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Host factors that influence mother-to-child transmission of HIV-1: genetics, coinfections, behavior and nutrition

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Abstract

Mother-to-child transmission (MTCT) is the most important mode of HIV-1 acquisition among infants and children and it can occur *in utero*, intrapartum and postnatally through breastfeeding. Great progress has been made in preventing MTCT through use of antiretroviral regimens during gestation, labor/delivery and breastfeeding. The mechanisms of MTCT, however, are multifactorial and remain incompletely understood. This review focuses on select host factors affecting MTCT, in particular genetic factors, coexisting infections, behavioral factors and nutrition. Whereas much emphasis has been placed on decreasing maternal HIV-1 viral load, an important determinant of MTCT, through use of antiretroviral agents, complementary focus on overall maternal health is often neglected. By addressing coinfections in mothers and infants, improving the mother's nutritional status and modifying risky behaviors and practices, not only is maternal and child health improved, but a direct benefit in reducing MTCT can be derived. The study of genetic variations in susceptibility to HIV-1 infection is rapidly evolving, and the future is likely to bring revolutionary changes in HIV-1 prevention by enhancing natural resistance to infection and by individually tailoring pharmacologic regimens.

Mother-to-child transmission of HIV-1 (MTCT) has been dramatically reduced, particularly in resource-rich settings, with comprehensive testing strategies during pregnancy; the use of anti-retroviral (ARV) drugs during pregnancy, intra-partum, and postnatally to the infant; elective cesarean delivery when HIV-1 viral load remains detectable near the end of pregnancy; and avoidance of breastfeeding [1]. Progress is being made in resource-limited settings as well, with extensive rollout of prenatal ARV programs and ARV prophylaxis during breastfeeding [1]. MTCT is multifactorial, with both virus and host factors playing a role (Box 1). In this review we will focus on host (maternal or infant) factors affecting risk of MTCT. Specifically, we will review how the following factors influence MTCT: host

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genetic factors, maternal or infant coinfections, behavior and nutrition. We will not discuss viral factors; these factors, such as viral phenotype and the amount of circulating or compartmentalized (i.e., in the mother's genital tract or breast milk) virus are important and reviewed elsewhere. We will also not discuss obstetric factors or the role of HIV-1-specific immunity (innate or adaptive) in mothers or infants. The latter comprises an important group of host factors affecting susceptibility to infection, which overlaps with genetics, and to that extent, it is addressed below. For a more comprehensive discussion of immune factors in the mother (blood, genital tract, breast milk) and the infant (peripheral blood, mucosal membranes) the reader is referred to other reviews [1].

Box 1

Selected host factors influencing mother-to-child transmission of HIV-1: genetic, coinfection, behavioral and nutritional

Genetic factors

- Fetal gender and HLA type
- Maternal–fetal HLA concordance
- SNPs for chemokines/chemokine receptors/innate immune factors

Maternal or infant coinfections

- Chorioamnionitis
- STIs: genital ulcer disease including HSV2 and syphilis
- Malaria
- TB
- Mastitis/breast abscess
- Oral candidiasis in the infant

Behavioral factors

- Illicit drug use during pregnancy
- Frequency of sexual intercourse during pregnancy
- Number of sex partners during pregnancy
- Infant feeding practices: breastfeeding, mixed feeding, food premastication

Maternal nutritional status

- Advanced maternal disease with immunosuppression and malnutrition
- Vitamin A deficiency
- Other micronutrient deficiencies

STI: Sexually transmitted infection.

Genetic factors affecting risk of MTCT of HIV-1

Most infants born to HIV-1-infected mothers escape HIV-1 infection, even in the absence of any intervention, strongly suggesting innate resistance to the virus. Such innate resistance may be determined to a large extent by the genetics of the host and can have effects at several levels and through different mechanisms, from antiviral activity of innate immune factors to inhibition of viral cell binding and entry. We will summarize the evidence that is available to date that links genetic variations with MTCT risk (TaBle 1).

Because HIV-1 predominantly uses CD4 and a coreceptor for cell entry, several genetic polymorphisms in the coding and regulatory regions of these receptors and their natural ligands influence the risk of infection. HIV-1 initially interacts, via its gp120 protein, with the cellular CD4 receptor, and a SNP in the *CD4* gene at position C868T was recently associated with a twofold increase in the rate of MTCT among infant heterozygotes compared with wild-type infants [2]. It was hypothesized that this SNP may sufficiently alter the tertiary structure of the CD4 receptor to allow HIV-1 to interact more efficiently with it or the coreceptors. Most transmitting maternal viruses use the CC chemokine receptor 5 (CCR5) as a coreceptor [3,4], and a 32-bp deletion in the coding region of the *CCR5* gene (*CCR5*-Δ32) in the homozygous state renders the coreceptor nonfunctional and provides seemingly complete protection from HIV-1 infection among infant carriers [5,6]. *CCR5*-Δ32 heterozygosity seems to confer no protection from MTCT when carried by the infant [3,6–13], but exerts a protective effect if carried by the mother, secondary to lower maternal R5 viral burden [4]. Polymorphisms in the promoter region of *CCR5* can upregulate or downregulate expression of a functioning CCR5 coreceptor on infant target cells, and SNPs in the promoter region have been associated with MTCT of HIV. A SNP at position 59029 (G→A) in the *CCR5* promoter region is associated with higher expression of CCR5, and when carried by infants has been associated with increased risk of MTCT [14–16]. In one study, the increased risk with *CCR5*-59029-A was independent of maternal CD4 count but was moderated by exposure to ARVs, whereas another study noted the protective association with the alternate 59029-G genotype among children of mothers with low maternal viral loads but not among those with high viral loads. There appears to be no association between maternal *CCR5*-59029G/A and MTCT [17,18]. *CCR5*-59029G/A is in linkage disequilibrium with *CCR5*-59353T/C, and the associations for each polymorphism with risk of MTCT are similar [15,16]. Another *CCR5* promoter variant, *CCR5*-59356C/T, has been associated with both increased and decreased risk of MTCT among infant carriers [15,19]. Other chemokine receptor polymorphisms in minor HIV coreceptors, including CX_3CR1 and CCR2, have been evaluated with less conclusive findings [13,15,18,20]. The *CX_3CR1*-745A allele induces expression of a mutant CX_3CR1 protein with impaired ligand binding and has been associated with a higher rate of early transmission among ARV-exposed, but not ARV-naive, infants [15]. The authors suggest that CX_3CR1 may confer effects via its role as a chemokine modulator of the immune system and that there may be a threshold level of maternal viral load below which the immunologic benefit of CX_3CR1 is important. The *CCR2*-180A/A genetic variant in the CCR2 coreceptor, which results in a valine to isoleucine amino acid change at position 64 (*CCR2*-64I), has been associated with protection from MTCT among Argentinian children, with increased risk of transmission

among children in sub-Saharan African, and with no impact on MTCT among HIV-exposed children in France and western Kenya [13,15,20,21]. Maternal carriers of the *CCR2*-64I polymorphism may confer reduced risk of MTCT to their infants secondary to the lower maternal HIV viral load associated with *CCR2*-64I [22,23]. Such conflicting findings for the role of chemokine receptors in MTCT may be due to differences in geographic allele frequencies, mediation of an effect by use of ARV prophylaxis, linkage disequilibrium with untyped polymorphisms, or the fact that that certain chemokine receptor polymorphisms confer only a modest effect in a complex transmission mechanism.

Polymorphisms in the genes coding for other natural ligands for HIV-1 coreceptors may alter susceptibility to MTCT. CCL3 (or macrophage inflammatory protein [MIP]-1) is a chemokine ligand for the CCR5 receptor and is encoded by two functional genes: *CCL3* and *CCL3L1*. Reduced *CCL3* and *CCL3L1* gene copy numbers in infants are associated with decreased chemokine expression and increased MTCT risk [24]. SDF-1 is the natural ligand for the CXCR4 coreceptor used by later-stage, syncytium- inducing viruses. A mutation at position 881 of the 3′-untranslated region of the *SDF-1* gene (*SDF-1* 3′A) in heterozygous mothers has been associated with increased perinatal transmission in one study from Kenya, yet another study found no association, and three studies found no effect of *SDF-1* 3′A in infant carriers [13,15,18,25].

There are other host genetic variations that may be associated with modulated risk of MTCT of HIV, including those in areas affecting innate immunity. Defensins are important innate antimicrobial peptides that may play a role in protection from HIV-1 infection. β-defensins are expressed primarily by epithelial cells and confer antiviral protection at critical mucosal sites via direct interaction with viral envelopes and target cells. Two SNPs in the 5′ untranslated region of the *DEFB1* gene affect expression and have been associated with MTCT of HIV: −52G/A and −44C/G. An association with reduced MTCT among children carrying the −52G/G genotype, and conversely an association for increased MTCT with −52G/A, have been reported in two respective studies [26,27]. In one of these studies, the −52G/G genotype, when present in the mother, was also predictive of lower risk of transmission and was associated with lower maternal viral load [26]. A third study found no significant association between MTCT and −52G/A, however it found that the −44C/C genotype significantly increased susceptibility to HIV among infant carriers [28]. In the study by Ricci *et al.*, -44C/C was the most frequent genotype among mothers with high viral load, and an alternate -44G/G genotype, when carried by the mother or infant, was significantly associated with lower MTCT risk, although it did not remain statistically significant after multiple test correction [26]. Expression of the defensin gene correlates with the number of gene copies present in the genome, and the copy number of the β-defensin gene, *DEFB104*, was found to be significantly lower among Brazilian HIV-positive children compared with HIV-exposed uninfected children, suggesting a potential protective role of *DEFB104* against MTCT [29].

Initial HIV-1 infection of infant $CD4^+$ cells may be mediated by dendritic cells (DCs) that exist in the intestinal mucosa and placenta, and express C-type lectin receptors that recognize pathogens and coordinate cell adhesion to trigger immune responses or transinfection. Two such DC receptors have shown strong affinity for HIV-1: DC-SIGN and

DC-SIGNR. DC-SIGN is also expressed on placental macrophages, and DC-SIGNR is also expressed on capillary endothelial cells of the placenta. Two variants in the *DC-SIGN* promoter gene (p-336C and p-201A) and four polymorphisms in exon 4 of the coding region (R198Q, E214D, R221Q, and L242V) have been associated with *in utero*, intrapartum, and postpartum MTCT [30]. Similarly, two SNPs in the coding region of *DC-SIGNR* at H1 and H3 have been associated with increased infant HIV-1 infection *in utero* and intrapartum [31].

DC maturation relies on the activation of transduction pathways triggered by pathogen-bound Toll-like receptors (TLR), type 1 transmembrane proteins differentially expressed among immune cells. Recently, specific variants in the *TLR9* gene (haplotypes A/A and G/G of the c.4-44G/A and c.1635A/G alleles), which may affect TLR9 expression or its functional ability to elicit a defense mechanism, have been associated with increased risk of MTCT of HIV [32]. MBP is a serum lectin that plays a role in natural immunity by aiding phagocytosis and activation of the complement pathway. MBP is encoded by the *MBL2* gene, and a SNP in the promoter region (−550G) is associated with high serum levels of MBP; the −550G SNP was observed more frequently in HIV-1-exposed, uninfected children compared with HIV-1-infected children. HIV-1-infected children who were classified as rapid disease progressors were more frequently homozygous carriers of the SNP [33]. This study also shows that a deletion of six bases at position −328 of the *MBL2* gene was associated with increased risk of infection [33]. Further studies are needed to confirm these associations and their role in modulating MTCT risk.

The ability of the infant immune system to recognize maternal, HIV-1-infected cells or free virions relies on the recognition of non-host HLA molecules embedded in the cellular membrane of infected maternal cells or the viral envelope of free virions. *HLA* class I and II are the most polymorphic human genes, allowing presentation of a diverse repertoire of endogenous and exogenous peptides to $CD8^+$ and $CD4^+$ T cells, respectively, for immune recognition and response. Infants share at least half of their *HLA* genes with the mother. Infants who share more *HLA* alleles with their mother have potential for decreased alloimmune responses against HLA alloantigens expressed on maternally infected cells or the virus envelope. As such, mother–child concordance at class I A, B, C or G loci has been associated with increased MTCT of HIV-1, whereas HLA discordance has been associated with decreased risk [34–37]. Furthermore, the risk of transmission appears to be higher when the mother is homozygous for a *HLA* class I allele, independently of the number of shared alleles and maternal viral load [36]. Specific *HLA* alleles have differing affinity for binding HIV-1 peptides, and certain class I alleles carried by the mother or infant have been associated with MTCT, albeit with inconsistency across studies: *A2/6802*, *A*2301*, *A3*, *B12*, *B18*, *B*3501*, *B*3503*, *B35-Cw4*, *B*1302*, *B*4402*, *B*4901*, *B*5001*, *B51*, *B52*, *B*5301*, *B58* and *B67* [37–44]. HLA-G is a nonclassical MHC class 1 molecule highly expressed in placental trophoblasts at the maternal-infant interface, and maternal–infant discordance at *HLA-G* exon 2, as well as dissimilarity between specific maternal and infant *HLA-G* DNA sequence variants (T3742A, C3743T and G3777C of exon 8 – 3′-untranslated region) have been associated with decreased risk of MTCT of HIV [45,46]. A 14-bp deletion polymorphism (rs16375) in the *HLA-G* 3′-untranslated region was also associated with lower risk of MTCT of HIV among infant carriers [46]. Class II HLAs regulate antigen presentation and certain alleles have also been reported to affect MTCT of HIV among

certain ethnicities: *DQB1*0604*, *DR3*, *DR13*, *DRB1*1501* [43,47,48]. Given the highly polymorphic nature of the HLA region and the multiple comparisons necessary to evaluate potential associations with perinatal HIV transmission, it is not surprising that associations with individual alleles have been inconsistent even within ethnic groups. As such, putative genetic associations should be interpreted with caution. The role of mother–infant HLA class I concordance with increased perinatal transmission is documented in multiple studies, has demonstrated an incremental effect with the number of alleles shared, and has been shown to be independent of known determinants of transmission including maternal viral load, chorioamnionitis and duration of ruptured membranes [34–37,49,50].

Strong associations between infant gender and *in utero* transmission have been reported in several cohorts [51,52]. Female infants have a twofold increased risk of infection at birth compared with male infants, perhaps because *in utero* mortality is higher for male HIV-1 infected infants or because the male Y antigens may activate maternal lymphocytes and cause release of cytokines with anti-HIV-1 effects or limit maternal HIV-1-infected lymphocyte survival [51].

The field of host genomics has been revolutionized with the advent of new technologies, and exponential progress is expected in the near future. As more associations are being reported, their clinical significance and potential utilization in formulating preventive or therapeutic approaches will need to be critically evaluated.

Maternal or infant coinfections

Several coexisting infections in the HIV-1-infected mother (or, less frequently, in her infant) have been shown to increase MTCT risk. We summarize the evidence for the most important ones below.

Chorioamnionitis

Chorioamnionitis (infection of the fetal membranes), has been associated with an increased risk of MTCT of HIV-1 in several studies [53–57]. Results are mixed, however, and not all studies have concluded that chorioamnionitis is an independent risk factor for increased MTCT [58–60]. Chorioamnionitis is strongly associated with preterm labor and premature rupture of the membranes, both of which are associated with increased MTCT [61–65]. Contributing factors increasing the risk of a premature infant are the immaturity of the skin and mucosal membranes and reduced immunocompetence, resulting in higher permeability to HIV-1. The purported mechanism through which the risk of infant HIV-1 infection is increased is through infection of the placenta, leading to disruption of the integrity of the placental barrier, with maternal white blood cells infected with HIV-1 entering the amniotic fluid. Several organisms are associated with chorioamnionitis, including bacterial vaginosis-associated bacteria: *N. gon-orrhoeae, C. trachomatis*, *Trichomonas vaginalis* and group B streptococcus [65].

Among 250 mother–infant pairs in a Kenyan study, chorioamnionitis was an independent risk factor for perinatal MTCT (adjusted OR: 5.2; 95% CI: 1.6–16.5), while controlling for viral shedding in the genital tract and maternal plasma viral load. The authors estimated that

12.8% of MTCT is attributable to chorioamnionitis, assuming a causal relationship between chorioamnionitis and MTCT [54]. An earlier study, also in Kenya, found chorioamnionitis was associated with MTCT of HIV-1 in univariate analysis, but no multivariate analysis was performed [55]. A study in former Zaire in 1993 found chorioamnionitis to be associated with MTCT in both univariate and multivariate analyses (adjusted OR: 2.5; 95% CI: 1.2–5.2). Among women with neither an elevated $CD8^+$ nor a low $CD4^+$ T-lymphocyte count, the association of chorioamnionitis with MTCT of HIV-1 was stronger (relative risk [RR]: 4.2; 95% CI: 1.3–13.7) than among women with either an elevated $CD8^+$ or a low $CD4^+$ T-lymphocyte count (RR: 1.5; 95% CI: 0.8–2.6) [53]. Similarly, a Ugandan study found an interaction of the effect of chorioamnionitis with immune status. In the absence of immune suppression, the rate of MTCT for those with chorioamnionitis was 25.5%, compared with a MTCT rate of 11.3% among those without chorioamnionitis [57].

In the Ariel Project, a study conducted at seven sites in the USA, acute histologic chorioamnionitis was found significantly more often in placentas from mothers who transmitted HIV-1 to their infants than in those from non-transmitting mothers. In multivariate analysis chorioamnionitis remained statistically significantly associated with increased MTCT risk [56]. In addition, chorioamnionitis was more likely to be associated with MTCT when prolonged rupture of the membranes was also present. There was a significant association between clinical diagnosis of chorioamnionitis and histologic chorioamnionitis; however the two were still frequently discordant. In light of research that has shown an association between chorioamnionitis and MTCT of HIV-1, a multisite, double-blind randomized controlled trial was conducted in Africa among HIV-1-infected and uninfected pregnant women to determine if two courses of antibiotic treatment at 24 weeks gestation (metronidazole 250 mg and erythromycin 250 mg three-times per day orally for 7 days) and during labor (metronidazole 250 mg and ampi-cillin 500 mg every 4 h) would reduce histologic chorioamnionitis compared with a placebo [65]. The study failed to show an effect and was terminated early by the data safety and monitoring board overseeing the study. The study did, however, show a significant reduction in bacterial vaginosis and trichomonas vaginalis carriage in HIV-1-infected women, indicating that the antibiotics were effective at treating a known infection [66]. Results from the same study, reported separately, found no difference in MTCT of HIV-1 by antibiotic treatment arm or by the presence of histologic chorioamnionitis [60].

Sexually transmitted infections

Due to shared acquisition risk factors and the synergistic relationship between HIV-1 and other sexually transmitted infections (STIs), STIs are common among HIV-1-infected women. It is well established that both ulcerative and nonulcerative STIs increase sexual HIV-1 transmission [67,68]. However, whether STIs are independent risk factors for increased HIV-1 transmission or the result of increased HIV-1 viral load is not clear. Furthermore, the role of STIs in MTCT of HIV-1 has not been fully characterized. Many studies have assessed the prevalence of any STI among HIV-1-infected pregnant women, making it difficult to elucidate the relationship that specific STIs have on MTCT of HIV-1. Inflammation of the maternal genital tract mucosa, as occurs in genital ulcer disease, has been shown to increase MTCT independently of maternal plasma HIV-1 load [69,70].

Syphilis and HSV-2 are both associated with genital lesions which increase local inflammation and genital shedding of HIV-1 [71].

HSV-2 is the most common cause of genital ulcer disease worldwide, and estimates of HSV-2 seroprevalence among HIV-1-infected individuals range from 70–90% [72]. Results from several studies have shown that HSV-2 is associated with increased genital shedding of HIV-1 among HIV-1-infected women [73–75]. A US study reported that clinical HSV-2 was associated with increased MTCT of HIV-1, while asymptomatic HSV-2 was not associated with increased transmission to the infant [76]. Similarly, results from a Kenyan study showed that genital ulcer disease was significantly associated with MTCT, whereas HSV-2 seropositivity was not [77]. More recently however, two nested case-control studies from Thailand and Zimbabwe found that serologically confirmed HSV-2 was associated with increased risk of MTCT of HIV-1, independently of maternal HIV-1 viral load [78,79]. In the Thailand study, genital HSV-2 shedding was associated with a threefold increase in intrapartum transmission of HIV-1 [78]. The proportion of HIV-1 intra-partum transmission potentially attributable to HSV-2 was 28.4% in the Zimbabwe cohort [79].

Acyclovir has been shown to significantly reduce HIV-1 disease progression and HIV-1 plasma RNA in HIV-1/HSV-coinfected adults [80,81]. To date, however, no studies have been conducted using acyclovir in pregnant HIV-1/HSV-2-coinfected women [82]. Therefore, it is not known whether viral suppression of HSV-2 through treatment is an effective strategy to reduce MTCT of HIV-1.

As previously noted, syphilis, though less common than HSV-2, also causes genital ulcer disease. The data on whether syphilis plays a role in MTCT of HIV-1 are not conclusive. In the Zimbabwe study mentioned above, active syphilis at the time of delivery was not associated with an increased risk of perinatal HIV-1 transmission [79]. This finding is consistent with results from a study in Uganda, which showed that presumptive treatment of STIs in HIV-1-infected pregnant women was associated with a reduction of maternal rates of bacterial STI but not with a reduction in rates of MTCT of HIV-1 [83]. Conversely, a recent study in the Ukraine among 521 HIV-1-infected pregnant women found that serologically-confirmed syphilis was associated with a fivefold increase in MTCT of HIV-1, however, this study was not able to adjust for maternal viral load, a likely confounder [84]. In a large prospective cohort study conducted in Malawi, syphilis infection was associated with a 2.7-fold increase in MTCT of HIV-1 after adjustment for maternal viral load and other confounders [57].

HPVs cause the most common STI; however, little data exists on HPV/HIV-1 coin-fection and its role on MTCT of HIV-1 [85]. Although results of univariate analyses in two studies demonstrated that genital warts were significantly associated with increased risk of MTCT of HIV-1, in both studies, the results of multivariate analyses showed no significant association [56,86]. These studies' use of genital warts as a proxy for HPV rather than serological evidence of HPV infection may be problematic, because the presence of genital warts may be an indication of advanced HIV-1 disease.

Malaria

Malaria infects the placenta and leads to adverse pregnancy outcomes [87]. This is especially true in primigravida women, among whom malaria tends to be more severe [88,89]. There are conflicting reports on the effect of malaria during pregnancy on MTCT of HIV-1. Several earlier studies have failed to reveal an interaction between malaria and MTCT [87,90], however more recent data indicate that malaria increases HIV-1 viral load and treatment of malaria reduces HIV-1 viral load [91]. A few recent studies have suggested an increased risk of MTCT of HIV-1 in pregnant women with malaria [92–94], yet others have not shown a significantly increased risk [88,95,96]. A study in western Kenya of women who were infected with HIV-1 and malaria found that higher parasitemia levels (>10,000 parasites/μl of blood) were associated with an increased risk of MTCT of HIV-1 compared to lower levels of parasitemia [97]. Inconsistencies in study results may be due, at least in part, to differences in the epidemiology of malaria in different settings, which could affect maternal immunity. Further research is needed to characterize the association between malaria and MTCT.

Viral hepatitis B & C & GB-virus C

HBV is a common coinfection among HIV-1 infected individuals. Up to 90% of HIV-1 infected individuals have serologic evidence of HBV infection, with 10% chronically infected [98]. HIV-1/HBV coinfection significantly alters the natural disease course of HBV infection, causing accelerated fibrosis and a faster rate of disease progression than in HBV mono-infection [98]. Coinfection with HIV-1 results in increased rates of hepatitis B e antigen carriage, higher rates of chronic HBV infection, and higher HBV DNA levels, all of which have been associated with increased MTCT of HBV [98–101]. Xu *et al.* demonstrated that in women with high HBV DNA levels during pregnancy, HBV transmission to the infant was substantial (at a rate as high as 39%), despite immunoprophylaxis with vaccine and immunoglobulin [102].

While HIV-1/HBV coinfection may be related to increased HBV transmission to the infant, HBV infection (as measured by presence of hepatitis B surface antigen) does not seem to be independently associated with increased MTCT of HIV-1 [103,104]. However, compared with HIV-1 mono-infected women, HIV-1/HBV coinfected women are significantly more immunosuppressed, which is an independent risk factor for MTCT of HIV-1 [105].

While HCV is less common than HBV, coinfection among HIV-1-infected individuals is frequent (~30%), owing to shared routes of transmission, mainly through injection drug use (IDU) [105,106]. Several studies have found that HCV coinfection increases the risk of MTCT of HIV-1 [107–113]. The likely mechanism through which this occurs is immunosuppression; HCV seropositivity is significantly associated with severe immunosuppression in those infected with HIV-1 ($p < 0.001$) [105].

Among HCV mono-infected pregnant women, HCV is rarely transmitted to the infant [112,114–119]. In the few cases in which mothers do transmit HCV to their infants, transmission is highly correlated with increased HCV plasma RNA [112,116,120]. HIV-1-

infection increases HCV RNA in plasma and therefore can substantially increase the risk of HCV transmission to the infant [112,115,120–122].

GB virus C (GBV-C) is a flavivirus closely related to HCV; it was called hepatitis G virus when it was discovered in 1995. Infection with GBV-C has no clinical significance; however several studies have found a beneficial effect of GBV-C in HIV-1 infected individuals. GBV-C is associated with slower progression of HIV-1 disease and inhibition of HIV-1 replication [123–125]. Furthermore, GBV-C can be transmitted vertically and is associated with reduced MTCT of HIV-1 [126,127]. In a Thai cohort of 245 women, maternal receipt of ART, high maternal GBV-C load, vaginal mode of delivery, and absence of infant HIV-1 infection were independently associated with MTCT of GBV-C. GBV-C and HIV-1 were rarely cotransmitted [126].

TB

TB is a leading cause of morbidity and mortality worldwide and is of particular concern among those infected with HIV-1, as people living with HIV-1 are 20–30-times more likely to develop TB [128]. In 2009 there were an estimated 1.1 million incident cases of TB in people living with HIV-1 [129]. For women, the greatest burden of TB occurs during the reproductive years (15–49 years old) [129]. Rates of TB in HIV-1-infected pregnant women in a study in South Africa were ten-times those in HIV-1-uninfected pregnant women [130]. Active TB infection increases HIV-1 viral load, which is a recognized risk factor for MTCT [131–134]. Given the high rates of TB among HIV-1-infected women, particularly those of reproductive age, a concern is whether TB increases the risk of MTCT of HIV-1 independently or through increased HIV-1 viral load. To date, however, there have been few studies that have investigated TB infection as an independent risk factor for MTCT of HIV-1.

In a South African study of 42 HIV-1 infected pregnant women with active TB disease, a 19% *in utero* HIV-1 transmission rate was observed [135]. This was in comparison to a 5–10% overall rate of *in utero* HIV-1 transmission in resource-limited countries at that time. Overall, the MTCT rate for the duration of study follow-up was 40% [135]. This study did not have a control group, nor was there statistical adjustment for confounders such as viral load. A recent study in India found that maternal TB was associated with a 2.5-fold increase in the odds of MTCT of HIV-1, after adjusting for maternal and infant factors [136]. This study supports that TB is an independent risk factor for MTCT of HIV-1, however given the limited data available additional studies are warranted.

Other infections

Because CMV seropositivity in HIV-1-infected adults is virtually universal, it is difficult to ascertain if CMV is associated with increased risk of MTCT of HIV-1 [137,138]. CMV and HIV-1 can infect the same cells, and the cellular proteins and viral gene products of each virus can activate the other virus *in vitro*. Positive cervical CMV cultures have been shown to be correlated with perinatal CMV infections [138]. However, positive CMV urine culture among HIV-1 infected pregnant women, which has a markedly lower prevalence than serologic evidence of CMV, and is a marker of active CMV replication, was not associated

with increased MTCT [137]. Incidence of *in utero* CMV infection was similar for HIV-1 infected and uninfected infants. However HIV-1-infected infants had a higher rate of CMV infection at 6 months of age. This suggests that rather than CMV virus being a risk factor for increased MTCT of HIV-1, HIV-1 may be a risk factor for CMV. Infants with early CMV infection had more rapid HIV-1 disease progression [139].

Similarly, evidence of EBV infection is very common among HIV-1-infected women; therefore few studies have investigated the role EBV has on MTCT of HIV-1. In a multisite study in the USA, EBV seropositivity was 100% for 279 HIV-1-infected pregnant women. EBV shedding was marginally associated with MTCT in this study; in multivariate analysis this association did reach statistical significance independently of maternal immune status and other confounders [137].

Human herpesvirus-8 (HHV-8) infection, the cause of Kaposi's sarcoma, is transmitted by oral secretions, semen, and the sharing of needles [140]. HHV-8 infection is common among HIV-1-infected individuals, and cross-sectional studies have demonstrated a signifi-cant association between HIV-1 and HHV-8 seroprevalence [141,142]. A small study among 15 pregnant women in Italy showed that HHV-8 may be reactivated during pregnancy in HIV-1 infected women. This study found a significant increase in genital HIV-1 shedding among women with detectable HHV-8 sequences, suggesting that HHV-8 coinfection may increase MTCT of HIV-1 [143]. However, results from a study in Zambia failed to show an association of HHV-8 infection among HIV-1-infected pregnant women with transmission of HIV-1 to the infant [141]. HHV-8 infection is common in childhood with seroprevalence increasing with age suggesting that the primary mode of transmission is horizontal (saliva) between children or from caregivers; MTCT of HHV-8 is infrequent [140,141,144–147]. Additionally, breast milk transmission is unlikely, as HHV-8 is rarely detected in breast milk [148]. Furthermore, studies have shown that neither maternal HIV-1 nor HHV-8 status is associated with HHV-8 infection among infants [141,147].

Mastitis (both clinical and subclinical, which is associated with breast engorgement and breast milk stasis) is associated with higher postnatal MTCT risk, with an increased risk as the mother's plasma HIV-1 load increases [149]. Oral candidiasis in the infant has also been associated with increased risk of postnatal HIV-1 transmission [150].

Behavioral factors

Illicit drug, alcohol & tobacco use

Whereas lifetime IDU is not associated with increased MTCT of HIV-1 [53,151–153], IDU during pregnancy has been associated with increased risk of MTCT in several studies, most of which were conducted before the advent of prenatal ARV prophylaxis to prevent MTCT. In a study conducted in 1997 in the USA, combined cocaine and heroin use was associated with a 19-fold higher MTCT risk [151,154]. This study also reported that IDU after the first trimester accounted for most of the association between preterm birth and MTCT. An increased risk of MTCT with IDU was also present in women without preterm birth and premature rupture of the membranes [151]. Another US study found that use of illicit drugs during pregnancy was independently associated with MTCT of HIV-1 after adjusting for

rupture of the membranes, $CD4^+$ T-lymphocyte count and birth weight [155]. This study was unique in that it collected data on drug use via self report and urine toxicology [156]. Two other studies demonstrated marginal significance in the association of illicit drugs and MTCT of HIV-1 [56,157].

There are several mechanisms by which illicit drugs could affect MTCT of HIV-1. First, drug use during pregnancy can increase the risk of preterm birth which is associated with increased MTCT [158]. Indeed, prenatal cocaine and amphetamine exposure have been associated with preterm birth [159–162]. Secondly, drug use may be associated with increased HIV-1 viral load or failure to suppress viral load in the presence of HAART. Cocaine, heroin and amphetamine use have been shown to independently increase HIV-1 plasma viral loads, despite the use of HAART [163–169]. Additionally, several studies have also demonstrated that drug use is associated with lower adherence to HAART regimens, which is in turn associated with reduced viral load suppression [158,164,167,168,170–175]. Other mechanisms by which illicit drugs may affect MTCT include drug interactions with ARV medications and placental injury [158]. Cocaine exposure during pregnancy has been associated with increased risk of placental abruption [176].

Self-reported rates of alcohol use among HIV-1-infected pregnant women are high, in the range of 18–21% [177,178]. Alcohol use alone and in combination with illicit drugs has been associated with decreased ART utilization, adherence, and viral suppression in HIV-1-infected individuals [45,168,179]. Additionally, alcohol use was a predictor of poorer ART adherence among HIV-1-infected pregnant women in univariate and multivariate analyses [177].

Studies suggest that women who continue to smoke moderately to heavily later in pregnancy have up to a twofold increase in the odds of preterm birth [158,159,180]. Additionally, HIV-1-infected smokers have a poorer immunological response to HAART [181]. Several studies have also demonstrated that use of tobacco is associated with lower adherence to HAART regimens [158,177,182]. It is to be noted that while mechanisms do exist by which alcohol and tobacco use can affect MTCT, studies that have examined this relationship have failed to find an association with increased MTCT of HIV-1 [58,104,183].

Sexual activity

Heterosexual contact is the prevailing route of transmission for HIV-1-infected pregnant women [301]. Several studies have examined the relationship of sexual activity, both through number of partners and frequency of intercourse during pregnancy, with transmission of HIV-1 to the infant. Burns *et al.* found a higher frequency of intercourse during pregnancy among women transmitting HIV-1 to their infants [154]. There was, however, a strong correlation between frequency of vaginal intercourse during pregnancy and drug use [154], and in a multivariate model that included drug use (reported separately), frequency of vaginal intercourse was no longer associated with increased MTCT of HIV-1 [151]. In another study, a dose-response relationship was found in the association of frequency of unprotected sexual intercourse and MTCT of HIV-1. This association remained after controlling for confounders including IDU, CD4 lymphocyte count, and clinical condition [184].

A US study failed to show an association with multiple sex partners during pregnancy and MTCT, however, very few women in this cohort reported more than one sex partner [151]. In contrast, a Rwandan study of 184 mother-infant pairs found multiple unprotected sex partners during the past 5 years to be strongly associated with MTCT of HIV-1. Women who had more than three sex partners during their pregnancy were significantly more likely to transmit HIV-1 to their infant than women with a single partner (adjusted OR: 4.5; 95% CI: 1.7–11.7) [185].

There are several plausible mechanisms by which increased sexual activity may increase MTCT. Increased sexual activity, particularly in populations with high HIV-1 seroprevalence, may be associated with increased strain diversity in the mother [65,151,185–187]. Several studies have found that women infected with specific HIV-1 subtypes and recombinant viruses may be at increased risk of transmitting the virus to their infant [188–190]. Multiple sex partners and increased sexual frequency are also likely to cause inflammation of the vagina and cervix through microabrasions or STIs, which may lead to chorioamnionitis [65].

Infant feeding practices

Breastfeeding

In sub-Saharan Africa, as much as 42% of MTCT of HIV-1 is attributable to breastfeed-ing [191,192]. Because replacement feeding in the USA is safe, affordable and culturally acceptable, the US CDC has recommended since 1985 that HIV-1-infected women in the USA avoid breast-feeding [193]. In the USA and other resource-rich settings, postnatal MTCT of HIV-1 has thus been virtually eliminated. However, in resource-limited countries, safe alternatives to breastfeeding do not exist, therefore the WHO recommends that HIV-1-infected women in such settings breastfeed their infants while the mother or the infant receives ARV prophylaxis [194].

HIV-1 level in breast milk is one of the most important determinants of breast milk transmission risk, with cell-associated virus being a stronger predictor for HIV-1 transmission to the infant than cell-free virus in some studies [195–198]. Abrupt weaning and local breast inflammation resulting from mastitis increase concentrations of HIV-1 viral load in breast milk [70,199], and risk of MTCT of HIV-1.

Longer duration of breastfeeding increases the infant’s exposure to HIV-1, and leads to a higher risk of transmission [191,200–203]. While some studies suggest that the highest risk of breast milk transmission of HIV-1 occurs soon after delivery [191,198,203–205], a meta-analysis suggested a more constant risk of postnatal transmission of HIV-1 of 0.9% per month after the first month of life [195].

Mixed feeding

HIV-1 transmission is lower when exclusive breastfeeding is practiced, rather than mixed feeding [206–208]. This may be due to damage to the infant’s gut mucosa induced from early introduction of non-breast-milk foods, leading to delayed closure of the enterocyte junctions in the intestinal mucosal barrier or, alternatively, from intestinal immune activation

resulting from early introduction of foreign antigens or pathogens [209]. Nonexclusive breastfeeding may be associated with less frequent breast emptying, increasing the risk of inflammation in the breast which, as mentioned above, is associated with increased HIV-1 viral load [70,199].

Premastication of food

Premastication, the practice of chewing foods or medicines before giving them to a child, has been shown to be a risk factor for MTCT [210]. Three children in the USA were recently reported to have become HIV-1-infected later in infancy after vertical transmission had been ruled out. In one of the reported cases the mother was not HIV-1-infected, but a caregiver who provided the infant with pre-masticated food was HIV-1 infected. Two out of the three of the caregivers reported having bleeding gums during the period in which they were providing premasticated food [210]. Two cross-sectional studies in the USA sought to determine the proportion of HIV-1-infected mothers and caregivers practicing premastication [211,212]. In a study conducted in an urban clinic with a high HIV-1 prevalence, 19% of HIV-1-infected mothers reported a history of providing premasticated foods to their children [211]. Another study conducted in nine US sites found that 31% of children of HIV-1-infected mothers received premasticated foods from the caregivers or someone else [211]. Both studies found the practice was more common among African–American caregivers, however in the first study the only significant predictor of premastication was whether the mother had received premasticated foods as a child [211,212]. Premastication is common worldwide and may be more common in Africa than in the USA; however, it would be difficult to define the route of transmission in settings where breast-feeding is also practiced among HIV-1-infected mothers.

Maternal nutritional status

The general state of health of the mother is an important predictor of MTCT risk [1]. Mothers with higher HIV-1 viral load, lower $CD4^+$ T-cell count and more advanced disease stage are at increased risk of transmitting HIV-1 to their infant, which is a result of the higher peripheral blood viral load, increased shedding in the genital tract and decreased maternal immune responses to contain the virus. In addition, advanced AIDS is associated with a poorer nutritional status and a catabolic state, and is also a predictor of increased MTCT risk. We will discuss below specific micronutrient deficiencies and their role in MTCT of HIV-1.

Vitamin A

Pregnancy and HIV-1 infection are risk factors for Vitamin A deficiency [213,214]. Vitamin A deficiency has been associated with faster HIV-1 disease progression and increased cervical and vaginal shedding of HIV-1 [69,215–217]. Several observational studies have investigated vitamin A deficiency among HIV-1-infected pregnant women and its association with HIV-1 transmission to the infant [218–221]. In 1994, Semba and colleagues showed a significant correlation between maternal vitamin A deficiency and increased risk of MTCT of HIV-1 in a Malawian cohort (RR: 4.38; 95% CI: 1.62–11.94) [221]. Of three US studies assessing this relationship, one found a similar association, but this was only

among women with severe vitamin A deficiency [220]. The two other studies failed to find an association, however the prevalence of severe vitamin A deficiency was low in both studies [218,219].

These findings led researchers to conclude that severe vitamin A deficiency was associated with increased MTCT of HIV-1, and four clinical trials of vitamin A supplementation in HIV-1-infected pregnant and post-partum women were subsequently conducted in Africa [222–225]. Collectively, these studies found no benefit from vitamin A supplementation during pregnancy or postpartum to reduce MTCT of HIV-1 [222–224]. There was, however, a significant improvement in infant birth weight and preterm delivery associated with vitamin A supplementation [222–224]. Unexpectedly, though, the Tanzania study found that vitamin A supplementation increased the risk of MTCT by age 24 months (RR: 1.35; 95% CI: 1.10–21.65) [223]. In another trial, vitamin A supplementation given to either the mother or the infant, but not both, increased the risk of HIV-1 infection or death by 2 years of age among infants who were uninfected at 6 weeks postpartum [226]. A Cochrane review concluded that the available evidence does not support vitamin A supplementation in HIV-1-infected pregnant women despite improvements in birth weight [226].

Other micronutrients

Studies assessing the effects of other micronutrients on MTCT of HIV-1 are more limited. Some data suggest that selenium and vitamin D deficiencies may be associated with MTCT of HIV-1 [227,228]. Selenium is an antioxidant, and laboratory experiments have shown it has an inhibitory effect on HIV-1 *in vitro* [229]. Selenium deficiency is associated with increased mortality among HIV-1-infected individuals [230–233], and with accelerated HIV-1 disease progression through increased viral load [234]. In a randomized controlled trial, selenium supplementation to pregnant women did not have a significant effect on HIV-1 viral load, $CD4^+$ T-lymphocyte count, pregnancy outcomes or maternal or infant mortality [235]. Zinc deficiency is common among HIV-1-infected women [236], and low zinc levels have been associated with accelerated HIV-1 disease progression [237]. A trial of zinc supplementation among 400 HIV-1-infected pregnant women in Tanzania found no effect on early MTCT of HIV-1 [238]; however, more research is needed in order to answer this question definitively.

A recent study from Tanzania indicated a higher risk of MTCT of HIV-1, perinatally and through breastfeeding, in women with low vitamin D levels [228]. Vitamin D has immunomodulatory properties [239] and contributes to the development of the fetal immune system, mechanisms that possibly mediate the observed effect. Further research is needed to determine the role of vitamin D in preventing MTCT of HIV-1.

Supplementation with vitamin B complex, vitamin C, and vitamin E may be protective against MTCT in HIV-1-infected women who are nutritionally or immunologically compromised; in a randomized clinical trial conducted in Tanzania [223], supplementation with multivitamins excluding vitamin A/β-carotene resulted in a nonstatistically significant reduction in transmission of HIV-1 through breast-feeding, and reduced mortality among the infants who were not infected at 6 weeks of age.

Future perspective

Despite the tremendous progress made in preventing MTCT of HIV-1, many challenges remain worldwide, particularly in resource-limited settings. In the next 5–10 years, extensive roll-out and implementation of ARV regimens during pregnancy and breastfeeding for HIV-1-infected women is expected throughout the world, as these have been shown to drastically curtail MTCT. Particular effort is required in resource-limited settings, where the magnitude of the problem, associated with poor health care infrastructure, poverty, and lack of political will, often presents tremendous difficulties. Intensive and long-term ARV regimens, however, are difficult to implement, have side-effects, can induce resistance and are costly. Addressing coinfections and improving the mother's nutritional status offer complementary approaches that have benefits both for the mother's and infant's health and for curtailing transmission of HIV-1 to the infant. Behaviors and practices that increase MTCT risk can be addressed with intensive education and counseling approaches. Finally, with the dramatic expansion of tools and investigative methods in the genomics field, many more genetic polymorphisms that modulate the risk of HIV-1 infection are being reported. Further studies to evaluate the importance of the observed associations in different populations may provide the tools for developing new preventive and therapeutic strategies to battle transmission of HIV-1 from mother to infant. In the not-so-distant future, one can envision approaches that take advantage of individual host variations in responding to early steps of viral entry and establishment of a productive infection or in enhancing natural protective immunity to sustain resistance against HIV-1 infection, which one day could be translated into a sterilizing vaccine to prevent infection.

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Executive summary

- Risk of mother-to-child transmission (MTCT) of HIV-1 has been associated with several genetic polymorphisms in genes encoding for chemokine receptors and ligands affecting virus entry, in HLA and other genes affecting innate immunity factors.
- Coinfections associated with risk of MTCT of HIV-1 include chorioamnionitis, sexually transmitted infections (especially those causing genital ulcer disease), malaria, HCV infection and TB.
- Mastitis in the mother and oral candidiasis in the infant are both associated with increased HIV-1 transmission through breastfeeding.
- During pregnancy, use of injection drugs, number of sex partners and frequency of sex may increase MTCT of HIV-1. In the postnatal period, prolonged breastfeeding, mixed feeding and premastication of the infant's food by HIV-1-infected child care providers are all associated with risk of HIV-1 transmission.
- Severe vitamin A deficiency is associated with increased MTCT of HIV-1, however supplementing pregnant women with vitamin A during pregnancy is not effective at reducing MTCT and some studies have found an increased risk of postnatal HIV-1 transmission. The role of other micronutrients needs to be further investigated.

Table 1

Genetic variations that have been associated with mother-to-child transmission of HIV-1.

Gene	Polymorphism	Carrier	Influence on
Receptors, coreceptors and their ligands			
CD4	C868T	Infant	Increased
CCR5	Δ32 deletion, homozygous	Infant	Decreased
	Δ32 deletion, heterozygous	Mother	Decreased
	59029A or 59353T in promoter region	Infant	Increased
CCR2	64I	Infant	Contradictory
		Mother	Decreased
CCL3	Gene copy number	Infant	Increased
SDF-1	3′-UTR 801A	Mother	Contradictory
HLA			
Class I A, B, C and G	Mother–child concordance	Mother–infant	Increased
	SNPs	Infant or mother	Contradictory
Class I A, B and C	HLA class I homozygosity	Mother	Increased
Dendritic cell receptors			
DC-SIGN	336C and 201A in promoter region	Infant	Increased
	R198Q, E214D, R221Q and L242V	Infant	Increased
DC-SIGNR	H1 (198A in promoter region) and H3 (180A)	Infant	Increased
Innate immunity			
DEFB1	52G/G	Infant	Decreased
MBL2	550G/G	Infant	Decreased
	-328delAAAGAG	Infant	Increased
TLR9	Haplotypes AA and GG at c.4-44G/A and c.1635A/G	Infant	Increased

MTCT: Mother-to-child transmission of HIV-1; UTR: Untranslated region.