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Elimination of perinatal HIV infection in the United States and other high-income countries: achievements and challenges

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Abstract

Purpose of review—To describe progress and challenges to elimination of mother-to-child HIV transmission (EMCT) in high-income countries.

Recent findings—Despite ongoing declines in the number of perinatally HIV-infected infants in most high-income countries, the number of HIV-infected women delivering may be increasing, accompanied by apparent changes in this population, including higher percentages with antiretroviral “pre-treatment” (with possible antiretroviral resistance), other co-infections, mental health diagnoses, and recent immigration. The impact of antiretroviral resistance on mother-to-child transmission is yet to be defined. A substantial minority of infant HIV acquisitions occur in the context of maternal acute HIV infection during pregnancy. Some infant infections occur after pregnancy, e.g., by premastication of food, or breastfeeding (perhaps by an uninfected woman who acquires HIV while breastfeeding).

Summary—The issues of EMCT are largely those of providing proper care for HIV-infected women. Use of combination antiretroviral therapy by increasing proportions of the infected population may function as a structural intervention important to achieving this goal. Providers and public health systems need to be alert for HIV-serodiscordant couples in which the woman is uninfected and for changes in the population of HIV-infected pregnant women. Accurate data about HIV-exposed pregnancies is vital to monitor progress toward EMCT.

Keywords

Human immunodeficiency virus; mother to child transmission; perinatal; elimination; prevention

Elimination of mother-to-child HIV transmission (EMCT) has been adopted as a goal in high-income countries such as the United States (US) [1] and the countries of Europe [2], and also in less-resourced countries [3] with much higher incidences of mother-to-child transmission (MTCT) of HIV. In the US, the achievements of the past two decades leading to this goal are the result of the following: 1) early and ongoing clinical research, 2)

proactive public health policies and recommendations, 3) dedicated funding for clinical care (including laboratory monitoring, antiretrovirals [ARV] for prophylaxis and treatment, and alterations in obstetric practice), 4) case management services through Medicaid and the federal Ryan White Program and, 5) federal and state public health support for surveillance for MTCT, HIV testing, and public education. Ongoing cases of MTCT continue, however, and will challenge clinicians and public health professionals to adapt as the population of HIV-infected pregnant women changes. If at one time the emphasis was on young women with untreated HIV infection diagnosed during pregnancy, the contemporary population also includes substantial numbers of older women who may have knowledge of their HIV status, experience with ARV's, viral strains resistant to antiretroviral therapy (ART), viral co-infections, or recently immigrated. After an epidemic of more than 30 years, after nearly 20 years of effective prevention of MTCT (PMTCT) and treatment of HIV, this paper describes changes in the population of pregnant HIV-infected women (Table 1) in the US and other high-income countries, as well as challenges (Table 2) for the health-care and public health systems which will affect EMCT in the years to come.

Numbers of cases

HIV-infected infants

The United States and nearly all western European countries report very low annual numbers of perinatally infected infants and children [4-8]. The numbers of infected children in the World Health Organization's European region, however, increased from 347 to 494 between 2004 and 2011, largely because of the number of infections in its eastern and central sub-regions [9].

Among HIV-infected children in the US and Europe, birth in lesser-resourced countries, most often sub-Saharan Africa, is becoming more frequent. During 2007-2010, foreign-birth was reported for 33% (295/884) of HIV-infected children diagnosed with HIV in the US [10], and an even greater proportion of foreign birth was reported for infected children in France and in the United Kingdom (UK), at 60% and 73%, respectively [6, 11].

HIV-infected pregnant women

In several resource-rich countries, an increase in the number of HIV-infected pregnant women delivering annually has been reported in the last decade [5, 12-14]. Repeat pregnancies among HIV-infected women are increasing in European countries [15-17]. The live-birth rate of HIV-infected women in the US increased 150% from the era before highly active antiretroviral therapy (HAART) (pre-HAART era, 1994-1995) to the HAART era (2001-2002) [18], while, on the other hand, pregnancy rates between 1994 and 2009 in HIV-infected women were approximately half those in HIV-uninfected women in the US [19, 20].

Characteristics of the population of HIV-infected pregnant women

Injection drug use among HIV-infected pregnant women appears to be declining, from 11% during 2000-2003 to 8% during 2005-2008 in U.S. Enhanced Perinatal Surveillance (EPS); use of any illicit drugs declined from 20% to 11% in the same periods [21, 22]. Another US

study, the Surveillance Monitoring of ART Toxicities (SMARTT) cohort reported ‘hard drug use’ by 3% of women in 2007-2010 [23], while also reporting positive behavioral screens for mental disorder (mainly post-traumatic stress disorder) or substance abuse in 35% compared to 26% in the general population [24].

Immigrants from lesser-resourced countries account for an increasing proportion of HIV-exposed deliveries, including 78.5% of infected women delivering in the UK during 2000-2009 [15] and 60% in Canada during 2007-2009 [25]. Among mothers of HIV-infected infants reported to US National HIV Surveillance during 2003-2007, 21% were born in countries other than the US [26]. The annual percentage of HIV-infected pregnant women born in Africa and delivering was 24-78% in several western European countries during the past decade [7, 12, 27, 28]. Immigrant women were at some risk of less frequent uptake of PMTCT interventions, specifically, accessing prenatal care and ARV initiation [27, 29].

An estimated 140,000 HIV-serodiscordant heterosexual couples reside in the US [30], but whether that number or its proportion of HIV-infected persons is changing is unknown. It is known that many HIV-infected women have HIV-uninfected partners. Of 181 HIV-infected US women of childbearing age, 62% had negative partners and 11% had partners of unknown status [31]. In France, among HIV-infected individuals, 41.5% of men and 43.6% of women had partners of unknown or negative status [32]. The patterns of serodiscordance offer different opportunities for prevention of HIV MCT, which become more relevant as the population's desire to conceive and bear children increases. One US study of 181 women of childbearing age reported that 59% desired children, of whom 66% intend to have children [31]. Studies from Canada and the UK have reported similar findings [33, 34]. Of HIV-infected persons in France, 20% of men and 33% of women expected to have children [32]. Finally, a study of perinatally infected females of childbearing age found that 70% intended to have children [35]. Safer conception for HIV-discordant couples is being made possible through the use of assisted reproductive technology [30, 36]—e.g., artificial insemination of an HIV positive woman, or so-called ‘sperm washing’, with intrauterine insemination or *in vitro* fertilization—and antiretrovirals for pre-exposure prophylaxis [37] or treatment as prevention [38]. It remains to be seen whether these approaches will lead to an increase in the annual number of HIV-exposed infants.

Perinatal Prevention Cascade—uptake of elements

In the US, MTCT has been organized around the perinatal HIV prevention cascade (see Figure), which begins with primary prevention of HIV infection and preconception care of women known to be infected prior to pregnancy a percentage which appears to be increasing [21, 22]. While more women may thus have opportunity to maximize their HIV care and plans for pregnancy, there is a paucity of data about how many HIV-infected women acquire such preconception care. One US study (2008-2010) reported that 50.6% of sexually active HIV-infected women had spoken with a provider within the past year about contraception plans [39]. At least one unplanned pregnancy after learning her HIV diagnosis was reported by 88% in a study of US women [40]. Maternal diagnosis was established before pregnancy in 60% and 68% of cases during 2000-2003 and 2005-2008, respectively [21, 22]. In Italy,

32.9% of HIV-infected pregnant women's diagnoses were made during pregnancy in 2008, a figure unchanged over the preceding decade [28]. In the US, once a diagnosis is made prenatal care was received by a large percentage (88% in 2000-2003 and 90% in 2005-2008) [21, 22]. In those periods, use of prenatal, natal (labor and delivery) and post-natal ARV use increased [21, 22]. In SMARTT during 2007-2011, effective combination antiretroviral therapy (cART) use was reported by 85% of women in the 'dynamic' cohort [23]. Similar high rates of cART use have been seen in several European countries [7, 28, 41], where its use is frequently reported at the time of conception [16, 41]. Though ARV resistance has been recognized in maternal and infant viral strains, it is not clear that the proportion of affected individuals has changed, nor is the effect on MCT clear [42]. Adherence to ARV's during pregnancy often exceeds that in the post-partum period [43, 44]. Uptake of PMTCT interventions and viral load suppression—but not MCT rate—are highly associated with a woman's disclosure of her diagnosis to her partner [45].

Maternal viral suppression appears to be increasingly common in recent years. In SMARTT, only 15% in the 'dynamic' cohort had VL > 1000 copies/ml [23]. In several European cohorts, viral RNA was frequently undetectable at the time of delivery: 65% in the European Collaborative Study [46]; 65% in the French Perinatal Cohort [17]; 80.9% in Italy [28]; and 77% in London [47].

Mode of delivery of infants to HIV-infected women in the US was by elective Cesarean-section in 36% during 2000-2003 [21] and 40% during 2005-2008 [22]. While the Cesarean-section rate has been higher in Europe [28, 46], the rates have declined in UK/Ireland, from a peak of 66.4% in 1999 to 50% in 2006 [12]. Similarly, in Spain the elective Cesarean delivery rate was 57.6% in 2000-3 and 46.5% in 2004-7 [7].

“Other” opportunities for HIV MCT—There are several opportunities for MTCT which don't fit neatly into, or whose issues transcend, the list of prevention interventions—and their converse, missed opportunities—in the perinatal prevention cascade. Women with acute HIV-infection—that is, women who seroconvert to HIV-positive status—during pregnancy or breastfeeding are more likely to transmit HIV to their infants, mainly because of higher HIV VL's which occur, albeit transiently, during acute HIV infections. Such infections are typically the result of partnerships of an HIV-infected man and HIV-uninfected woman. That number is not precisely known, but it is vital that individuals be alerted to the additional risk attendant to such partnerships. The proportion of perinatal HIV transmissions which occur under these conditions in recent years is 8% in the U.S. among cases reported to EPS during 2005-2010 [48], 11.5% in the UK audit of transmissions which occurred during 2002-2005 [49], and 14% in cases reported to New York State during 2002-2006 [50]. As overall MCT rates decline among women with established HIV diagnoses, it is possible that those with acute infection may comprise an increasing proportion of MCT. It has been suggested that the rate of acute infection in adolescent females may be high because of the high HIV incidence among adolescent males [51], some of whom have sex with both males and females. Among HIV-infected females of reproductive age is an increasing number who acquired infection perinatally [52]. Though these women may deliver prematurely or require Cesarean delivery more frequently, they appear to transmit HIV to their infants at a rate similar to other HIV-infected women [52].

Finally, there are the so-called “late” perinatal transmissions, which may result from infants ingesting “pre-masticated” food, from being breastfed by an HIV-infected woman, or from behaviors which are difficult to characterize; some of these infants, though born to HIV-infected women, have repeatedly negative nucleic acid amplification tests (NAAT) before they have a NAAT result which establishes their diagnosis [53].

Challenges for EMCT

The annual number of HIV-infected infants born in the US and most other high-income countries is decreasing. Though the numbers of deliveries by HIV-infected pregnant women appears to be increasing, at least in the US, this trend is not the result of increasing incidence among women, as HIV incidence is actually decreasing [54]. The increased number of deliveries appears to be the result of improved survival and overall well-being, accompanied by increasing desire to conceive and increasing numbers of women with ‘repeat’ pregnancies. Whether the number of HIV-exposed pregnancies will further increase as the availability of assisted reproductive technologies increases—and how such technologies will change PMTCT—remains to be seen. The evident connection between survival and ART means that increasing numbers of women will be ART-experienced when they conceive. It can be anticipated that recent ART guidelines, which recommend treatment for all HIV-infected persons [55], when implemented, will constitute an important structural intervention for EMCT, leading to an increasing proportion with viral suppression among women of childbearing age. This experience leads not only to increased prenatal ARV exposure, but also the possibility of an increasing prevalence of ARV-resistant HIV, which in turn could result in more women being on second- and third-line regimens whose effectiveness may differ. So far, MTCT does not appear to be substantially affected by ARV-resistance [42]. Additional antiviral exposure—as well as additional maternal morbidity—in this population may occur as a result of maternal co-infection with other viruses, notably hepatitis B and hepatitis C viruses. Though immigrant HIV-infected women of childbearing age comprise an increasing percentage in many resource-rich countries, their PMTCT problems relate more to health care access and utilization (e.g., timely diagnosis, linkage to and retention in primary and prenatal care) than to biomedical issues (e.g., resistant virus, adherence).

In the US, most of the ongoing mother-to-child transmissions are apparently attributable to incomplete uptake of elements of the Perinatal Prevention Cascade, e.g., identification of HIV-infected women and effective retention of them in care [56]. It is likely that many of such transmissions are from women who are extremely difficult to reach, for reasons in addition to illicit drug abuse, reasons which include the substantial degree of poverty [57] and mental health problems in the population. The expansion in medical care access in the U.S. anticipated from the Affordable Care Act may mitigate some of poverty's effects, but it can be predicted that the social instability and segregation associated with poverty will continue to aggravate problems of access. Indeed, in this era of low MCT rates, as each transmission's specific characteristics take on heightened importance, it remains important to review cases, with the goal of changing the local system in ways that may prevent further transmissions and improve the care of HIV-infected women to optimize their health prior to—and between—pregnancies, as well as to prevent unwanted pregnancies. The Framework

for EMCT [1] incorporates Case Review and Community Action as one of its key components, as the Fetal-Infant Mortality Review—HIV (FIMR-HIV) Prevention Program. The US Centers for Disease Control and Prevention includes FIMR-HIV among activities encouraged by its prevention grantees. These reviews have identified issues of domestic violence and maternal mental health diagnoses [58]. FIMR-HIV has also recognized the dramatic effect on women—including depression and decreased linkage to care and medication adherence—when they lose custody of children after birth.

Conclusion

It will remain a challenge for public health institutions to commit new funds to PMTCT as the numbers of perinatal cases decline in contrast to the number of adult cases and when comparing resource-rich to resource-poor settings. Actionable data on the number of HIV-infected women delivering, and on the kind of care they receive, is essential for public health authorities to monitor EMCT adequately. Support for this can come from state laws and policies which advocate “opt-out” HIV testing and encourage perinatal HIV exposure reporting. Medical care providers must be made aware of changes in these policies. Vital to all of these considerations, however, is the recognition that “elimination” of mother-to-child transmission is not a single event, but, rather, is an ongoing process. That process necessarily must address the needs of successive annual waves of HIV-infected pregnant women as long as there are new cases of HIV in women, underscoring the importance of primary prevention and appropriate HIV care for women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Perinatal HIV Prevention Cascade

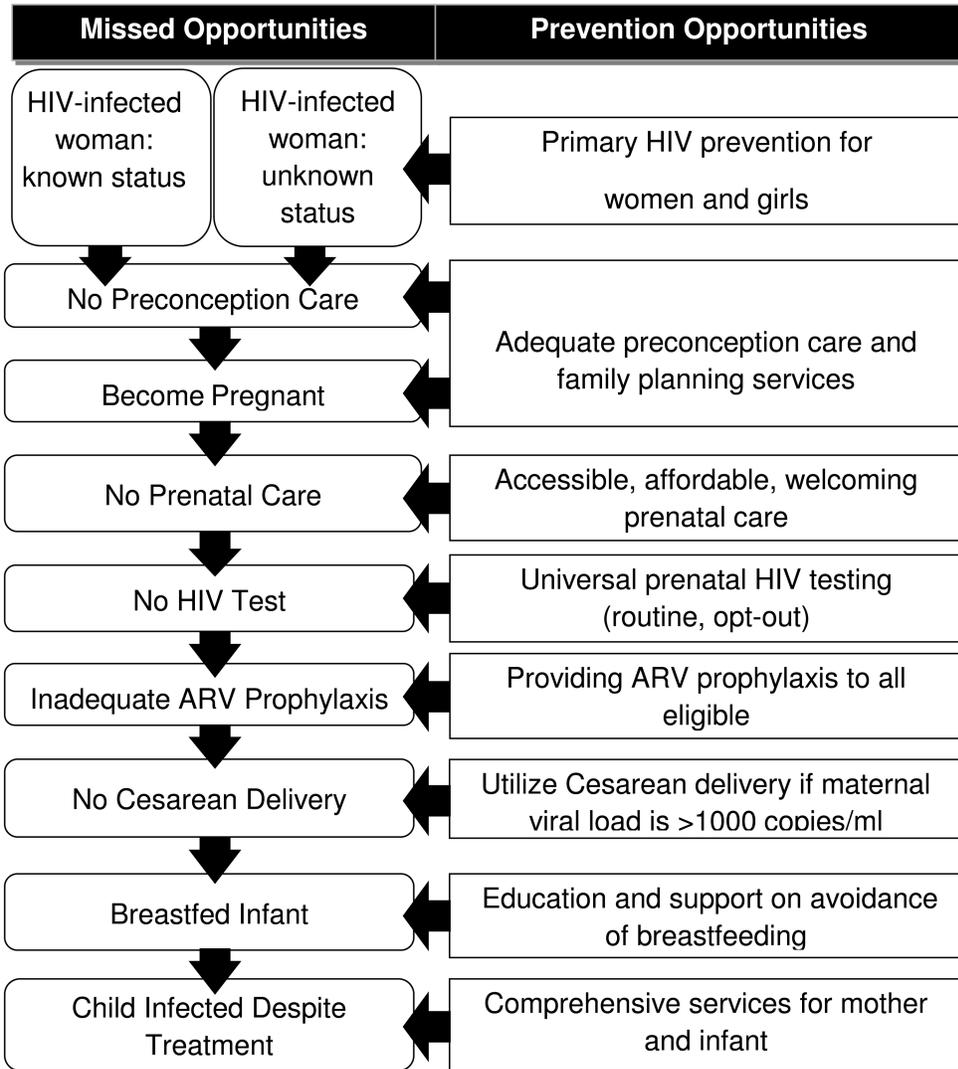


Figure. Perinatal HIV Prevention Cascade

Table 1
Perinatal HIV infections in resource-rich countries: numbers, maternal and infant characteristics, and preventive interventions

Characteristics and countries	Study period	Estimates
Numbers of Cases		
Perinatal Infections		
MCT Rates		
USA [21, 22]	2000-2003	3.7%
	2005-2008	2.2%
Spain [7]	2000-2003	1.4%
	2004-2007	1.8%
Numbers per year		
USA [4, 8]	2009	151
	2010	164
Europe [9]	2004	347
	2011	494
Incidence per million		
UK [5]	-	10
France [6]	2003-2006	9
HIV-infected women delivering		
USA [14]	2006	8700
USA (number/1000 person years) [18]	1994-1995	57/1000 PY
	2001-2002	142/1000 PY
UK/Ireland [5, 13]	2006-2010	>1300/yr
	2000-2001	3.4%
	2008-2009	4.5%
Foreign birth (%) among:		
Infected children		
USA [10]	2007-2010	33%
France [6]	2006	69%
UK [11]	2011	73%
HIV-infected mothers of infected children		
USA [26]	2003-2007	21%
HIV-infected women delivering		
Canada [25]	2007-2009	60%
UK/Ireland [12, 15]	1990-1993	43.5%
	2004-2006	78.6%
	2000-2009	78.5%
France [27]	1984-1986	12%
	2003-2004	64%

Characteristics and countries	Study period	Estimates
Italy [28]	2002	23.9%
	2008	45.2%
Spain [7]	2000-2003	11.4%
	2004-2007	22.1%
Characteristics of HIV-Infected women		
Repeat Pregnancies		
UK/Ireland [15]	1997	20.3%
	2009	38.6%
Europe [16]	1989	2%
	2003-2004	14%
France [17]	2009	30%
	Use of cART/HAART at time of conception	
UK [41]	2000-2006	24%
Adherence during pregnancy and postpartum [43]		
USA (pregnancy)	2001-2005	61%
USA (post-partum)	2001-2005	44%
Injection Drug Use		
USA [21, 22]	2000-2003	11%
	2005-2008	8%
Illicit drug use		
USA [21, 22]	2000-2003	20%
	2005-2008	11%
Hard drug use		
USA [23]	2007-2010	3%
Positive mental health screen & drug use		
USA [24]	2007-2010	35%
Acute HIV infection during pregnancy or breastfeeding		
USA [48]	2005-2010	8%
USA (NYS) [50]	2002-2005	14%
UK [49]	2002-2005	11.5%
Co-infection w/hepatitis B		
Puerto Rico [59]	1989-1990	12.5%
USA (Dallas) [60]	1993-2003	1.5%
Europe [61]	1999-2005	4.9%
Netherlands [62]	1997-2008	4.9%
Italy [28]	2000-2008	4%
UK (London) [47]	2000-2009	4%
USA (hepatitis B or C) [63]	2006-2010	29%
Co-infection w/hepatitis C		

Characteristics and countries	Study period	Estimates
Puerto Rico [59]	1989-1990	12.5%
USA [64]	1989-1995	29%
Italy [28]	2002	29.2%
USA (Dallas) [60]	1993-2003	4.9%
Europe [61]	1999-2005	12.3%
Netherlands [62]	1997-2008	2.1%
Italy [28]	2008	17.3%
UK (London) [47]	2000-2009	1.6%
USA (hepatitis B or C) [63]	2006-2010	29%
Negative male partner		
USA (n=181) [31]	-	62%
France (n=555) [32]	-	43.6%
Desire/Intention to have children		
USA (n=181) [31]		
Desire	-	59%
Intend	-	66%
USA (n=50) [35]		
Intend	2003-2004	70%
Canada (n=490) [34]		
Desire	2007-2009	69%
Intend	2007-2009	56%
UK (n=450) [33]		
Desire	2003-2004	75%
France (n=555) [32]		
Expect	-	33%
Perinatal Prevention Cascade		
Discussed contraception with provider		
USA [39]	2008-2010	50.6%
Unplanned pregnancy after diagnosis		
USA [40]	2007-2009	88%
Diagnosed before pregnancy		
USA [21, 22]	2000-2003	60%
	2005-2008	68%
Established HIV dx during pregnancy		
Italy [28]	2008	32.9%
Use of cART in pregnancy		
USA [23]	2007-2011	85%
Spain [7]	2004-2007	99.4%
Italy [28]	2007-2008	95.5%

Characteristics and countries	Study period	Estimates
UK/Ireland [41]	2000-2006	82.1%
Maternal viral suppression (undetectable)		
USA (VL >1000c/ml) [23]	-	15%
Europe [46]	2000-2010	65%
Europe (ARV naïve) [65]	1997-2004	73%
France [17]	2005-2008	65%
Italy [28]	2000	37.3%
	2008	80.9%
London [47]	2000-2009	77%
Pregnant women with VL<50		
After 3 months of tx [66]	-	61.5%
After 6 months of tx	-	67.9%
Mode of delivery: Cesarean		
USA [21, 22]	2000-2003	36%
	2005-2008	40%
Europe [46]	2000-2010	58%
Italy [28]	2008	63.2%
UK/Ireland [12]	1997	38.3%
	1999	66.4%
	2006	50%
Spain [7]	2000-2003	57.6%
	2004-2007	46.5%

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Table 2
Challenges and Opportunities

Antiretrovirals:	
"Pre-treatment"	
Resistant HIV	
Prenatal exposure increasing	
HIV-infected pregnant women:	
Age	
Numbers of pregnancies increasing	
Acute HIV infection	
Substance abuse	
Mental health	
Viral co-infections	
Morbidity, additional drug exposure	
Immigration	
Poverty/housing instability	
HIV-discordant couples with seronegative women	
Contraception and family planning services, consistent access	
Health-care system:	
Affordable Care Act	
Ryan White Care Program	
Local systems failures in consistently providing the full cascade of interventions	
Public Health system:	
Financial support for programs	
Data	
Testing laws, state	

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