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The Role of Co-Infections in Mother-to-Child Transmission of HIV[§]

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Abstract

In HIV-infected women, co-infections that target the placenta, fetal membranes, genital tract, and breast tissue, as well as systemic maternal and infant infections, have been shown to increase the risk for mother-to-child transmission of HIV (MTCT). Active co-infection stimulates the release of cytokines and inflammatory agents that enhance HIV replication locally or systemically and increase tissue permeability, which weakens natural defenses to MTCT. Many maternal or infant co-infections can affect MTCT of HIV, and particular ones, such as genital tract infection with herpes simplex virus, or systemic infections such as hepatitis B, can have substantial epidemiologic impact on MTCT. Screening and treatment for co-infections that can make infants susceptible to MTCT *in utero*, peripartum, or postpartum can help reduce the incidence of HIV infection among infants and improve the health of mothers and infants worldwide.

Keywords

Co-infections; HIV; infections; infant; mother-to-child transmission

INTRODUCTION

Despite the success of antenatal HIV screening and prevention of mother-to-child transmission of HIV (PMTCT) programs, in 2009, an estimated 370,000 children became infected during the perinatal or breastfeeding period [1]. Highly effective interventions for PMTCT, such as antiretroviral agents during pregnancy and labor [2-9], caesarean section delivery [10-13], postexposure prophylaxis to the infant [14-18], and avoidance of breastfeeding [19, 20], can reduce risk for mother-to-child transmission of HIV (MTCT) to

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

PATIENT CONSENT

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HUMAN/ANIMAL RIGHTS

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<2% [21-23]. Unfortunately, these interventions are not uniformly administered, particularly in resource-limited countries with the greatest need [24].

Effective PMTCT interventions address the main risk factors for MTCT, which are maternal HIV load and infant exposure to infected fluids [25, 26]. High maternal HIV load is the strongest risk factor for MTCT, and reduction of HIV load with antiretroviral interventions significantly reduces risk [27-34]. Infant exposure to infected fluids during labor and delivery is associated with duration of ruptured membranes [35], type of delivery [10, 11], and presence of other active sexually transmitted infections (STIs) in the vaginal canal [25, 36, 37]. Postnatal exposure to HIV-contaminated milk is correlated with duration of breastfeeding, which is associated with MTCT [20]. Without PMTCT intervention, the overall risk for HIV transmission to the infant is 25%-40%, with an estimated 10%-25% of infections occurring during pregnancy, 35%-40% during labor and delivery, and 35%-40% during breastfeeding [26, 38].

In the absence of antiretroviral treatment, natural defense mechanisms can protect against MTCT. The human placenta is an efficient barrier to the exchange of maternal and fetal circulations, despite HIV tropism for placental cells and frequent infection of the placenta [39]. Postpartum, the blood-milk barrier keeps the HIV load in breast milk generally 100 times lower than the HIV load in plasma [40], possibly because of the many antimicrobial and immunomodulatory factors in breast milk [41, 42], including cell-free HIV inhibitors that likely inactivate many potentially infectious virions [43-45]. Disruption of natural barriers to infection occurs during chorioamnionitis, labor and delivery, or mastitis, and these barrier breaches can increase risk for MTCT. Co-infections can trigger the release of inflammatory agents that increase tissue permeability and cytokines that stimulate HIV replication [46, 47]. Several co-infections in the HIV-infected mother or exposed infant have been shown to increase MTCT risk, and addressing these co-infections may reduce MTCT and improve overall maternal and child health (Table 1) [48].

MATERNAL REPRODUCTIVE TRACT INFECTIONS

Infections of the Placenta and Fetal Membranes

In HIV-infected, pregnant women who are not taking antiretrovirals, the placenta is a reservoir for HIV replication [49]; however, it can also provide an efficient barrier to HIV transmission for more than 90% of exposed infants [39]. Evolution of the placenta's structure and function during gestation generates a barrier between maternal and fetal circulations through which HIV must cross by endocytosis or by an injured villous surface, such as occurs in chorioamnionitis. The placenta also confers protection by producing soluble factors and receptors, such as cytokines, chemokines, and MHC class I molecules. Co-infections of the placenta may affect its anti-HIV properties by altering local expression of cytokines, chemokines, and their co-receptors, as evidenced by increased expression of the CCR5 HIV co-receptor on placental macrophages infected with malaria in a *Plasmodium falciparum* dominated region [50], or by stimulating HIV replication, as evidenced *in vitro* with an antigen of *P. falciparum* [51].

Chorioamnionitis is inflammation of the membranes surrounding the fetus that is caused primarily by infection ascending from the lower genital tract. It can be caused by several different microorganisms, such as bacterial vaginosis-associated bacteria, Neisseria gonorrhea, Chlamydia trachomatis, Trichomonas vaginalis, or *Group B Streptococcus* [52]. Chorioamnionitis may disrupt the placental barrier allowing HIV-infected maternal lymphocytes to enter the amniotic fluid. It has been associated with increased intrauterine risk for MTCT [53-57], but it has not necessarily been found to be an independent risk factor [29, 58]. Chorioamnionitis is also associated with preterm labor and premature rupture of the membranes [59]. These conditions have been associated with increased MTCT [60-63], but the causality of the association is unclear because HIV infection predisposes women to preterm delivery [64]. In a Kenyan study of 250 mother-infant pairs, histologic chorioamnionitis was found to be an independent risk factor for peripartum MTCT (adjusted odds ratio [AOR], 3.9; 95% confidence interval [CI], 1.2-12.5) after researchers assessed the effect of prolonged rupture of membranes and controlled for low infant birth weight and maternal plasma and genital tract HIV load [53]. Similarly, in a study conducted at seven sites in the United States (n=175), acute histologic chorioamnionitis was found significantly more often in placental tissue from HIV-infected mothers who transmitted the virus to their infants than from mothers who did not transmit the virus to their infants (37.5% *vs* 11.3%, p=0.008), and it remained a predictor after adjustment for HIV load and prolonged rupture of membranes [54]. In this study, histologic chorioamnionitis was significantly correlated with clinical chorioamnionitis, but clinical chorioamnionitis was not a predictor of MTCT. This study also assessed whether HIV load influenced the association between histologic chorioamnionitis and transmission and found no interaction. A study in former Zaire (now DRC) found chorioamnionitis to be associated with MTCT in both univariate and multivariate analyses (AOR, 2.5; 95% CI, 1.2-5.2), with a significant interaction between maternal immune status and the effect of chorioamnionitis; only among nonimmunocompromised women (as indicated by neither a low CD4+ T lymphocyte count nor an elevated CD8+ T lymphocyte count) was chorioamnionitis associated with significantly increased risk of HIV transmission (relative risk, 4.2; 95% CI, 1.3-13.7) [55]. An interaction between maternal immune status and the effect of chorioamnionitis on MTCT was also observed in a Ugandan study in which, in the absence of immune suppression, the AOR for MTCT was 2.87 (95% CI, 1.04-7.90) for women with chorioamnionitis when they were compared with women who did not have chorioamnionitis [56]. These data suggest that inflammation of the placental membranes may have a greater effect on risk for transmission among women who might otherwise be at low risk for perinatal transmission. Using the assumption that the association between chorioamnionitis and HIV transmission among nonimmunocompromised women is causal, the authors in the Ugandan study estimated that up to 34% of HIV transmissions could be prevented with treatment of placental inflammation in non-immunocompromised women. However, a randomized controlled trial that evaluated two courses of antibiotic treatment at 20-24 weeks gestation (metronidazole 250 mg and erythromycin 250 mg, three times per day, orally for 7 days) and during labor (metronidazole 250 mg and ampicillin 500 mg every 4 hours) among HIV-infected and uninfected pregnant women in Africa failed to show an effect on histologic chorioamnionitis or risk for MTCT [65, 66]. As a result, the study was terminated early by the data safety and monitoring board overseeing the research. This trial, as well as

an observational cohort study in Africa that systematically screened and treated common STIs, documented no difference in MTCT by the presence of histologic chorioamnionitis [66, 67].

Lower Genital Tract Infections

Genital tract infections increase intrapartum risk for MTCT by increasing infant exposure to HIV in genital secretions from the mother during labor and delivery. Common vaginal infections such as bacterial vaginosis (BV) and vulvovaginal candidiasis, STIs such as trichomoniasis and herpes simplex virus type 2 (HSV-2), and cervicitis are associated with increased HIV shedding in the genital tract that declines upon treatment for these infections [26, 68-72].

HSV-2 is the leading cause of genital ulcers. With a seroprevalence of 60%-90% among HIV-infected populations, it likely has a significant effect on HIV infection [73]. HSV-2 ulcers contain high levels of HIV RNA, possibly from the homing of activated T cells [74, 75], and also provide a breach in the mucosa that increases infant exposure to HIV virions or infected cells beneath the epithelium. Consequently, genital ulcers are an important risk factor for MTCT [25,36,37,76]. Even among clinically asymptomatic, serologically positive women, HSV-2 shedding remains common and is associated with increased HIV shedding in the genital tract of co-infected women [77, 78]. Two studies, one in the United States and one in Kenya, found that clinical HSV-2 was associated with increased MTCT but asymptomatic HSV-2 was not [36, 37]. More recently, two nested case-control studies from Thailand and Zimbabwe found that serologic HSV-2 was associated with increased risk for MTCT, independent of maternal HIV load [76, 79]. In the Thai study, genital HSV-2 shedding was independently associated with a threefold increase in intrapartum HIV transmission [76]. In the Zimbabwe study, an estimated 28.4% of intrapartum HIV transmissions were potentially attributable to serologic HSV-2 infection [79]. Asymptomatic HSV-2 infection may affect MTCT through more generalized effects on the mother's HIV load because of immune activation or direct interactions between the viruses [80]. Plasma HIV load increases upon subclinical HSV-2 reactivation and declines upon successful viral suppression with acyclovir treatment [81-83]. Clinical trials have shown that HSV-2 suppressive therapy significantly reduces plasma and cervical HIV load [46, 83-88]. However, results from clinical trials of acyclovir on sexual transmission of HIV have shown no reduction in acquisition or transmission [86,89,90].

Acyclovir is actively transported to the amniotic fluid and breast milk [91], and both acyclovir and valacyclovir, which is rapidly absorbed and converted to acyclovir, have good safety profiles in pregnant women and have not been associated with congenital malformations or infant toxicity [92-94]. The maternal and infant safety profile for maternally administered valacyclovir suppressive therapy was not altered in the context of antiretroviral prophylaxis for PMTCT in a randomized trial [95]. In another report from this trial, which was conducted among pregnant and postpartum Kenyan women co-infected with HSV-2 and HIV, valacyclovir significantly reduced HIV load in plasma by 0.5 $\log_{10}$ copies/mL during pregnancy and after 6 weeks postpartum, compared with the placebo, and reduced the levels of HIV load in breast milk at 6 and 14 weeks postpartum [96].

Theoretically, suppression of HIV load in plasma and breast milk should translate to reduced MTCT. The Kenyan trial found no difference in HIV transmission at 12 months, but the study was not designed to answer this question. Larger clinical trials are warranted because suppressive therapy for HSV-2 could be easily administered within the existing PMTCT infrastructure and could provide maternal benefits of reduced frequency and severity of HSV-2 reactivations, which may slow HIV disease progression, and reduce the risk for HIV transmission.

Syphilis, caused by infection with the bacterium *Treponema pallidum*, is a less common cause of genital ulcer disease, and its role in MTCT is unclear [79, 97-100]. One large prospective cohort study conducted in Malawi reported that syphilis was associated with a 2.7-fold increase in both intrauterine (HIV-positive at birth) and intrauterine/postpartum (HIV-positive at 6 or 12 weeks postpartum) MTCT after adjustment for maternal HIV load and other confounders [97]. A study in Ukraine in which researchers were unable to adjust for maternal HIV load reported that serologically confirmed syphilis was associated with a fivefold increase in MTCT [98]. However, studies conducted in Zimbabwe and Texas found no association between active syphilis and perinatal HIV transmission [79, 100]. These findings are consistent with the Rakai trial of presumptive treatment of STIs, which reported reductions in maternal rates of bacterial STIs but not in perinatal HIV transmission [101].

Human papilloma virus (HPV) infection is the most common STI, and its prevalence, incidence, and persistence are highly correlated with HIV infection and immune status [102, 103]. Some HPV types may cause genital warts, and two studies have reported a significant, unadjusted association between genital warts and increased risk for MTCT among co-infected women [54, 104]. This finding may be secondary to genital warts acting as a proxy for advanced HIV disease and higher maternal HIV load.

In women who have BV, the healthy vaginal flora is replaced with high levels of anaerobic microorganisms and byproducts that can damage vaginal epithelium and degrade cervical mucus. Evidence suggests that BV increases women's risk for STIs, including gonorrhea, chlamydial infection, trichomoniasis, HPV, herpes simplex virus, and HIV [105-109]. Among HIV-infected women, BV is associated with increased shedding of HIV in the genital tract. In a recent prospective study in Kenya, HIV-infected women diagnosed with BV at 32 weeks gestation had a threefold higher risk for *in utero* HIV transmission than women with normal vaginal flora [110]. However, a multi-site randomized controlled trial of metronidazole versus placebo found no difference in MTCT rates, despite a 16% reduction in BV [66]. Further studies are needed to answer the question of whether restoration of normal vaginal flora can reduce MTCT.

Treatment of concurrent genital infections can reduce genital HIV shedding [72], but whether this translates to reduced MTCT is unknown. Besides the aforementioned treatments for specific infections, randomized trials of virucidal vaginal washes, such as benzalkonium chloride or diluted chlorhexidine, on MTCT have failed to consistently demonstrate an effect [111-114].

MASTITIS

Breast milk contains both antimicrobial and immunomodulatory factors that protect infants against various infectious diseases and support the development of the infant's immune system. Because breast milk contains cell-free HIV inhibitors and because of the milk-blood barrier [42], the concentration of HIV is typically 10-100 times lower in breast milk than in plasma [34]. However, infection or inflammation of breast tissue can increase the HIV load in breast milk, which is a strong predictor of postnatal transmission [34].

An estimated 10%-33% of women experience mastitis, typically during the early breastfeeding period or during the mixed feeding and weaning stages. Clinical mastitis may be characterized by cracked nipples and sores, suppuration, pain, swelling, and erythema. Cracked nipples frequently bleed during infant feeding, thereby increasing the exposure to plasma and cell-associated virus, and several studies have reported associations between cracked or bleeding nipples and increased postnatal transmission of HIV [115, 116]. Subclinical mastitis is characterized by an elevated milk leukocyte count or elevated sodium or sodium/potassium ratio. Like clinical mastitis, it can alter the cellular tight junctions that regulate breast epithelial permeability. Both clinical and subclinical mastitis are associated with increased HIV load in breast milk [117-122] and its correlate, postnatal HIV transmission [25, 116, 117, 119, 121], and researchers have estimated that up to 50% of postnatal transmissions may be attributable to the more common subclinical mastitis [123].

Most mastitis is sterile inflammation with isolation of only normal skin flora, but up to 40%-50% of subclinical and clinical mastitis cases may be attributable to *Staphylococcus aureus* [124, 125]. A study among 75 HIV-infected, postpartum women with subclinical mastitis in Malawi evaluated the effect of oral amoxicillin/clavulanic acid on breast milk leukocyte count and HIV load. One week after treatment, there was a >50% reduction in the proportion of mothers with elevated breast milk leukocyte counts; after 4-12 weeks, study results showed a significant reduction in breast milk HIV load compared with baseline data [126]. However, the HIV load remained higher among women with past clinical mastitis than among those without mastitis at baseline. These findings suggest that the effect of inflammation on the alveolar ducts persists for several weeks after treatment.

Interestingly, mastitis has been associated with increased breast milk concentrations of α-defensins, a group of anti-HIV peptides released by the innate immune system, and researchers have suggested that mastitis may provide a protective effect when HIV load is low in plasma [127]. An analysis of plasma and breast milk samples collected as part of a study in Zimbabwe found that mastitis was associated with postnatal transmission of HIV only when HIV load was high in maternal plasma (>3.7 $\log_{10}$ copies/mL) [121]. For women with HIV loads <3.7 $\log_{10}$ copies/mL, the point estimate for the odds of postnatal transmission was in the direction of a protective effect (0.26; 95% CI, 0.04-1.94). These data suggest that, when HIV loads are low in maternal plasma, the increased immune factors in breast milk associated with mastitis may outweigh the effect of any increase in HIV replication.

GINGIVITIS

In many parts of the world, including sub-Saharan Africa, it is common for mothers to premasticate food for their infants during the weaning period [128]. In 2009, there was a case series report of three pediatric HIV infections among infants who were HIV-negative at birth, not breast fed, and had no known causes of infection besides exposure to food premasticated by a HIV-infected caregiver [129]. For two of the infants, it was a HIV-infected mother who premasticated the food; for the other infant of an HIV-negative mother, it was an HIV-infected great aunt. In two of the cases, there was evidence of bleeding gums. The exposure to blood in premasticated food along with the compromised oral mucosa of an infant may facilitate transmission via premasticated food. A case-control investigation in 2010 at 6 U.S. HIV clinics found no significant difference between 11 infants with late-diagnosed HIV-infection and 35 HIV-exposed, uninfected infants in the proportion that were fed food premasticated by an HIV-infected caregiver (27% *vs* 20%, respectively) [130]. This report also presented the findings from a cross-sectional investigation of premastication prevalence, which was 31% among 154 primary caregivers of children aged ≥6 months. Premastication appears to be a rather common practice of caregivers, but it is contraindicated for HIV-infected caregivers [131].

MATERNAL SYSTEMIC CO-INFECTIONS

As mentioned, maternal HIV load is highly correlated with risk for HIV transmission to the infant [29, 30, 132-134], and concurrent, systemic maternal infections can inadvertently stimulate HIV replication and increase HIV load. Any infection that raises maternal plasma HIV load, and its correlates, HIV load in the genital tract and in breast milk, could affect the risk for HIV transmission.

Hepatitis B

Up to 90% of HIV-infected persons worldwide have serologic evidence of hepatitis B virus (HBV) infection, and 10% have chronic HBV [135, 136]. Co-infection with HIV accelerates the rate of disease progression of HBV infection and is associated with an increased carriage rate for the hepatitis B e antigen, chronic HBV infection, and high HBV DNA levels, all of which are associated with increased risk for MTCT of HBV [136-141]. Among women with very high HBV DNA levels during pregnancy ($>10^9$ copies/mL), HBV transmission to the infant is substantial (as high as 32%) despite immunoprophylaxis with vaccine and immunoglobin [142]. Although HIV/HBV co-infection may be related to increased HBV transmission to the infant, HBV infection, as measured by the presence of hepatitis B surface antigen, does not seem to be independently associated with increased MTCT of HIV [143, 144]. However, women co-infected with HIV/HBV are significantly more immunosuppressed than HIV-monoinfected women, which is an independent risk factor for MTCT [145].

Hepatitis C

Although hepatitis C virus (HCV) infection is less common than HBV, rates of co-infection among HIV-infected persons are about 30% worldwide, and the prevalence of HCV

infection is particularly high among HIV-positive injection drug using women [145, 146]. HIV-infected persons exposed to HCV are less likely to clear the virus spontaneously, and upon infection, co-infected persons have increased HCV RNA levels in plasma and progress to cirrhosis faster than HCV-monoinfected persons [147-149]. Increased maternal HCV RNA levels are associated with perinatal transmission of HCV [150-154], and HIV-co-infected mothers are at increased risk for perinatal transmission of HCV [150, 151, 155, 156]. With respect to the role of HCV infection on MTCT of HIV, HIV disease progression, and death, the data are conflicting. HCV seropositivity is associated with severe immunosuppression among HIV-infected persons ($p<.001$) [145], and several studies have documented increased risk for MTCT of HIV among co-infected women [155-159]. The likely mechanism for increased MTCT associated with HCV seropositivity is increased maternal HIV load.

GB Virus C

GB virus C (GBV-C) is a flavivirus closely related to HCV that was discovered in 1995 [160]. Although no clinical disease has been associated with GBV-C, it can be transmitted vertically and has been associated with reduced MTCT of HIV [161, 162].

Cytomegalovirus

Cytomegalovirus (CMV) seropositivity in HIV-infected adults is almost universal, and the two viruses can infect the same cell types, with the viral products of each virus capable of activating the other virus *in vitro*. Researchers have hypothesized that the two infections are interrelated, with each virus predisposing a person to a higher risk of contracting the other virus. The prevalence of congenital CMV infection among infants born to HIV-infected women is relatively high, with rates ranging from 2% to 7% [163-168]; rates in the general newborn population are 0.7% [169]. A simple bivariate analysis of data from eight studies (n=6,265) suggests that congenital CMV infection occurs significantly more often among HIV-infected infants (9%) than those who are not infected (2%) [165], but this comparison was heavily weighted by the largest study of 4,797 infants in the French Perinatal Cohort Study. Findings from that study also suggest a role of maternal immunosuppression in increased CMV transmission based on a lower risk for congenital CMV infection among HIV-infected mothers after highly active antiretroviral therapy became available [166]. A recent study in Thailand of 97 HIV-infected infants and 196 HIV-exposed uninfected infants matched for maternal HIV load reported that congenital CMV infections were more common in HIV-infected (14%) than HIV-uninfected (3%) infants [170]. This study also examined the timing of CMV infection relative to HIV infection and found that *in utero* CMV infection correlated with both *in utero* and intrapartum HIV infection, whereas intrapartum CMV infection correlated with intrapartum, but not *in utero*, HIV infection, suggesting that fetal CMV infection may predispose infants to *in utero* HIV infection. *In vitro* studies have also described the ability of CMV to facilitate HIV infection [171-173]. Infants with CMV and HIV infection may be more prone to rapid progression of HIV disease [167].

Epstein-Barr Virus

Another almost universal HIV co-infection is Epstein-Barr virus (EBV). In a multi-site U.S. study of 279 HIV-infected, pregnant women who were also EBV seropositive, EBV shedding was marginally associated with MTCT of HIV [61]. However, this association did not reach statistical significance in a multivariate analysis that adjusted for maternal immune status and other confounders.

HHV-6

HIV-infected mothers also seem to transmit human herpes virus 6 (HHV-6) to infants more frequently than HIV-uninfected mothers [174]. However, a study of perinatally HIV-infected infants from Thailand found the rate of HHV-6 infection was lower in HIV-infected children, but that HHV-6 co-infection correlated with faster progression of HIV disease [175].

HHV-8

Cross-sectional studies have demonstrated a significant association between the seroprevalences of HIV and HHV-8, also known as Kaposi's Sarcoma-associated herpesvirus [176-179]. In Sub-Saharan Africa, where HHV-8 is highly prevalent, infection is commonly acquired in childhood through exposure to infected saliva from other children or caregivers, with the seroprevalence generally increasing with age [180-182]. Vertical transmission of HHV-8 during birth or through breast milk is rare [177, 180-185]; HHV-8 is rarely detected in breast milk [186]. Two large studies, a prospective study in Zambia [184] and a cross-sectional study in South Africa [187], found that maternal HHV-8 status was not an independent risk factor associated with HHV-8 transmission to children, suggesting that other household or non-familial contacts contribute to horizontal transmission. These studies also reported that maternal HIV status does not affect infant HHV-8 status. Infant HIV status, however, was an important predictor, and both studies reported a significant increased risk for HHV-8 among HIV-infected children [184, 187]. A small study of 15 co-infected, pregnant women in Italy found that HHV-8 load significantly increased late in pregnancy and was associated with a significant increase in HIV-1 shedding in the genital tract, suggesting that HHV-8 co-infection may increase MTCT of HIV [188]. However, results from a study in Zambia failed to show an association between HHV-8 infection and transmission of HIV to the infant [177].

Tuberculosis

Tuberculosis (TB) is a leading cause of disease and death worldwide and is of particular concern among those infected with HIV, who are 20-30 times more likely to develop TB [189]. For women, the greatest burden of TB occurs during the reproductive years (ages 15-49 years) [190]. Active TB infection increases HIV load and is associated with immunosuppression, which may explain the association between TB and MTCT [191-195]. To date, few studies have investigated whether TB increases the risk for MTCT independently of HIV load. A small study of 42 HIV-infected, pregnant women with active TB in South Africa reported a 19% rate of *in utero* transmission, which was higher than the 5%-10% rate reported in resource-limited countries at that time [195]. A recent study in

India found that maternal TB was associated with a 2.5-fold increase in the odds for MTCT after adjusting for maternal and infant factors [196].

Malaria

Populations with a high prevalence of both HIV and parasitic infections overlap geographically and socio-economically. In addition, the level of immune compromise associated with HIV increases a person's susceptibility to parasitic diseases. Concurrent infection causes chronic immune activation, which increases the risk for reactivation of both infections and higher HIV load.

In the most severely affected countries in Sub-Saharan Africa, more than 10% of adults are HIV-infected and more than 90% are exposed to malaria. Pregnant women are at increased risk for malaria which is associated with intrauterine growth retardation, preterm delivery, low birth weight, still birth, early neonatal death, and maternal anemia [197, 198], especially among primigravidae women, among whom malaria tends to be more severe. HIV infection further increases the risk for malaria parasitemia and clinical malaria, and among pregnant women, the risk of placental malaria and adverse birth outcomes [199-202]. Furthermore, new evidence suggests that malaria parasites may be more likely to develop wild-type mutations after exposure to sulfadoxine-pyrimethamine as intermittent preventive treatment during pregnancy among HIV-infected women [203]. Malaria also has been associated with a temporary increase in HIV replication and plasma HIV load [204, 205], and associations with blood parasitemia and MTCT of HIV may be secondary to an increase in maternal HIV load. Placental malaria has been associated with increased placental and plasma HIV load [206]. Several studies have examined the association between placental malaria and MTCT of HIV independently of HIV load or CD4+ T lymphocyte count, with inconsistent results [207-212]. The effect may be limited to cases with high parasitemia (>10,000 parasites/ml), as suggested by a study in Western Kenya, where the risk for MTCT increased when parasitemia was high but decreased when it was low (<10,000), compared with malaria-negative controls [202]. Other studies have shown associations between placental malaria and placental characteristics that may increase susceptibility to *in utero* HIV infection, such as placental inflammation [213], increased CC-chemokine production [214, 215], a shift in cytokine production from Th2 to Th1-type responses [216], and increased expression of the CCR5 HIV co-receptor on placental macrophages [50]. Inconsistencies in study results may be due, in part, to differences in the epidemiology of malaria in different settings, which could affect maternal immunity, or to different methods of detecting placental parasitemia. Although it remains unknown whether malaria increases MTCT, malaria during pregnancy is associated with obstetrical problems and adverse birth outcomes and warrants extensive screening and intervention programs in endemic areas.

Other Parasitic Co-Infections

Toxoplasmosis is a parasitic disease caused by the protozoon *Toxoplasma gondii*, and it is estimated that 25% to 30% of people world wide are infected [217]. Congenital toxoplasma infection results from primary maternal infection or reactivation of a past infection during pregnancy, with the risk of congenital toxoplasma transmission ranging from 10% during the first trimester, when the placental barrier is most efficient, to 60-70% in the third

trimester [218]. Conversely, the severity of fetal damage is greatest when infection occurs earlier in gestation, which often leads to severe abnormalities or abortion [219]. In HIV-infected women, the risk of toxoplasmosis, primarily from reactivation of a past infection, increases substantially when the CD4+ T lymphocyte count falls below 100 cells/μl. In the pre-HAART era, there were case reports of transmission of both toxoplasmosis and HIV to infants of co-infected mothers, with many of these infants having rapid HIV disease progression [220, 221]. A recent retrospective study of HIV-infected pregnant women and their infants in Brazil evaluated predictors for MTCT of HIV, which occurred among 3.7% (15/401) of infants. Maternal neurotoxoplasmosis during gestation was associated with a 7 times higher risk for infant HIV infection, and congenital toxoplasmosis, which occurred in 6 infants, was associated with 24 times higher risk of infant HIV infection [222].

The protozoan parasite *Trypanosoma cruzi*, which is endemic to Latin America, causes Chagas disease and can be transmitted transplacentally to the fetus. Human placental histocultures co-infected with *T. cruzi* and HIV have shown lower levels of chemokines that downmodulate *T. cruzi* replication (IL-6, IL-8, IP-10, and MCP-1) [223]. Another study suggests that *T. cruzi* inhibits HIV replication at the placental level [224]. However, simultaneous congenital transmission of *T. cruzi* and HIV has been reported [225].

Helminth infections are very prevalent in areas of Asia and Africa [226-229]; they affect immune homeostasis [230], which may influence risk for HIV acquisition and progression. One study found that women with HIV and helminth infections had a higher risk for MTCT of HIV [231]. Two randomized clinical trials have evaluated treatment of helminthic infections as a strategy to reduce the progression of HIV disease and found improvements in immune responses and CD4+ T lymphocyte counts in persons infected with some helminths [232, 233]. Periodic deworming is now recommended in Sub-Saharan Africa as a component of comprehensive HIV care for women and children.

INFANT CO-INFECTIONS

Although some infants become infected with HIV *in utero*, the majority are infected perinatally or postnatally. During labor and delivery, infants whose mothers have HIV are exposed to infected blood and vaginal secretions that may be inadvertently ingested. Prematurity of the skin, mucous membranes, and gastrointestinal tract is the likely mechanism for increased risk of HIV infection to premature infants. In newborns, the gastrointestinal tract is immature: it has a thin mucosa; lower levels of gastric acidity, enzyme activity, and mucus production; and no secretory IgA. These factors increase gastrointestinal permeability and make it possible for HIV to traverse the epithelium to the lamina propria, where HIV likely infects lymphocytes or is taken up by macrophages [234]. Inflammation of the gastrointestinal tract due to infection could weaken barrier defenses and facilitate passage of HIV. Some infants may develop oral candidiasis upon colonization from exposure to *Candida* during vaginal delivery. Candidiasis results in inflammation of the infant's oral mucosa and gastrointestinal tract and an influx of activated CD4+ T lymphocytes and macrophages; it has also been associated with increased risk for postnatal HIV transmission [116].

Diarrhea is associated with increased intestinal permeability [235], and any infection that causes diarrhea has the potential to increase MTCT to exposed infants. Although studies on the effects of diarrheal diseases on MTCT are lacking, increased intestinal permeability due to contamination of other liquids and foods given to the infant is a proposed biological mechanism for the increased risk for postnatal HIV transmission during the first few months of life among infants in resource-limited countries who are fed a mix of breast milk and other foods compared with infants who are exclusively breastfed [20, 236-238]. Mixed feeding poses the same risks for contamination and diarrhea as artificial feeding, but also increases intestinal permeability and risk for HIV infection because of continued exposure to HIV-infected breast milk.

Co-infections in HIV-infected infants are thought to in part explain the higher risk for death by 2 years of age among untreated, HIV-infected children in Sub-Saharan Africa (45%-59%) compared to those in Europe and the United States (10%-20%) [239-245]. A major cause of stillbirth and neonatal death is untreated maternal syphilis [246]. HIV-infected women have a higher prevalence of untreated or inadequately treated syphilis during pregnancy, which places their newborns at higher risk for congenital syphilis and its outcomes, including blindness, deafness, progressive intellectual deterioration, and death [100]. In Sub-Saharan Africa, up to 80% of children may acquire CMV during their first year of life, regardless of HIV status [247], and MTCT appears to be more frequent among infants with congenital CMV infection [167]. HIV and CMV co-infection in infants is associated with higher peak CMV viral loads, prolonged detection of CMV in plasma, rapid progression of HIV disease, and a greater than twofold increase in risk for death [167, 247, 248]. Other perinatal viral infections, such as HHV-6, have also been associated with faster progression of HIV disease [175].

STRATEGIES FOR PREVENTION AND TREATMENT

Antiretroviral treatment for HIV-infected women during pregnancy, delivery, and breastfeeding decreases the risk for MTCT by reducing the HIV load in plasma and breast milk, and it improves maternal health by reconstituting CD4+ T lymphocytes and lowering her risk for opportunistic infections. Administration of antiretrovirals is the most important intervention to decrease MTCT, and these medications should be made available to pregnant women in all settings.

Existing PMTCT programs could also incorporate available, inexpensive, and safe strategies for the prevention and treatment of co-infections during pregnancy and breastfeeding to further reduce MTCT of HIV. The World Health Organization (WHO) currently recommends prevention, screening, and treatment for certain infections at antenatal consultations [249]. In areas with endemic malaria, WHO recommends that pregnant women sleep under insecticide-treated mosquito bed nets and receive 2-3 treatment courses of sulfadoxine-pyrimethamine. Screening and treatment for syphilis are recommended at the first antenatal visit and ideally repeated at 36 weeks or delivery in areas of high risk. For other curable genital tract infections, WHO suggests using syndromic-based algorithms for diagnosis and treatment [250]. However, syndromic management has poor sensitivity and specificity for many of these infections, which can lead to overtreatment or under treatment

in many cases [251, 252]. Several trials are evaluating the use of azithromycin-based combination therapies for intermittent use during pregnancy. Azithromycin has shown high cure rates (>96.5%) for syphilis, *N gonorrhoeae*, and *C trachomatis*, as well as efficacy in reducing risk for *T vaginalis* [253-256]. A meta-analysis of antibiotic therapy for treatment of BV in pregnancy showed high efficacy (odds ratio, 0.17: 95% CI, 0.15-0.20; 10 trials, 4,357 women) and, when administered before 20 weeks, significantly reduced the risk for preterm birth [257]. Postpartum, WHO recommends prophylaxis against bacterial and protozoan opportunistic infections with cotrimoxazole for HIV-infected mothers and for HIV-infected or exposed infants from age 6 weeks throughout breastfeeding and longer for infants that are HIV-infected [258].

Given the limitation of syndromic management of certain co-infections, presumptive, intermittent treatment of prevalent co-infections for all women may be the preferable approach to improving pregnancy outcomes and reducing MTCT of HIV in resource-limited countries [259]. Alternatively, novel rapid diagnostic tests are becoming increasingly available, and frequent screening throughout the antenatal period and targeted treatment may be a better option in some settings. Testing of HIV-infected women for HBV infection during pregnancy should be part of routine antenatal care in all settings. This practice can guide decisions on selection of appropriate antiretroviral regimens and ensure timely administration of HBV vaccine and immunoglobulin to exposed infants [141]. Finally, ensuring that women are immunized against important pathogens, such as tetanus, influenza, or pertussis, before or during pregnancy can help prevent infections that are associated with concurrent immune activation and transient increases in HIV load during pregnancy. Immunization of the mother can also protect infants from these pathogens. Expanding HBV and HPV vaccine programs to cover young women before pregnancy has the potential to offer far-reaching health benefits at the population level.

CONCLUSION

Screening and treatment for co-infections that predispose infants to *in utero*, peripartum, or postpartum HIV infection can help to further reduce the incidence of HIV among infants while providing health benefits to both the mother and infant.

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Table 1
Maternal and Infant Co-Infections that have an Impact on MTCT of HIV

Co-Infection	Mechanisms of Affecting MTCT of HIV	Intervention Strategies
Chorioamnionitis	Potenital to increase MTCT *in utero* via placental inflammation or intrapartum via association with preterm labor and premature rupture of membranes	Treatment with antibiotics during pregnancy has not shown value in preventing MTCT of HIV [65, 66]
Lower genital tract infections (HSV, syphilis, BV, trichomoniasis, etc.)	Potential to increase MTCT *in utero* and intrapartum by increased peripheral blood HIV load and increased genital tract HIV shedding and local mucosal inflammation	Treatment of HSV with valacyclovir in pregnant and postpartum women reduced HIV RNA in plasma and breast milk [95] but did not reduce MTCT; further studies are needed Trials of vaginal cleansing have not shown benefit in reducing MTCT [111-114]
Mastitis	Increased MTCT during breastfeeding from increased viral load in breast milk	Counseling on proper breastfeeding technique. Exclusive breastfeeding was associated with reduced MTCT of HIV, compared with mixed feeding [20, 236-238] Antibiotic treatment of mastitis may reduce breast inflammation [126], however effects on MTCT are unknown
Gingivitis/Periodontal Disease	Bleeding gums or increased HIV shedding in oral secretions associated with periodontal inflammation when food is premasticated for infants by an HIV-infected caregiver	HIV-infected caregivers should not premasticate food for infants [131]
Viral Co-infections (HBV, HCV, CMV, others)	Increased MTCT due to increased prevalence of co-infections among more immunosuppressed women and increased maternal HIV load associated with co-infections	Prenatal maternal screening for HBV. If positive, infants should receive hepatitis B vaccine and immune globulin soon after birth [141] Antiviral regimens against HBV may be considered during pregnancy [141]
TB	Associated with maternal immune suppression and higher HIV load.	Appropriate maternal treatment with antiretrovirals and regimens against TB may result in improvement in immune status and decreases in VL
Malaria	Possibly increased MTCT *in utero* and intrapartum due to increase in maternal viral load, preterm delivery and low birth weight	Appropriate malaria preventive measures during pregnancy (intermittent preventive therapy, insecticide-treated bed nets)
Other parasitic infections (toxoplasmosis, trypanosomiasis, helminths)	Associated with maternal immune suppression and with increased HIV load	Periodic deworming in endemic areas may be associated with improvement in immune status and decreases in HIV load Screening for toxoplasmosis during pregnancy; appropriate prophylaxis or treatment, as necessary [260]
Infant Oral Candidiasis	Increased MTCT during breastfeeding due to breaches in oral mucosa and influx of activated CD4+ T lymphocytes and macrophages as well as HIV into the GI tract	Treatment of oral candidiasis will decrease oral mucosal inflammation
Infant Diarrhea	Increased MTCT during breastfeeding due to increased intestinal permeability	Promotion of breastfeeding in resource-limited settings decreases infant diarrheal disease