ARV to prevent MTCT was estimated at 50% [21••]. The combined effect estimate of using antiretrovirals was 10.6% (95% CI, 8.6–13.1) transmission at 4–6 weeks as compared with 21% (95% CI, 15.5–27.7) transmission without antiretrovirals [21••]. In a study involving 48 sub-Saharan African countries, about 31 472 infant-HIV infections and deaths were averted because of the use of sc-ARV to prevent MTCT in the years 2004 and 2005 [22•].

The Drug Resource Enhancement against AIDS and Malnutrition program demonstrated that PMTCT outcomes can be improved significantly if programs to protect the unborn child are accompanied by antiretroviral treatment of the mother's infection [23]. Transmission rates were compared between two cohorts of pregnant

women. The first cohort gave supplemental formula to their infants for the first 6 months after delivery, and the second cohort received HAART during the first 6 months while exclusively breast-feeding [24••]. MTCT rates were 4/341 (1.2%) and 7/809 (0.8%) among formula-fed and breast-fed infants at 1 month of age, respectively. Tonwe-Gold *et al.* [25••] evaluated a two-tiered PMTCT strategy in which treatment was selected on the basis of maternal medical status (as indicated by $CD4^+$ T cell count and WHO clinical staging) in pregnant women enrolled in Abidjan, Cote d'Ivoire, in the MTCT-Plus initiative. The first cohort included 107 women who received HAART (combination of zidovudine, lamivudine, and nevirapine) at a median gestational age of 30 weeks and continued treatment postpartum. The second cohort of 143 women was not eligible for HAART, and they received sc-ARV (combination of zidovudine and lamivudine with SDNVP during labor) for PMTCT. The rate of peripartum HIV transmission was 2.2%, the cumulative rate of infant HIV infection at 12 months was 5.7%, and the 12-month HIV-free survival was 88.3%, without significant difference between the two groups.

Thailand's national PMTCT program established in 2000 is the most successful in a resource-limited setting [26]. Plipat *et al.* [27•] assessed the effectiveness of the PMTCT program in Thailand using a registry of children born to HIV-infected mothers from 2001 to 2003 in six provinces. They found a transmission risk of 6.8% (95% CI, 5.2–8.9%) among 761 mother–infant pairs in whom the mothers received zidovudine during pregnancy and labor and the infants received zidovudine after birth. Among the mother–infant pairs who received PMTCT zidovudine combined with other antiretrovirals (usually nevirapine), the transmission risk was 3.9% (CI, 2.2–6.6%) [27•]. These studies and others continue to demonstrate that a comprehensive PMTCT program (including provision of antiretrovirals to mothers for their infection) in resource-limited countries could achieve MTCT rates as low as currently observed in resource-rich countries [24••,25••,27•,28••].

Prevention of mother-to-child transmission challenges in resource-limited countries

The obstacles facing PMTCT programs in resource-limited countries are multifaceted: lack of healthcare infrastructure, slow integration of PMTCT programs to traditional maternal child health (MCH) services, limited manpower, limited donor funding, and competing public health priorities with limited healthcare budget [29•–31•].

Low coverage of antiretroviral treatment and mother-to-child transmission programs

At the end of 2007, 55 of 136 (40.4%) countries had less than 25% coverage of antiretrovirals to adults and children with advanced AIDS [1]. Moreover, 61 of 113 resource-limited countries had less than 25% coverage of antiretrovirals for PMTCT (Table 3) [1]. Some of the reasons for the low coverage of PMTCT in these countries are lack of integration of MCH services with PMTCT [29•], lack of knowledge about HIV and PMTCT [30•], and health system failures leading to missed opportunities, that is, nonavailability of counselors and supplies such as HIV test kits, health staff giving incorrect instruction, and short supply of antiretroviral drugs [31•]. Routine offer of antenatal HIV counseling and testing ('opt-out' approach) and availability of rapid HIV kits in antenatal care and labor ward could improve the coverage and uptake of PMTCT among pregnant women [32•,33•].

Development of drug-resistant HIV to prevention of mother-to-child transmission antiretroviral agents

A 5-year follow-up study of the HIV Network for Prevention 012 Trial to examine the persistence of the mutation at codon 103 of the reverse transcriptase gene from 'lysine' to 'asparagine' (K103N) in women who received SDNVP found that, of the 60 women who harbored the K103N mutation, 16, 43, 55, and 55 women demonstrated fading of the mutation by 2, 3, 4, and 5 years, respectively [34•]. The K103N mutation confers resistance to HIV nonnucleoside analogs. For women who were reexposed to SDNVP for PMTCT, the detection of K103N was independently associated with its detection at 6–8 weeks after the first SDNVP exposure and prenevirapine viral load [35•]. Recent studies suggest that treatment with a nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimen may still be effective in SDNVP-exposed women, provided that treatment is not initiated too soon (<6 months) after SDNVP exposure [36•,37•]. Combination of other antiretrovirals with SDNVP reduces the emergence of NNRTI-associated resistance mutations. The addition of intrapartum and 4–7 days of maternal postpartum zidovudine/lamivudine significantly reduced the prevalence of NNRTI-associated resistant mutations [38•]. Moreover, the addition of a single intrapartum dose of tenofovir/emtricitabine to sc-ZDV and SDNVP significantly reduced the prevalence of NNRTI-associated mutations in mothers at 6 weeks postpartum [39••]. Further studies are needed to determine the optimal time for treatment initiation with NNRTI-based HAART and the effect of NNRTI-associated mutations on subsequent treatment with HAART.

Malaria coinfection and the risk of mother-to-child transmission in resource-limited countries

The risk of MTCT of HIV associated with HSV-2 coinfection or other sexually transmitted infections (e.g., infections resulting in genital ulcers) described above applies also to transmissions in resource-limited settings. Moreover, in some resource-limited countries,

Table 3 Percentage coverage of antiretroviral for prevention of mother-to-child transmission in resource-limited countries, 2007

Coverage by quartiles	$n = 113$	Countries		
Less than 25% coverage	61	Afghanistan	Equatorial Guinea	Mexico
		Algeria	Eritrea	Mongolia
		Angola	Gabon	Morocco
		Azerbaijan	Ghana	Nepal
		Bolivia	Guatemala	Niger
		Bosnia and Herzegovina	Guinea	Nigeria
		Burkina Faso	Guinea-Bissau	Pakistan
		Burundi	Haiti	Panama
		Cameroon	Hungary	Papua New Guinea
		Chad	India	Philippines
		China	Indonesia	Senegal
		Colombia	Islamic republic of Iran	Serbia
		Comoros	Kyrgyzstan	Sierra Leone
		Republic of the Congo	Lao People's Democratic Republic	Somalia
		Costa Rica	Liberia	Sri Lanka
		Cote d'Ivoire	Madagascar	Tajikistan
		Democratic Republic of the Congo	Malaysia	Togo
		Djibouti	Mali	Tunisia
		Egypt	Mauritania	Venezuela
		El Salvador	Mauritius	Vietnam
25– 40% coverage	27	Armenia	Honduras	Romania
		Belize	Lesotho	Singapore
		Benin	Malawi	Suriname
		Cambodia	Mozambique	Uganda
		Central African Republic	Myanmar	United Republic of Tanzania
		Chile	Nicaragua	Uruguay
		Dominican Republic	Paraguay	Uzbekistan
		Gambia	Peru	Zambia
		Guyana	Poland	Zimbabwe
50– 75% coverage	14	Brazil	Kenya	South Africa
		Ecuador	Latvia	Swaziland
		Fiji	Lithuania	Trinidad and Tobago
		Jamaica	Namibia	Ukraine
		Kazakhstan	Rwanda	
More than 75% coverage	11	Argentina	Botswana	Moldova
		Bahamas	Cuba	Russian Federation
		Barbados	Czech Republic	Thailand
		Belarus	Georgia	

Adapted and modified from Fig. 29a of [1].

there are endemic infectious diseases that may have an impact on MTCT of HIV. There are conflicting reports on the effect of malaria during pregnancy on MTCT. A recent study found that placental malaria was associated with increased MTCT, even at low maternal viral loads [40••]. The authors suggested that prevention of malaria during pregnancy in malaria-endemic areas should be part of PMTCT programs. Further research is needed to characterize the association between malaria and MTCT.

Feeding practices and mother-to-child transmission

The WHO recommends exclusive breast-feeding in settings where replacement feeding is not acceptable, feasible, affordable, sustainable, and safe [20]. Breast-feeding is known to offer protection against diarrheal and respiratory diseases that contribute to the high rates of infant mortality in resource-limited countries. To balance the protective effect of breast-feeding with the potential risk of transmission of HIV, there have been several studies on the optimum duration of breast-feeding. In a mathematical model based on data from Uganda and Kenya, researchers found that reducing exclusive breast-feeding delayed the time to death rather than reducing it altogether; breast-feeding reduced mortality at very young ages; however, infants who got infected progressed rapidly to AIDS, with most dying by 2 years of age [41•]. Lehman *et al.* [42••] found that sc-ARVs used in PMTCT reduced the cell-free virus in the breast milk to a greater extent than the cell-associated virus in breast milk. These and other ongoing studies will have an impact on future recommendations on appropriate feeding practices in resource-limited settings to prevent MTCT.

Lack of PCR-based diagnosis for pediatric HIV

In most resource-limited countries, PCR-based assays are not available for the early diagnosis of pediatric HIV. The high mortality rate of pediatric HIV in resource-limited countries is partly due to the lack of early diagnosis and low coverage of pediatric HAART treatment. There is an urgent need to integrate low-cost and accessible viral nucleic acid-based assays [43•,44•].

Conclusion

Much progress has been made in the PMTCT; however, challenges that threaten to reverse the gains remain. Resource-rich countries should be unrelenting in their efforts to provide access to HIV testing to all women and PMTCT to HIV-infected pregnant women. Furthermore, access to comprehensive PMTCT, including antiretroviral treatment for HIV-infected women and children, should be paramount in resource-limited countries.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 176).

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