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Prevention of mother-to-child transmission of HIV infection

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ABSTRACT

This review aims to evaluate the prevention strategies of perinatal HIV infections and their efficacy worldwide, both in resource-limited and in resource-rich regions. Furthermore, it presents the most recent aspects of obstetric management of HIV-infected mothers.

The introduction of combined antiretroviral therapy (ART) has decreased mother-to-child HIV transmission in high-income settings to historically low levels. Efforts to implement antiretroviral agents in resource-limited countries were also successful in reducing perinatal transmission. However, there are differences in prevention strategies between low and high-resource settings regarding the mode of delivery and infant feeding advice. The three-part prevention strategy (antepartum, intrapartum, and infant prophylaxis) is the most effective approach. Viral load suppression by antiretroviral treatment up to the time of birth is the most effective way to reduce perinatal transmission. Viral load and not HIV status should be used to determine the mode of delivery. Furthermore, the duration of prolonged rupture of membranes is not associated with an increased risk of HIV transmission in women with low viral load. Breastfeeding is contraindicated for mothers living with HIV in resource-rich settings, whereas in low-income areas breastfeeding remains the main nutritional source for infants. ART should be initiated as early as possible in newly diagnosed pregnant women and should be continued for life.

Preventive strategies of perinatal HIV transmission have become extraordinarily successful, especially due to the introduction of antiretroviral therapy. Key strategies in the prevention of mother-to-child transmission are prompt identification and treatment of HIV-infected mothers and postpartum infant prophylaxis.

Keywords: HIV, screening, transmission, pregnancy, prevention, antiretroviral therapy

INTRODUCTION

According to The Joint United Nations Program on HIV/AIDS (UNAIDS) [1], the global prevalence of HIV/AIDS in 2019 was 0.7%, with 36.2 million adults and 1.8 million children (<15 years old) living with HIV worldwide. Out of these, 600,000 adults and 95,000 children died of AIDS that year. The majority of HIV infections (60%) are located in sub-Saharan Africa. Women account for approximately half of the population with HIV. This is due to the high prevalence of HIV in sub-Saharan Africa, where heterosexual exposure is the primary mode of transmission. In high-income settings, the most common route of transmission is among men who have sex with men (MSM).

The main routes of acquiring HIV infection are sexual transmission, parenteral transmission, and perinatal transmission [2]. Ninety percent of HIV infections among children occur through mother-to-child transmission. In most affected regions in the world, such as in sub-Saharan Africa, the prevalence of HIV in pregnant women reaches 20% to

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40%. Without treating these women with antiretroviral therapy (ART), one-third of their newborns could acquire HIV [3].

In high-income settings, the use of ART has decreased HIV perinatal transmission from 20-30% to less than 1% [4,5]. Worldwide in 2019, it was estimated that 85% of pregnant or breastfeeding women with HIV were on ART treatment. It has been recognized that, globally, the incidence of HIV infections among children has been reduced by 50 percent since 2010 [3].

This review aims to evaluate the prevention strategies of perinatal HIV infections and their efficacy worldwide, both in resource-limited and in resource-rich regions. Furthermore, it presents the most recent aspects of obstetric management of HIV-infected mothers.

MECHANISM OF PERINATAL TRANSMISSION

Mother-to-child HIV transmission can occur in utero, intrapartum, or postnatal through breastfeeding. Without ART the risk of perinatal transmission is estimated between 15% and 45% [6]. The most common period of transmission is around the time of labor, accounting for 50% of cases, followed by in utero infections with about 25% to 40% of cases and the remainder during breastfeeding [7]. In utero fetal infections occur mostly during the third trimester. This may be due to microtransfusions of viremic maternal blood across the placenta to the fetus [8]. Furthermore, chorioamnionitis and genital tract infections may increase the risk of transmission [9]. Intrapartum transmission happens through contact of the newborn mucosa with maternal blood and secretions. The mechanism of HIV transmission during breastfeeding is not fully understood. It may occur either through the presence of HIV RNA or through HIV-infected cells within the colostrum or breast milk [10]. The portal of entry of HIV in newborns is represented by breaches in the intestinal epithelia or the tonsillar tissue [11].

PREVENTION OF MOTHER-TO-CHILD TRANSMISSION

The cornerstone of the prevention of vertical transmission is the antiretroviral therapy. In high-income countries, the risk of perinatal transmission has reached less than 2 percent [12]. Additionally, universal screening of pregnant women for HIV infection, delivery by cesarean section, and avoidance of breastfeeding contribute to the successful prevention of infant HIV infections. Subsequently, the three-part prevention strategy (antepartum, intrapartum, and infant prophylaxis) is more effective than treating mothers or infants only during labor or in the postpartum period [13].

SCREENING

Early identification of HIV infections plays an important role both in the prevention of HIV perinatal transmission and in improving the mother's health. All pregnant women should be tested as part of the routine panel of prenatal tests using the opt-out strategy, meaning that HIV testing is performed for all women unless they specifically decline. Furthermore, if at any time during pregnancy a woman reaches a delivery facility with undocumented HIV status, she should be tested, including if she arrives already in labor [14].

Women at high risk of acquiring HIV infection with initial negative HIV tests should repeat HIV testing in the third trimester. According to The American College of Obstetricians and Gynecologists (ACOG), pregnant women at high risk are as follows: those who have been diagnosed with another sexually transmitted disease in the past year; those who are injection drug users; those who exchange sex for money or drugs; those who live in regions with high HIV incidence; those who are incarcerated; those who have signs or symptoms consistent with acute HIV infection [15].

US Food and Drug Administration introduced in 2012 the first over-the-counter self-administered test for HIV [16]. Since then, HIV self-testing has gathered interest. A new systematic review revealed that this strategy combined with digital support could be very successful in increasing HIV testing [17]. Consequently, this strategy may improve HIV testing among pregnant women who are more difficult to reach.

ANTIRETROVIRAL THERAPY

All pregnant women should receive ART, regardless of CD4 cell count or plasma viral load. Firstly, it decreases the risk of vertical transmission, and secondly, it treats the maternal disease by suppressing the maternal viral load. ART should be initiated as early as possible in pregnant women who are not already on it. Earlier initiation of ART has been shown to decrease viral suppression by the time of delivery, consequently leading to a lower risk of perinatal transmission [18]. One study showed that each additional week of ART decreases the risk of perinatal transmission by 8% [19].

According to ACOG, HIV RNA levels during pregnancy should be monitored as follows: at the first prenatal visit (every woman should be screened for HIV infection using the opt-out approach); 2-4 weeks after initiation/changing of ART regimen; monthly until RNA levels are undetectable; then at least every three months during pregnancy. Furthermore, at approximately 34 to 36 weeks of gestation RNA levels should be determined in order to establish the optimal mode of delivery [20].

MODE OF DELIVERY

Women on ART who have not reached viral suppression (HIV viral load >1000 copies/ml) should deliver by cesarean section in order to decrease the risk of vertical transmission [21]. This recommendation is not applicable in resource-limited regions because it may increase maternal morbidity. Consequently, HIV status of the mother does not influence decisions on the delivery mode in this setting. In resource-rich regions, the mode of delivery depends on viral load near the time of delivery. Women on ART with HIV RNA less than 1000 copies/ml have a low risk of perinatal transmission during labor. Therefore, they may deliver vaginally. Research has established that pregnant women on ART, with less than 1000 copies/ml, have a risk of vertical transmission lower than 1-2 %, regardless of the mode of delivery or duration of ruptured membranes before delivery [22]. Conversely, if viral load is >1000 copies/ml before 38 weeks of gestation, cesarean delivery at 38 weeks of gestation is recommended to prevent the onset of labor or rupture of membranes [23].

Nevertheless, according to ACOG clinicians should respect the woman's desire regarding the mode of delivery. The patient may wish to undergo cesarean delivery even if the viral load is less than 1000 copies/ml. Inversely, a patient can opt for vaginal delivery despite the viral load higher than 1000 copies/ml [20].

Women should continue taking their ART treatment intrapartum regardless of the mode of delivery. Additionally, zidovudine is an antiretroviral that is given during labor depending on maternal viral load. It is administered intravenously with a 2mg/kg dose followed by a continuous infusion of 1 mg/kg/hour until delivery. In the case of cesarean delivery, zidovudine is initiated 3 hours before the procedure. A landmark study conducted in 1994 which evaluated the efficacy of zidovudine administration during the antepartum and intrapartum period, revealed that the prophylaxis treatment reduces perinatal transmission by 66% [24].

If the viral load of HIV RNA is less than 50 copies/ml at the time of delivery or during late pregnancy, zidovudine use is not necessary. Given that data is scarce on prevention benefits with zidovudine in women on ART with HIV RNA between 50 and 1000 copies/ml, some experts recommend zidovudine in this setting as the transmission risk may be slightly higher [25]. Intrapartum zidovudine administration is highly indicated in the following settings: HIV RNA levels over 1000 copies/ml; women with no antepartum ART; women with intrapartum HIV diagnosis or with unknown HIV RNA status.

Other aspects during labor should be taken into account as follows: fetal scalp electrode monitoring, and operative vaginal delivery should be avoided [20]. Furthermore, if membrane rupture occurs before 37 weeks gestation the presence of HIV infection does not outweigh the risks of prematurity. It was believed that duration of membrane rupture longer than four hours represented an increased risk of transmission. An older study showed that the presence of ruptured membranes for more than four hours doubled the risk of transmission, regardless of the mode of delivery. This study was conducted before ART treatment became successful [26]. Subsequently, it has been demonstrated that the viral load of the mother is an independent risk factor for intrapartum transmission, no matter the duration of membrane rupture. Recent studies support vaginal delivery, even in the situation of prolonged rupture of membranes before delivery, provided that the woman is on ART and has a viral load of less than 1000 copies/ml [27,28]. For women with viral load more than 1000 copies/ml or with unknown viral load, who originally were scheduled for cesarean delivery and present in labor or with ruptured membranes, it is unclear how soon the benefit of cesarean delivery is lost [29]. In this situation, it is up to the clinician to establish the route of delivery.

Clinicians should be aware of the potential interactions of medications used during delivery and antiretroviral medication. Precisely, simultaneous use of methergine and other ergotamines with protease inhibitors or cobicistat can cause exaggerated vasoconstrictive responses leading to acute leg ischemia [30]. Therefore, in the case of uterine atony, other uterotonic agents such as misoprostol or oxytocin should be used.

INFANT HIV PROPHYLAXIS

All newborns of HIV-infected mothers should receive antiretroviral prophylaxis. Treatment should be started within 6 to 12 hours after delivery. Because the risk of infection is low for infants of mothers on ART with viral load less than 50 copies/ml, only zidovudine should be administered for four weeks. Newborns at high risk (mothers on ART with more than 50 copies/ml, unknown viral status, or women with no antepartum ART) should receive empiric HIV therapy with zidovudine, lamivudine plus either nevirapine or raltegravir for 6 weeks. The latter treatment should be applied also to infants born to mothers with low viral load who present additional risk factors such as genital infections, genital ulcers, or excessive bleeding during birth [23].

During the postnatal period, HIV transmission to infants occurs through breastfeeding, therefore the Centers for Disease Control recommend replace-

ment feeding instead of breastfeeding. This is the standard of care in resource-rich settings [31]. Nevertheless, in resource-limited countries breastfeeding offers multiple benefits for the infant such as limiting the risk of diarrheal disease, pneumonia, other infectious diseases, and decreasing infant mortality [32]. With growing antiretroviral drug availability in these settings, the risk of HIV transmission through breastfeeding has been reduced. The World Health Organization (WHO) recommends breastfeeding in resource-limited countries, provided that the mother is on ART and the infant receives antiretroviral prophylaxis [33,34].

According to WHO recommendations for resource-limited regions, ART should be initiated in all women with HIV, both during pregnancy and during breastfeeding, regardless of CD4 cell count [35]. The first-line treatment consists of a once-daily dose of tenofovir, lamivudine (or emtricitabine), and dolutegravir. Regarding the latter antiretroviral, there were some concerns about the association of dolutegravir use and a small risk of neural tube defects. Subsequently, studies have shown that the risk is not statistically significant and that benefits of dolutegravir outweigh the potential risks. Women who are still worried about these risks can choose efavirenz as an alternative [36].

Breastfeeding infants with a low risk of infection (born to mothers with viral suppression on ART or with ART treatment for more than four weeks) should receive nevirapine for six weeks. Infants whose mothers have a viral load greater than 1000 copies/ml or acquired HIV during pregnancy / breastfeeding should take nevirapine and zidovudine for 12 weeks, or after the first six weeks nevirapine alone. If the virologic test confirms that the infant has HIV, prophylaxis should be stopped, and combination ART introduced. If the mother interrupts ART during breastfeeding, the infant should take nevirapine continuously throughout breastfeeding and one week after breastfeeding stoppage. A study revealed a 0.57% transmission rate with nevirapine infant prophylaxis and without maternal ART during breastfeeding [33].

In resource-limited settings, prophylaxis for infants who are on replacement feeding has the aim to prevent transmission during delivery. If there is a low risk of transmission the prophylactic regimen consists of zidovudine or nevirapine for four to six weeks. In case of high-risk transmission, infants should receive zidovudine plus nevirapine for six weeks [33].

Studies have shown that the use of ART for mothers associated with infant prophylaxis has decreased the risk of transmission during breastfeeding to less than 3% [37]. Although maternal ART and infant prophylaxis have similar efficacy in preventing HIV vertical transmission during breastfeeding, maternal ART is the preferred strategy. This is due to WHO recommendation of lifelong ART for persons with HIV, including pregnant and breastfeeding women [33].

CONCLUSIONS

The introduction of combined antiretroviral therapy has decreased mother-to-child HIV transmission in resource-rich settings to historically low levels, reaching less than 1%. Given that vertical HIV transmission occurs antepartum, intrapartum, and postpartum, prevention strategies addressing all three periods are most efficient. Consequently, universal screening of pregnant women for HIV infection, treating all HIV positive women with ART (regardless of CD4 cell count), delivery by cesarean section, and avoidance of breastfeeding contribute to the successful prevention of infant HIV infections.

Efforts are made to decrease mother-to-child HIV transmission in resource-limited countries, but differences still exist regarding the management of labor and breastfeeding between resource-rich and resource-limited settings. In low-income countries, HIV status of the mother does not influence the decision on delivery mode and breastfeeding remains the most beneficial feeding practice, provided that proper HIV prophylaxis treatment is implemented. In high-income countries, breastfeeding is contraindicated, and the mode of delivery depends on viral load near the time of delivery.

Recent data on the prevention of perinatal HIV transmission is promising. It represents an ongoing process and a continuous international effort toward eliminating mother-to-child HIV transmission.

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